

Use of Hormone Replacement Therapy and Adenocarcinomas and Squamous Cell Carcinomas of the Uterine Cervix

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Introduction. Exogenous hormones may influence the development of cervical adenocarcinomas. Incidence rates of adenocarcinomas and use of noncontraceptive hormones have increased since the 1970s, but few studies have investigated this potential relationship.

Methods. We conducted a multicenter case-control study of 124 women with adenocarcinomas, 139 women with squamous cell carcinomas matched on age, diagnosis date, clinic, and stage of disease (*in situ* or invasive) to adenocarcinoma cases, and 307 healthy community controls who were also matched on age, ethnicity, and residence to adenocarcinoma cases. Participants completed in-person interviews regarding exogenous hormone use before diagnosis and other risk factors and volunteered cervical samples for human papillomavirus (HPV) testing via a PCR-based method. Odds ratios (ORs) with 95% confidence intervals (CIs) estimated relative risks.

Results. Only 13 adenocarcinoma cases (10.5%), 7 squamous carcinoma cases (5%), and 20 controls (6.5%) had used noncontraceptive hormones for menopausal symptoms, irregular periods, or disease prevention; most use was short-term, former use. Ever-use was associated with adenocarcinomas (OR = 2.1, 95% CI 0.95–4.6) but not squamous carcinomas (OR = 0.85, 95% CI 0.34–2.1). No trends were seen with duration of use or ages at first use, but unopposed estrogens were positively associated with adenocarcinomas (OR = 2.7). Unopposed estrogens remained associated with adenocarcinomas (OR = 2.0) when analyses were restricted to the HPV-positive controls. Menopausal status was not associated with adenocarcinomas or squamous carcinomas and did not modify the other associations.

Conclusion. Although small numbers warrant tentative conclusions, exogenous estrogens, especially unopposed estrogens, were positively associated with adenocarcinomas. Noncontraceptive hormones were negatively but weakly associated with squamous carcinomas. © 2000 Academic Press

Key Words: cervical carcinomas; hormone replacement therapy; human papillomavirus; HPV; cervical adenocarcinomas.

INTRODUCTION

The extent to which nonviral factors interact with human papillomaviruses (HPV) in cervical carcinogenesis remains unclear [1]. The presence of estrogen and progesterone receptors in the cervix [2] and in HPV-related cervical lesions [3] suggests that the cervical epithelium may respond to exogenous hormones and that these hormones might contribute to the development of carcinomas of the uterine cervix. Adenocarcinomas of the uterine cervix constitute approximately 15% of all cervical carcinomas [4] and appear to share some risk factors with adenocarcinomas of the endometrium [5], which are strongly associated with use of exogenous hormones [6]. Increasing relative and absolute incidence rates of adenocarcinomas since the 1970s [7] coincide with increasing utilization of exogenous hormones [8]. Few studies have considered risk of cervical carcinomas among users of noncontraceptive hormones [9, 10]. We thus explored this issue in a case-control study of adenocarcinomas and squamous cell carcinomas of the uterine cervix.

MATERIALS AND METHODS

Study Population

This study was designed to evaluate risk factors for adenocarcinomas and to assess whether the risk factors for adenocarcinomas are similar to the risk factors for squamous carcinomas. We briefly summarize the study methods, which are described elsewhere [11]. The study received institutional review board clearance at the National Cancer Institute and at each participating clinical center. Women between the ages of 18 and 69 who were newly diagnosed with *in situ* or invasive primary adenocarcinoma of the uterine cervix, adenosquamous carcinoma, or other rare histological types of cervical carcinoma with glandular involvement at one of six U.S. medical

centers between 1992 and 1996 were eligible. We retrospectively identified women diagnosed between January 1992 and June 1994 (the date the study began) and prospectively recruited women diagnosed between July 1994 and March 1996. A panel of three pathologists performed a simultaneous microscopic review of adenocarcinoma cases and provided the study diagnoses.

