Age of Diagnosis of Squamous Cell Cervical Carcinoma and Early Sexual Experience

Zoe R. Edelstein,[1,4] Margaret M. Madeleine,[1,4] James P. Hughes,[2] Lisa G. Johnson,[4] Stephen M. Schwartz,[1,4] Denise A. Galloway,[3,4] Joseph J. Carter,[4] and Laura A. Koutsky[1]

Departments of [1]Epidemiology, [2]Biostatistics, and [3]Microbiology, University of Washington, Seattle Washington; [4]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle Washington

Abstract

Background: **Given the established links among young age at first intercourse (AFI), number of sex partners, high-risk human papillomavirus infection, and squamous cell cervical cancer (SCC), we hypothesized that women diagnosed with SCC at younger ages would be more likely to report young AFI than women diagnosed later in life.**

Methods: **We performed a population-based investigation among invasive SCC cases who were diagnosed between 1986 and 2004, were ages 22 to 53 years, and lived in the metropolitan Seattle-Puget Sound region (n = 333). Using multivariate linear regression, we estimated coefficients and 95% confidence intervals (95% CI) to assess the association between age at SCC diagnosis and AFI (<15, 15-18, ≥19 years) and number of sex partners at age <20 years (0, 1, 2-4, 5-14, ≥15), accounting for birth year and other factors. Interactions were assessed using the likelihood ratio test.**

Results: **The interval between AFI and SCC diagnosis ranged from 4 to 35 years. In a multivariate model, compared with SCC cases reporting AFI ≥19, the mean age of diagnosis was 3.1 years younger for SCC cases reporting AFI <15 (95% CI, -5.8 to -0.5) and 2.6 years younger for SCC cases reporting AFI 15 to 18 (95% CI, -4.6 to -0.6). Although number of sex partners at age <20 years was associated with age at SCC diagnosis in a crude analysis, the association was not independent of AFI. However, in the AFI ≥19 and <15 groups, differences in effect were seen by number of sex partners at age <20 years ($P_{interaction}$ = 0.08), with the association remaining strong and significant only in the AFI <15 group that had ≥2 partners at age <20 years (coefficient, -4.2; 95% CI, -6.3 to -2.1).**

Conclusion: **Among younger and middle-aged women with SCC, early age of diagnosis was associated with early AFI, although the effect appeared to be modified by number of sex partners at age <20 years.** (Cancer Epidemiol Biomarkers Prev 2009;18(4):1070–6)

Introduction

Cancer of the uterine cervix is the second most common cancer in women worldwide (1). In the developing world, it is thought to be responsible for the most years of life lost due to cancer in part because it affects relatively young women (2). The majority of women with invasive squamous cell carcinoma of the cervix (SCC) are diagnosed in their mid-40s or 50s, although some women are diagnosed much earlier (3-5). In the United States, the annual incidence is <1 per 100,000 among women ages 15 to 24 years and ~7 per 100,000 among women ages 25 to 34 years (6). Although SCC incidence has decreased considerably among women ages >34 years during the last 30 years in the United States due to implementation of Papanicolaou (Pap) smear screening programs, the rate among younger women has remained relatively unchanged (6). In addition to the direct effect SCC can have on mortality and morbidity for cases of any age, a significant consequence especially relevant to cases who are of childbearing age is infertility resulting from standard treatment (7, 8).

That SCC occurs in young women is perplexing given the current estimates for sojourn time from the necessary high-risk human papillomavirus infection of the cervix to invasive cancer diagnosis (3-5). The modal time between high-risk HPV infection in the late teens or early 20s and diagnosis of the high-grade intraepithelial lesion that precedes invasive SCC (cervical intraepithelial neoplasia 3) has been estimated as 7 to 15 years with diagnoses peaking at ages 27 to 30 years (3, 5), although there is some indication that it may be shorter (9). The transit time from cervical intraepithelial neoplasia 3 to invasive cervical cancer has been harder to estimate because women diagnosed with cervical intraepithelial neoplasia 3 are treated by ablation or excision of the lesion. The range has been estimated as 1 to 20 years (4). However, if one uses the difference between median age of cervical intraepithelial neoplasia 3 diagnosis (ages 27-30 years) and that of invasive cervical cancer (age ~48 years) to estimate median sojourn time, it appears to be at the longer end of the estimated range (3, 5). As sexual contact is thought to be the mode of transmission for virtually all anogential HPV infections (5), these estimates suggest that women diagnosed with SCC in their 20s or younger could have a very young age at first intercourse (AFI), perhaps as early as age 10 or 12 years. Early-onset SCC may also occur due to particularly rapid disease progression (10, 11), a controversial phenomenon (12).

Received 7/30/08; revised 12/24/08; accepted 1/27/09; published OnlineFirst 3/24/09.