A sample of women diagnosed with squamous carcinomas was included in this study to address potential referral bias and to evaluate whether risk factors differ according to tumor histology. Using the same eligibility criteria, squamous carcinoma cases were individually matched to adenocarcinoma cases on clinic, age at diagnosis (± 5 years), diagnosis date, and stage of disease at diagnosis (*in situ* vs invasive). Using random-digit dialing, we generated a random sample of telephone numbers within the telephone exchange of each adenocarcinoma case, enumerated all adult women in households at those numbers, excluded women who reported a hysterectomy, and individually matched a healthy population control group to adenocarcinoma cases at a 2:1 ratio on age (5 years), race, and geographic region (i.e., telephone exchange).

Interviews

Participants completed personal risk factor interviews with trained staff. To minimize the potential effect of disease onset or diagnosis on exposures and to exclude recent cervical cytologic screening (Pap smears) that led to their diagnosis, adenocarcinoma and squamous carcinoma cases reported only exposures that occurred before a reference date, which was 12 months before their date of diagnosis. Controls were assigned the reference date of their index adenocarcinoma case. Participants reported their usual adult weight and current height.

HPV DNA Testing

With consent, we collected both self-administered and clinician-administered samples of cervicovaginal cells from cases and controls. Self-administered specimens were collected with Dacron swabs and stored in 1-ml specimen transport medium (STM; Digene Corp., Silver Spring, MD). Clinician-administered samples were collected during pelvic examinations using two Dacron swabs, each stored in 1 ml STM. For population controls, cases who were sampled before treatment, and cases whose treatment did not include removal of the entire cervix, clinicians collected one specimen from the ectocervix and one sample from the endocervix. For cases sampled after surgical treatment who no longer had an intact cervix, clinicians obtained both Dacron swab specimens from the vaginal cuff. Frozen specimens were regularly shipped to the National Cancer Institute for storage and analysis. Controls visited the clinic from which their index adenocarcinoma case was recruited for data collection, but all participants had the option of an in-home interview and sample collection. Home visits included self-administered samples only. A PCR-based reverse line blot

detection method [12] that uses the MY09/11 L1 consensus primer system to individually discriminate 27 HPV genotypes determined HPV status, which was grouped according to type [11] after confirming HPV 16 status with a second set of primers [13].

Exposure Assessment

Women reported their menstrual status at the interview and the date of last menstrual period, which were used to determine menopausal status at the reference date and age at menopause. Respondents indicated whether they ever took noncontraceptive hormones before the reference date for relief of menopausal symptoms, regulation of irregular menstrual periods, or prevention of diseases such as bone loss. We asked about pills, shots, creams or suppositories, and patches and obtained dates of use for each. Aided by a photo book, pill users reported pill names and doses. Current use, duration of use, age at first use, time since first use, and time since last use were calculated relative to the reference date, i.e., at least 1 year before diagnosis in cases or interview in controls. We excluded two adenocarcinoma cases for whom we could not determine whether exposure preceded the reference date. Duration of use was unknown for one adenocarcinoma case.

Two hundred three women with adenocarcinomas were identified, but 27 chose not to participate, 2 were too ill to participate, 11 could not be located, 7 died before they could be enrolled, and 10 could not be enrolled for other reasons. Four of the 146 eligible cases could not be interviewed, while 18 cases diagnosed with cervical carcinomas that were not adenocarcinomas were excluded from this analysis. Cervical samples were available from 116 of the 124 final adenocarcinoma cases. Two hundred fifty-five women with squamous carcinomas were identified, but 38 chose not to participate, 3 were too ill, 29 could not be located, 25 had died, 12 could not be enrolled for other reasons, and 2 did not speak English. Of these 146 remaining eligible cases, 139 completed the interview and 129 contributed a cervical sample. Four hundred seventy controls were identified, but 126 chose not to participate, 1 was too ill, 15 could not be located, and 21 could not be enrolled for other reasons. All of these 307 eligible controls completed the interview and 255 contributed a cervical sample. The final analytic group included 124 adenocarcinomas (33 *in situ* and 91 invasive), 139 squamous carcinomas (48 *in situ* and 91 invasive), and 307 community controls.

Statistical Analysis

We used unconditional logistic regression in favor of conditional logistic regression to avoid loss of cases without a matched control and since controls were individually matched to adenocarcinoma cases but not to squamous carcinoma cases [14]. Odds ratios (ORs) with 95% confidence intervals (CIs) estimated the relative risk (RR) of adenocarcinomas or squamous carcinomas associated with use of noncontraceptive hor-

mones. We examined multiple combinations of confounding and modifying variables, but no single confounder or combination of confounders dramatically altered the estimates compared to the models that were adjusted for age and race only; parsimonious models are presented. Clinic, a matching variable, was dropped from final models since it did not influence the associations. The SAS system [15] computed all analyses.

RESULTS

Compared to controls, adenocarcinoma and squamous carcinoma cases reported lower incomes, more sexual partners, and fewer recent Pap smears. Adenocarcinoma cases were more likely and squamous carcinoma cases less likely to be Caucasian-American, and smoking was more common among squamous carcinoma cases (Table 1). Hormone use before the reference date was reported by 13 adenocarcinoma cases (10.5%), 7 squamous carcinoma cases (5%), and 20 controls (6.5%) and was associated with increased education, higher income, higher body mass index (kg/m^2), an earlier menarche, long-term (>20 years) smoking, annual and recent Pap smears, fewer recent sexual partners, later ages at last pregnancy, and HPV positivity, but not with prior use of oral contraceptives (data not shown). Collection of cervical samples preceded treatment for 31% of adenocarcinoma cases and 42% of squamous carcinoma cases. Eighty-two percent of adenocarcinoma and 73% of squamous carcinoma samples collected before treatment contained HPV DNA, whereas 38 and 42%, respectively, of those collected after treatment contained HPV; 19% of the control samples contained HPV DNA. Adenocarcinomas were significantly associated with HPV types 18 and 16 (age- and ethnicity-adjusted OR for all cases vs controls: OR = 11.7 and 5.6, respectively; cases sampled before treatment: OR = 104.1 and 43.2, respectively). Squamous carcinomas were more strongly associated with HPV type 16 than type 18 (all cases: OR = 10.0 and 5.2, respectively; cases sampled before treatment: OR = 38.0 and 2.3, respectively).

Few participants were postmenopausal at the reference date, but most of those who were had experienced natural menopause. A few women were no longer having menstrual periods because of other medical reasons (e.g., ovarian failure or use of other medications). Age at menopause was slightly but not significantly different in cases compared to controls. Postmenopausal status was not significantly associated with adenocarcinomas (OR = 1.9, 95% CI 0.6–6.0) or squamous carcinomas (OR = 1.6, 95% CI 0.55–4.4). Restriction to women between the ages of 45 and 55 to account for the strong correlation between age and menopausal status among younger or older women slightly diminished that OR for adenocarcinomas (OR = 0.91, 95% CI 0.23–3.5) and squamous carcinomas (OR = 1.0, 95% CI 0.32–3.2).