Grant support: NIH grants P01CA042792, N01-PC-35142, and 5T32CA009168 and Fred Hutchinson Cancer Research Center institutional support.

Requests for reprints: Laura A. Koutsky, University of Washington, HPV Research Group, Box 359933, 1914 North 34th Street, Suite 300, Seattle, WA 98103. Phone: 206-616-9784; Fax: 206-616-9788; E-mail: kouts@u.washington.edu

doi:10.1158/1055-9965.EPI-08-0707

Although early sexual debut has been identified as a risk factor for HPV infection (13, 14) and invasive SCC (15-17), we know of no study in which the association between AFI and age at invasive SCC diagnosis has been assessed. Exploring this relationship could contribute to the known natural history of SCC and help to inform the continuing refinement of recommendations for both age at HPV vaccination and age at initiation of routine Pap testing. Thus, we conducted a population-based, case-only study to test the hypothesis that early AFI is associated with early-onset SCC independent of other SCC risk factors.

Materials and Methods

Study Population. SCC cases in this investigation were a subset of participants from a population-based epidemiologic study in western Washington of invasive cervical cancer, for which methods have been described previously (15). Briefly, a woman was eligible for the original study if she was diagnosed with first primary invasive squamous cell cancer of the cervix (*International Classification of Diseases for Oncology* morphology 8010 and 8070-8081 and topography codes 1800-1809) from January 1986 to June 1998 or from January 2000 to December 2004, a resident of King, Pierce, or Snohomish County at the time of diagnosis, and able to communicate in English. The cases were originally identified by the Cancer Surveillance System, a population-based cancer registry that is part of the Surveillance, Epidemiology and End Results program of the National Cancer Institute. Of the 1,189 cases eligible for the original study, 62.6% (n = 744) were interviewed, 10.4% died before contact, 21.8% refused to participate or were lost to follow-up before interview, and for 5.2% the physician approached refused contact for the participant. For analysis purposes (see Statistical Methods), only women diagnosed with invasive SCC born between 1951 and 1967 were included (n = 333), which limited the age range at diagnosis to ages 22 to 53 years.

Data Collection. Each woman was interviewed in-person using a structured questionnaire administered by trained female study staff. The participant was asked to refer to the time before her diagnosis when answering questions on a range of topics including sexual, reproductive, screening, and cigarette smoking histories as well as other questions relevant to health history and demographic characteristics. To address AFI, each woman was asked, ''How old were you when you first had sexual intercourse with a male?'' Questions regarding the number of sex partners by decade of life and over a woman's lifetime were asked categorically (0, 1, 2-4, 5-14, 15-29, 30-49, ≥50 partners) using show cards. Age at diagnosis was calculated by subtracting date of birth from date of SCC diagnosis and rounding down. Both date of birth and diagnosis were obtained from the Cancer Surveillance System and the former was verified during the interview.

At the time of interview, each participant was asked to provide a serum sample, and from consenting cases, we attempted to retrieve tumor blocks from the diagnosing pathology laboratory. The serologic HPV antibody response and PCR testing methods used have been described in detail elsewhere (15, 18, 19). Serologic antibody testing for HPV-16, HPV-18, *Chlamydia trachomatis*, and herpes simplex virus type 2 was only done for participants with diagnosis dates between 1986 and 1998, which in this investigation meant that younger cases tended to be more likely to have test results. In the original study, blood samples were obtained from 86.5% of cases and tissue blocks were retrieved for 80.0%. The institutional review boards of the Fred Hutchinson Cancer Research Center and University of Washington approved all research protocols.

Statistical Methods. Linear regression was used to estimate the relationship between AFI and age at SCC diagnosis in years. For each independent variable, the corresponding regression coefficient estimated the difference in mean age at SCC diagnosis per 1-unit change in that independent variable.

We modeled AFI both as a continuous variable and as a categorical variable with three categories [age <15, 15-18, or ≥19 (reference) years]. The range of the middle category of this variable was chosen based on the AFI interquartile range. With AFI as a continuous variable, we calculated univariate linear regression coefficients. We present the Spearman correlation and a scatter plot showing the data points for all cases, which are jittered to avoid overlap, as well as fitted regression lines and loess smoothes, which graphically represent weighted regressions. We used the categorical variable for the remainder of our investigation, reporting the unadjusted coefficients, and those that were adjusted using multivariate modeling.