Ever-use of estrogen pills (OR = 2.1), use for less than 3 months (OR = 3.5), at least 2 years since last use (OR = 3.4), and unopposed estrogen use (OR = 2.7) were positively asso-

TABLE 1
Percentage Distribution of Demographic and Other Factors for 124 Women with Cervical Adenocarcinomas (AC), 139 with Squamous Cell Carcinomas (SCC), and 307 Controls

	AC	SCC	Controls
Age at reference date			
<30 years	21.8	20.4	21.8
30–39 years	31.5	37.4	34.9
40–49 years	32.3	26.6	27.4
50–59 years	4.8	7.2	11.7
≥60 years	9.7	8.6	4.6
Ethnicity			
Caucasian-American	90.3	80.6	86.5
Non-Caucasian-American	9.7	19.4	13.5
Education			
High school graduate or less	36.1	57.6	34.6
Beyond high school	62.9	42.3	65.4
Household income			
<\$30,000	35.0	48.6	27.4
≥\$30,000–\$50,000	65.0	51.4	72.6
Number of sexual partners in lifetime			
0–1	20.5	13.8	33.8
2–3	17.2	21.1	25.3
4 or more	62.3	65.2	41.0
Body mass index (kg/m^2)			
<22	21.8	27.0	28.5
22–23	19.4	21.2	23.8
24–26	21.8	18.3	17.8
≥27	37.1	33.6	29.9
Number of Pap smears in past 10 years ^a			
Less than 10	42.3	58.4	51.0
10 or more	57.7	41.6	49.0
Months since most recent Pap smear ^a			
12–23	51.6	47.5	65.2
24 or more	41.1	46.0	27.0
Unknown	7.3	6.5	7.8
Premenopausal ^b	83.7	83.9	86.2
Natural menopause	9.8	12.4	12.8
Surgical menopause	4.1	3.7	0.0
Other medical reasons	2.4	0.0	1.0
Mean age at natural menopause (years)	46.8	46.4	48.7

^a Relative to reference date.

^b Menopausal status was unknown for 1 adenocarcinoma case, 2 squamous carcinoma cases, and 3 controls.

ciated with adenocarcinomas (Table 2). Adjustment for HPV (types 16 or 18 vs all other types or HPV-negative), Pap smear frequency (annual over the past 10 years vs less than annual), number of lifetime sexual partners (<4 vs ≥4), income (<\$30,000 vs ≥\$30,000), and menopausal status only slightly decreased these associations (ever-use, OR = 1.8; <3 months of use, OR = 2.8; ≥2 years since last use, OR = 2.9; unopposed estrogens, OR = 2.1). Estrogen use was not associated with squamous carcinomas, and full adjustment had minimal impact on squamous carcinoma associations. Odds ratios for more than 12 months of use and recent last use were below 1.0 but were each based on only one exposed squamous carcinoma

TABLE 2
Frequencies and Odds Ratios (ORs) with 95% Confidence Intervals (CIs) for Exogenous Estrogen (E) Use among Controls, Adenocarcinoma Cases (AC), and Squamous Cell Carcinoma Cases (SCC)

	Controls N	AC		SCC	
		N	OR ^a (95% CI)	N	OR ^a (95% CI)
Never used E	287	109	1.0 ^b	132	1.0 ^b
Used E	20	13	2.1 (0.95–4.6)	7	0.85 (0.34–2.1)
Duration of use					
<3 months	5	6	3.5 (1.0–12.2)	4	2.0 (0.53–7.7)
3–12 months	5	2	1.3 (0.22–7.1)	2	0.80 (0.15–4.4)
>12 months	10	5	1.7 (0.52–5.6)	1	0.25 (0.03–2.0)
Age at first use					
≤40	8	7	2.4 (0.57–9.9)	4	0.79 (0.15–4.2)
>40	12	6	0.7 (0.06–8.0)	3	0.60 (0.06–6.0)
Years since last use					
<2	13	4	1.2 (0.34–3.9)	1	0.19 (0.02–1.5)
≥2	7	9	3.4 (1.2–9.5)	6	1.9 (0.62–5.9)
Unopposed E	10	10	2.7 (1.1–6.8)	4	0.86 (0.26–2.8)
E plus progestins	10	3	1.1 (0.26–5.0)	3	0.85 (0.21–3.4)
Analyses restricted to HPV-positive controls					
	N	N	OR ^a (95% CI)	N	OR ^a (95% CI)
Never used E	44	109	1.0 ^b	132	1.0 ^b
Used E	5	13	1.1 (0.31–3.9)	7	0.49 (0.13–1.9)
Duration of use					
<3 months	2	6	1.4 (0.23–8.4)	4	0.80 (0.13–5.1)
≥3 months	3	7	0.90 (0.17–4.7)	3	0.28 (0.04–1.9)
Age at first use					
≤40	1	7	3.4 (0.39–30.1)	4	1.5 (0.15–15.5)
>40	4	6	0.39 (0.07–2.2)	3	0.22 (0.04–1.3)
Years since last use					
<2	4	4	0.45 (0.08–2.6)	1	0.05 (0.01–0.71)
≥2	1	9	3.0 (0.34–26.8)	6	2.3 (0.25–21.1)
Unopposed E	2	10	2.0 (0.39–10.7)	4	0.80 (0.13–5.1)
E plus progestins	3	3	0.29 (0.03–2.5)	3	0.28 (0.04–1.9)