We hypothesized *a priori* that the number of male sex partners a woman had at age <20 years could also be associated with age at SCC diagnosis, as another measure of early sexual experience, and could confound or modify the association between AFI and age at SCC diagnosis. Thus, we calculated unadjusted coefficients for the association between age at SCC diagnosis and number of partners at age <20 years, modeled categorically (0, 2-4, 5-14, ≥15 partners), as well as those adjusted for AFI and other measures. Finally, we also explored stratifying AFI results by number of partners at age <20 years (0-1 versus ≥2) using a variable that combined AFI and number of male sex partners at age <20 years in the following six mutually exclusive categories: (*a*) AFI ≥19 and 0 to 1 sex partner at age <20 years (reference), (*b*) AFI ≥19 and ≥2 sex partners at age <20 years, (*c*) AFI 15 to 18 and 0 to 1 sex partner at age <20 years, (*d*) AFI 15 to 18 and ≥2 sex partners at age <20 years, (*e*) AFI <15 and 0 to 1 sex partners at age <20 years, and (*f*) AFI <15 and ≥2 sex partners at age <20 years.

We also hypothesized *a priori* that estimated associations would be confounded by birth cohort because (*a*) there have been changes in sexual and reproductive behavior during the last century (20) and (*b*) the study design linked birth year to age at SCC diagnosis, which were observed in our own preliminary examination of the data from the full case-control study (data not shown). The latter was a result of SCC cases being drawn from a study that only included women diagnosed

between 1986 and 2004, which restricted the age range for each birth year with a 19-year maximum age range and smaller ranges for earlier and later birth years. In anticipation of adjustment for birth year, we restricted the study population to SCC cases born between 1951 and 1967. We choose these years from among the full range of birth years for SCC cases (1913-1981) because each year of the restricted range had at least one case that was in a designated ''younger case group'' (ages 22-35 years) and at least one in an ''older age group'' (ages 36-53 years) among the original study participants. This selection reduced the likelihood of attenuation of coefficients that can occur from restricting the range of the dependent variable in a regression. Within the years selected, birth year was associated with AFI (P for linear regression with AFI continuous = 0.01) and age of SCC diagnosis (P for linear regression < 0.01). Therefore, we adjusted for year of birth in multivariate models.

Several other potential characteristics were considered for inclusion in the multivariate model with the aim of estimating the relationship between AFI and age at SCC diagnosis over and above any factors that may also be associated with earlier diagnosis of SCC. As there have been no studies that examine the risk factors for younger versus older age at SCC diagnosis, the factors considered included established risk factors for invasive SCC that might also be associated with early AFI. Risk factors for high-risk HPV infection and persistence were also examined, because risk of cervical carcinoma cannot be considered independent from them (21). Sexual history characteristics considered included lifetime number of sex partners (3) and serologic evidence of herpes simplex virus type 2 (15, 22) or *C. trachomatis* (11, 19, 23) infection. Reproductive history variables examined included age of first menses, combined oral contraceptive use (3, 24), and multiparity (15, 24, 25). Parity was considered both as number of full-term pregnancies and as a rate constructed as number of full-term pregnancies divided by the number of reproductive years to standardize the exposure. Screening history was examined as frequency of Pap in the most recent decade and interval since last screening Pap smear in months (described in ref. 26). Other behavioral and socioeconomic characteristics examined included cigarette smoking history (3, 15, 27), race (28), income level, years of education, and marital status (15). All characteristics were considered in the categories presented in Table 1.

The process of choosing characteristics to include in the multivariate model was done in steps. Each of the potential covariates was added sequentially to a model that included AFI, number of sex partners at age <20 years, and birth year. If, with the addition of the potential covariate to the model, any of the AFI coefficients changed by ≥10%, then the potential covariate was left in the model. Once those covariates were chosen, likelihood ratio tests were done to determine whether each characteristic could be modeled with fewer categories. Of those characteristics still in the model, if its removal did not change any of the levels of AFI's terms by at least 10%, then the characteristic was removed from the multivariate model.

Once the multivariate model was established, we explored stratification of AFI by number of partners at age <20 years, as discussed above, and also the association between AFI and age at diagnosis in among women with International Federation of Gynecology and Obstetrics stage Ia cancer. This restriction was done to explore the relationship in a potentially more homogenous group in terms of timely diagnosis and/or disease aggressiveness and the factors that are associated with these conditions. Stratification by stage and HPV type was not possible given the small number of cases of later stage cancer. The effect of stratifying AFI by number of partners at age <20 years was tested using likelihood ratio tests comparing a model with an interaction term of these two factors to one without.

Statistical significance by level of exposure, including P values and 95% confidence intervals (95% CI), was estimated by individual Wald tests, whereas significance of characteristics at any level, interactions, and sufficiency of modeling covariates with fewer categories were judged by likelihood ratio tests at a two-sided significance level of 5%. Two participants missing data on the AFI and number of sex partners at age <20 years were excluded from the analysis. The final multivariate model and the models to which it was compared included only those with information for every covariate incorporated. Covariates with missing data are detailed in Table 1. All statistical procedures were done using Intercooled Stata 9.0 for Windows.

Results

The distributions of many characteristics differed when comparing SCC cases who were ages 22 to 35 years at diagnosis (''younger cases'') with those who were ages 36 to 53 years (''older cases''; Table 1). Younger cases were more likely to be White, to have had less education, to have a lower annual income at diagnosis, to have ever smoked cigarettes, and to have never been married. They were also more likely to have had one Pap per year in the most recent decade and twice as likely to have had multiple Pap smears per year. Younger cases were more likely to have had an older age at first menses and to use combined oral contraceptives for >6 months, although less likely to have had more than one full pregnancy. Younger cases were less likely to have had only one sex partner in their lifetime. Of those cases with serologic test results, younger cases were less likely to have herpes simplex virus type 2 antibodies and slightly more likely to have positive antibody results for *C. trachomatis*. The percentage with anti-HPV-16 antibodies was similar for the younger cases (34%) and the older cases (36%), although there was a higher proportion of older cases that were HPV-18 positive with no evidence of HPV-16 antibodies.

Most younger and older cases were diagnosed at International Federation of Gynecology and Obstetrics stage I, with 57% and 42% diagnosed at stage Ia and Ib, respectively. Among those with HPV DNA results, most were HPV-16 or HPV-18 positive. The mean AFI of younger cases was ~1 year earlier than older cases and they were more likely to have a greater number of sex partners at age <20 years (Table 2). The number of years between AFI and age at SCC diagnosis ranged between 4 and 35 years.

The unadjusted coefficient for AFI measured continuously estimated that each 1-year change in AFI resulted

Table 1. Selected characteristics of SCC cases by age at diagnosis

Characteristics	Age 22-35 y (n = 165)	Age 36-53 y (n = 168)
	Frequency* (%)	Frequency (%)
Age (y)		
Mean (SD)	31.0 (3.2)	41.1 (4.0)
Median	32	40
Birth year		
1951-1959	73 (44)	120 (71)
1960-1967	92 (56)	48 (29)
Race		
White	152 (92)	143 (85)
Non-White	13 (8)	25 (15)
Education		
High school or less	74 (45)	62 (37)
More than high school	91 (55)	106 (63)
Income		
<$30,000/y	93 (57)	64 (39)
≥$30,000/y	71 (43)	100 (61)
Unknown	1	4
Marital status		
Never married	27 (16)	21 (13)
Ever married †	138 (84)	147 (88)
Cigarette smoking		
Never	49 (30)	74 (44)
Former	48 (29)	33 (20)
Current	68 (41)	61 (36)
Age at menses (y)		
<12	32 (19)	34 (20)
12-13	80 (48)	94 (56)
≥14	53 (32)	40 (24)
Combined oral contraceptive use		
Never to <6 mo	29 (18)	52 (31)
6 mo to <5 y	57 (35)	59 (35)
≥5 y	79 (48)	57 (34)
No. full-term pregnancies		
0	46 (28)	30 (18)
1	41 (25)	30 (18)
≥2	78 (47)	108 (64)
Full-term pregnancy rate		
None	18 (11)	15 (9)
<1 per 10 y	29 (18)	57 (34)
1 per 10 to <2 per 10 y	55 (34)	61 (37)
2 per ≥10 y	62 (38)	34 (20)
Pap frequency in most recent decade		
None	7 (4)	2 (1)
1-5 per decade	67 (41)	102 (63)
6-8 per decade	10 (6)	15 (9)
1/y	61 (37)	34 (21)
>1/y	19 (12)	10 (6)
Unknown	1	5
Lifetime no. sex partners		
1	5 (3)	11 (7)
2-4	46 (28)	52 (31)
5-14	74 (45)	69 (41)
≥15	40 (24)	35 (21)
Unknown	0	1
C. trachomatis serology ‡		
Negative	45 (52)	26 (58)
Positive	41 (48)	19 (42)
Test not done or unknown	79	123
Herpes simplex virus type 2 serology§		
Negative	79 (56)	34 (47)
Positive	61 (44)	39 (53)
Test not done or unknown	25	95
International Federation of Gynecology and Obstetrics stage		
I	151 (92)	131 (81)
II-IV	13 (8)	30 (19)
Unknown	1	7
HPV DNA results		
HPV negative	14 (11)	9 (9)
HPV-16 positive	88 (71)	60 (62)
HPV-18 positive	8 (6)	10 (10)
HPV-16 and HPV-18 positive	6 (5)	9 (9)
HPV positive for other types§	8 (6)	9 (9)
HPV positive, type unknown	3	0
Insufficient sample	8	3
Test not done or unknown	30	68
HPV-16/HPV-18 serology		
HPV-16 and HPV-18 negative	80 (56)	30 (42)
Only HPV-16 positive	29 (20)	14 (19)
Only HPV-18 positive	13 (9)	16 (22)
HPV-16 and HPV-18 positive	20 (14)	12 (17)
Test not done or unknown	23	96

*Unless otherwise indicated.

† Includes currently or formerly married or lived with a partner for >6 mo.

‡ *C. trachomatis*, herpes simplex virus type 2, HPV-16, and HPV-18 serology only available on cases enrolled before 1999, which excludes 94 cases (88 diagnosed at ages 36-53 y and 8 diagnosed at ages 22-36 y).

§ Includes HPV types 6, 31, 33, 45, 53, 58, and/or 73.

in a 0.6-year change in age at diagnosis (95% CI, 0.4-0.8; $P < 0.01$); the Spearman correlation between AFI and age at diagnosis was 0.26. The relationship among those with ≥2 sex partners at age <20 years (unadjusted coefficient, 0.5; 95% CI, 0.1-0.8; $P = 0.01$) was similar to those with 0 or 1 sex partner at age <20 years (unadjusted coefficient, 0.4; 95% CI, -0.1 to 0.8; $P = 0.13$), although the latter was not statistically significant. These results assume a linear relationship between AFI and age at SCC diagnosis, although the loess curve results suggested that the relationship may not be linear, particularly around the minimum and maximum AFI (Fig. 1).

In both univariate and multivariate models, an association was seen between age at SCC diagnosis and AFI in three categories (Table 3). In the univariate analysis, compared with SCC cases whose AFI was ages ≥19 years (reference group), the mean age of diagnosis was 3.5 years younger for an AFI between 15 and 18 and 5.8 years younger for an AFI <15. The AFI coefficients from the multivariate model were decreased but remained statistically significant, with the mean age of SCC diagnosis 2.6 years younger for an AFI between 15 and 18, compared with the reference group, and 3.1 years younger for an AFI <15. The multivariate model was adjusted for number of sex partners at age <20 years, birth year, age at first menses, and annual income at diagnosis. All other characteristics examined did not appreciably affect the AFI coefficients.

Although number of sex partners at age <20 years is significantly associated with age at SCC diagnosis in the univariate model, this relationship was not independent of AFI (Table 3). To address our *a priori* hypothesis that the relationship between AFI and age at SCC diagnosis might be modified by number of sex partners at age <20 years, we stratified AFI by a binary measure of number

Table 2. Early sexual experience characteristics of SCC cases by age at diagnosis

Characteristics	Age 22-35 y (n = 165)	Age 36-53 y (n = 168)
	Frequency* (%)	Frequency (%)
AFI (y)		
Mean (SD)	16.0 (2.7)	17.3 (2.7)
Median	16	17
≥19	16 (10)	52 (31)
15-18	118 (72)	96 (57)
<15	30 (18)	19 (11)
Unknown	1	1
Difference between AFI and age at SCC diagnosis (y)		
4-10	20 (12)	1 (1)
11-20	137 (83)	39 (23)
21-30	7 (4)	114 (68)
31-35	0 (0)	13 (8)
No. sex partners at age <20 y		
None	9 (5)	26 (15)
1	43 (26)	56 (33)
2-4	70 (42)	69 (41)
5-14	34 (21)	14 (8)
≥15	9 (5)	3 (2)

*Unless otherwise indicated.

partners at age <20 years (Table 4). In the multivariate analysis, number of partners at age <20 years appeared to affect the coefficients for AFI ≥19 and <15, although the number of participants in these categories was small. There was little difference between the coefficients for the two groups of AFI between 15 and 18. The interaction between AFI and number of partners at age <20 years was statistically significant in a model with no other covariates ($P_{interaction}$ = 0.02, likelihood ratio test) and of borderline statistical significance in the model adjusted for birth year, age at first menses, and annual income at diagnosis ($P_{interaction}$ = 0.08, likelihood ratio test).

In analyses restricted to stage Ia cases, the coefficients were similar to those presented in Tables 3 and 4.

Discussion

In this investigation of younger and middle-aged women with invasive SCC, sexual experience at younger ages was associated with younger age of diagnosis. The association between AFI and age at SCC diagnosis was independent of several sexual, reproductive, heath behavior, and demographic factors, including birth cohort. Although number of sex partners at age <20 years was associated with age at SCC diagnosis in the univariate analysis, this relationship was not independent AFI. However, it appeared that that the effect of AFI may be modified by number of partners at age <20 years, although the number of participants in some categories was small.

One of the main goals of this investigation was to help address questions regarding sojourn time between HPV infection and SCC diagnosis in young women. Our primary results suggest that young AFI, especially in combination with having multiple sex partners at age <20 years, contributes to an earlier age at SCC diagnosis. A young AFI could be a risk factor for younger SCC diagnosis simply because of the time needed for disease progression or, possibly, the adolescent cervix, compared with the adult cervix, is more susceptible to persistent high-risk HPV infection (29). The possible effect of number of sex partners at age <20 years suggests that factors that increase the probability of HPV infection at a young age also may increase the probability of young SCC diagnosis. Two other observations from this investigation may provide some clues about SCC sojourn time. One was the time interval between AFI and age at SCC diagnosis. For 21 cases, the interval was ≤10 years, with a minimum of 4 years, providing evidence for the previously described phenomenon of rapid onset cervical cancer (10, 11). The other observation of interest was that the youngest ages of AFI are not inevitably associated with the youngest ages of SCC diagnosis. These observations, and the low Spearman correlation between AFI and age at diagnosis, appear to indicate that young AFI is related to earlier diagnosis of SCC diagnosis, but not strongly.

To our knowledge, the relationship between AFI and age at SCC diagnosis has not been reported previously. Our ability to examine this question was aided by the fact that the original study from which data for this investigation were obtained had a wide range of ages at diagnosis of invasive SCC and a high number of younger cases. Another strength is the population-based design of the original study, with active recruitment of all cases of invasive SCC residing in the Puget Sound area. However, the case participation rate (63%) of the original study may have limited how representative these cases are compared with all SCC cases, especially if the association between AFI and age at diagnosis non-participants differed from participants (15). For example, if rapidly progressing young cases (with older AFI) or older cases with young AFI, who did not want to answer questions with regard to sexual history, were less likely to participate, then our results could be biased toward finding an association between younger AFI and earlier age at diagnosis.

The main limitation in interpretation of our results is that the timing of the HPV infection that led to an invasive lesion is unknown. Although AFI has been suggested as a crude method to estimate first HPV exposure (30), we acknowledge that estimation of sojourn time was not possible because infection may

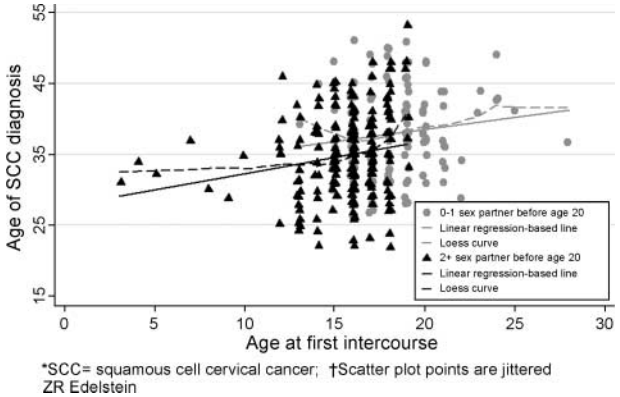

Figure 1. Age of squamous cell cervical carcinoma (SCC) by age at first intercourse by number of partners before age 20*. *Includes scatter plot with joints jittered, linear regression based lines (—) and loess curves (---). Grey indicates 0-1 partner before age 20 and black indicates 2+ partners before age 20.

Table 3. Linear regression coefficients, 95% CIs, and *P* values for association between age at SCC diagnosis and AFI and number of sex partners at age <20 y

Characteristics	*n*	Univariate model*	Adjusted for each other	Adjusted for each other and birth year	Multivariate model †
		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
AFI (y)					
≥19	66	Reference	Reference	Reference	Reference
15-18	121	-3.5 (-5.2 to -1.9)	-3.0 (-5.3 to -0.7)	-3.1 (-5.0 to -1.1)	-2.6 (-4.6 to -0.6)
<15	48	-5.8 (-8.0 to -3.5)	-4.0 (-7.0 to -1.0)	-4.1 (-6.7 to -1.4)	-3.1 (-5.8 to -0.5)
No. sex partners at age <20 y					
None	32	Reference	Reference	Reference	Reference
1	98	-1.1 (-3.5 to 1.3)	1.1 (-1.8 to 3.9)	1.2 (-1.3 to 3.7)	0.6 (-1.9 to 3.1)
2-4	136	-3.0 (-5.3 to -0.7)	0.01 (-3.2 to 3.2)	1.0 (-1.8 to 3.7)	0.6 (-2.2 to 3.3)
5-14	48	-5.6 (-8.3 to -2.9)	-2.2 (-5.8 to 1.3)	-0.1 (-3.2 to 3.1)	-0.5 (-3.6 to 2.6)
≥15	12	-7.2 (-11.2 to -3.2)	-3.4 (-8.2 to 1.5)	-0.6 (-4.8 to 3.6)	-1.0 (-5.2 to 3.2)

*All models presented include only cases with information on all characteristics included in the multivariate model.
† Adjusted for each other birth year, age at first menses (age <14/≥14 y), and annual income at diagnosis (<$30,000/≥$30,000).

have occurred later. Other limitations of this investigation and its interpretation are mainly consequences of its retrospective study design, although given the current state of medical treatment for cervical preneoplasia a prospective study would not have been possible. Although differential recall based on case-control status is not an issue in this analysis, it is possible that younger cases remembered sexual activity events from adolescence more clearly because they were more recently experienced. If the difference between younger and older SCC cases was systematic, in this regard, the effect on our results would depend on whether the older cases estimated their AFI as younger or older than their actual AFI, and if it was the latter, then our results would be biased toward an association. It is also possible that answers to questions about AFI and number of sex partners could have been influenced by the social undesirability for reporting young sexual experience, especially experience related to abuse. Misreporting of AFI and especially failing to report very early sexual experience could influence our results if it was also related to age at SCC diagnosis. Additionally, although we consider the ability to adjust for birth year a strength, the inclusion of birth year in the model necessitated limiting our analysis to women ages 22 to 53 years.

Taking these limitations into account, our results regarding the relationship between AFI and age at invasive SCC diagnosis appear to support the recommendations for HPV vaccination during early adolescence or younger. The Advisory Committee on Immunization Practices at the Centers for Disease Control and Prevention recommends the routine HPV vaccination for girls ages 11 to 12 years, although it can be administered as young as 9 years (31). According to the most recent estimates from the Centers for Disease Control and Prevention, 3.7% of girls in the United States have had sex at age <13 years and 13% at age <15 years (32, 33). Girls with young AFI are at higher risk for invasive SCC (15-17), and as our results indicate, among SCC cases, they may also be at higher risk for a younger age of diagnosis. Although cases of young SCC are rare (6), its effect on fertility in young women (7, 8) may influence those parents, clinicians, and policy-makers who have been resistant to vaccinating pre-teen girls (34-36).

Another clinical implication of the association found between AFI and age at SCC diagnosis, as well as the minimum time interval between the two (4 years), is that they support current recommendations for initiation of Pap smears no earlier than age 21 years or 3 years following AFI (37). Lastly, although changes in screening practices have certainly been the main driver of the declining age of invasive SCC diagnosis over the last 50 years in the United States (6), this investigation suggests that the increasingly higher percentages of women having sex in their teens during the 1970s and 1980s (20, 38), combined with higher numbers of sex partners, could have also contributed to the lack of a decline in the incidence in early-onset SCC.

Table 4. Linear regression coefficients, 95% CIs, and *P* values for association between age at SCC diagnosis and the combination of AFI and number of sex partners at age <20 y

Characteristics		*n*	Univariate model*		Multivariate model †	
AFI	No. sex partners at age <20 y		Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
≥19	0-1	60	Reference		Reference	
≥19	≥2	6	4.2 (-0.8 to 9.1)	0.10	2.2 (-2.1 to 6.4)	0.32
15-18	1	68	-1.9 (-3.9 to 0.2)	0.08	-2.3 (-4.1 to -0.6)	0.01
15-18	≥2	144	-3.7 (-5.5 to -2.0)	<0.01	-2.5 (-4.0 to -0.9)	<0.01
<15	1	2	3.2 (-5.2 to 11.5)	0.46	3.2 (-4.1 to 10.4)	0.39
<15	≥2	46	-5.8 (-8.1 to -3.5)	<0.01	-4.2 (-6.3 to -2.1)	<0.01

*Univariate model includes only cases with information on all characteristics included in the multivariate model.
† Adjusted for each other birth year, age at first menses (age <14/≥14 y), and annual income at diagnosis (<$30,000/≥$30,000).

In summary, our results suggest that, among younger and middle-aged women with invasive SCC, there is a positive relationship between AFI and age at diagnosis. Although AFI is probably one of many factors that determine the age at invasive SCC diagnosis, this association should be considered in the refinement and implementation of recommendations for age at HPV vaccination and age at Pap screening initiation.

Disclosure of Potential Conflicts of Interest

D.A. Galloway: Merck & Co., honoraria from speakers' bureau, Merck & Co., consultant/advisory board; L.A. Koutsky: Merck & Co., commercial research grant.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The authors would like to express great appreciation to the study participants, without whom this investigation would not be possible, and to the study staff who were responsible for collecting the data.

References

1. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006;24 Suppl 3:S11–25.
2. Yang BH, Bray FI, Parkin DM, Sellors JW, Zhang ZF. Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. Int J Cancer 2004;109:418–24.
3. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: updating the natural history of HPV and anogenital cancer. Vaccine 2006;24:S42–51.
4. Pinto AP, Crum CP. Natural history of cervical neoplasia: defining progression and its consequence. Clin Obstet Gynecol 2000;43:352–62.
5. Schiffman M, Kjaer SK. Chapter 2: natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 2003;31:14–9.
6. Wang SS, Sherman ME, Hildesheim A, Lacey JV, Jr., Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among White women and Black women in the United States for 1976-2000. Cancer 2004;100:1035–44.
7. Maltaris T, Seufert R, Fischl F, et al. The effect of cancer treatment on female fertility and strategies for preserving fertility. Eur J Obstet Gynecol Reprod Biol 2007;130:148–55.
8. Seli E, Tangir J. Fertility preservation options for female patients with malignancies. Curr Opin Obstet Gynecol 2005;17:299–308.
9. Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis 2005;191:731–8.
10. Hildesheim A, Hadjimichael O, Schwartz PE, et al. Risk factors for rapid-onset cervical cancer. Am J Obstet Gynecol 1999;180:571–7.
11. Bain RW, Crocker DW. Rapid onset of cervical cancer in an upper socioeconomic group. Am J Obstet Gynecol 1983;146:366–71.
12. Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health 1995;85:791–4.
13. Kahn JA, Rosenthal SL, Succop PA, Ho GY, Burk RD. Mediators of the association between age of first sexual intercourse and subsequent human papillomavirus infection. Pediatrics 2002;109:E5.
14. Burchell AN, Winer RL, de SS, Franco EL. Chapter 6: epidemiology and transmission dynamics of genital HPV infection. Vaccine 2006; 24:S52–61.
15. Daling JR, Madeleine MM, McKnight B, et al. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. Cancer Epidemiol Biomarkers Prev 1996;5:541–8.
16. Berrington de GA, Sweetland S, Green J. Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis. Br J Cancer 2004;90:1787–91.
17. Brinton LA, Herrero R, Reeves WC, de Britton RC, Gaitan E, Tenorio F. Risk factors for cervical cancer by histology. Gynecol Oncol 1993; 51:301–6.
18. Carter JJ, Madeleine MM, Shera K, et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. Cancer Res 2001;61:1934–40.
19. Madeleine MM, Anttila T, Schwartz SM, et al. Risk of cervical cancer associated with *Chlamydia trachomatis* antibodies by histology, HPV type and HPV cofactors. Int J Cancer 2007;120:650–5.
20. Aral SO, Holmes KK. Social and behavioral determinants of epidemiology of STDs: industrialized and developing countries. In: Holmes KK, Mardh P-A, Sparling PF, et al. editors. Sexually transmitted diseases. 4th ed. New York (NY): McGraw-Hill; 1999. p. 36–76.
21. Wacholder S. Chapter 18: statistical issues in the design and analysis of studies of human papillomavirus and cervical neoplasia. J Natl Cancer Inst Monogr 2003;31:125–30.
22. Smith JS, Herrero R, Bosetti C, et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J Natl Cancer Inst 2002;94:1604–13.
23. Smith JS, Bosetti C, Munoz N, Herrero R, Bosch FX, Eluf-Neto J, et al. *Chlamydia trachomatis* and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. Int J Cancer 2004;111: 431–9.
24. Castellsague X, Munoz N. Chapter 3: cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 2003;31:20–8.
25. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. Int J Cancer 2006;119:1108–24.
26. Madeleine MM, Daling JR, Schwartz SM, et al. Human papillomavirus and long-term oral contraceptive use increase the risk of adenocarcinoma *in situ* of the cervix. Cancer Epidemiol Biomarkers Prev 2001;10:171–7.
27. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006;118:1481–95.
28. Xi LF, Kiviat NB, Hildesheim A, et al. Human papillomavirus type 16 and 18 variants: race-related distribution and persistence. J Natl Cancer Inst 2006;98:1045–52.
29. Kahn JA, Rosenthal SL, Succop PA, Ho GY, Burk RD. The interval between menarche and age of first sexual intercourse as a risk factor for subsequent HPV infection in adolescent and young adult women. J Pediatr 2002;141:718–23.
30. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007;370: 890–907.
31. Centers for Disease Control and Prevention. HPV and HPV vaccine—information for healthcare providers. Centers for Disease Control and Prevention; 2007 [cited 2007 Jun 28]. Available from: URL: http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-hcp.htm.
32. Centers for Disease Control and Prevention. 2005 Youth risk behavior survey. Centers for Disease Control and Prevention; 2007 Jun 6 [cited 2007 Jun 30]. Available from: www.cdc.gov/yrbss.
33. Dailard C. Legislating against arousal: the growing divide between federal policy and teenage sexual behavior. Guttamacher Policy Rev 2006;9:12–6.
34. Charo RA. Politics, parents, and prophylaxis—mandating HPV vaccination in the United States. N Engl J Med 2007;356:1905–8.
35. Kahn JA, Zimet GD, Bernstein DI, et al. Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health 2005;37: 502–10.
36. Marlow LA, Waller J, Wardle J. Parental attitudes to pre-pubertal HPV vaccination. Vaccine 2007;25:1945–52.
37. Cervical cancer. NIH consensus statement. 1996;14:1–38.
38. Centers for Disease Control and Prevention. Current trends premarital sexual experience among adolescent women—United States, 1970-1988. MMWR 1991;39:929–32.

Age of Diagnosis of Squamous Cell Cervical Carcinoma and Early Sexual Experience

Zoe R. Edelstein, Margaret M. Madeleine, James P. Hughes, et al.

Cancer Epidemiol Biomarkers Prev 2009;18:1070-1076.