^a Adjusted for age (<30, 40–49, 50–59, ≥60) and ethnicity (non-Caucasian-American vs Caucasian-American).

^b Reference group for the column.

case. Only one adenocarcinoma case and one squamous carcinoma case were current users, i.e., using hormones at the reference date. Restriction to postmenopausal cases and controls did not change the estrogen results for either adenocarcinomas or squamous carcinomas.

Recognizing that small numbers make interactions difficult to evaluate, we addressed the potential interaction between BMI and hormones through stratification. Hormones and adenocarcinomas were not associated among thinner women (BMI < 24 kg/m²; OR = 1.4, 95% CI 0.29–6.3) but were among heavier women (BMI ≥ 24 kg/m²; OR = 2.2, 95% CI 0.84–5.6). There were opposite associations for squamous carcinomas (OR = 2.0, 95% CI 0.57–7.0 among thinner women; OR = 0.31, 95% CI 0.06–1.5 among heavier women).

An appropriate analytic approach for addressing the effects

of HPV on other risk factors is to assume that all cases were HPV-infected and exclude HPV-negative controls, since non-infected women should be considered not at risk for cervical carcinomas. Restricting the analyses to HPV-positive controls showed that ever-use of hormones was not associated with adenocarcinomas (OR = 1.1, 95% CI 0.31–3.9) or squamous carcinomas (OR = 0.49, 95% CI 0.13–1.9; Table 2). Unopposed estrogens remained positively associated with adenocarcinomas (OR = 2.0, 95% CI 0.39–10.7).

We stratified the case groups according to stage of disease at diagnosis (carcinoma *in situ* vs invasive carcinoma). Only one of the exposed adenocarcinoma cases was diagnosed with adenocarcinoma *in situ*, and the results for the 12 invasive adenocarcinoma cases were similar to those for all cases (ever-use, OR = 2.4, 95% CI 1.1–5.4). Three of the exposed squa-

mous carcinoma cases were diagnosed with carcinoma *in situ* (ever-use, OR = 1.5, 95% CI 0.39–5.5) while four were diagnosed with invasive carcinomas (ever-use, OR = 0.65, 95% CI 0.21–2.0).

DISCUSSION

These results demonstrate some positive associations between adenocarcinomas and noncontraceptive hormones. Menopause itself appears to have minimal influence on risk of cervical adenocarcinoma, since few of the women diagnosed with adenocarcinomas in this study were postmenopausal at diagnosis. Adenocarcinomas have been increasing in incidence, especially in younger women [4], and the mean age at diagnosis of adenocarcinoma in this study was 40.

This analysis allowed us to evaluate the hypothesis [5] that cervical adenocarcinomas resemble endometrial carcinomas, which are diagnosed almost exclusively in postmenopausal women and result from estrogen excess [16]. The age distribution of these adenocarcinoma cases, their menopausal status, and the low prevalence and characteristics of estrogen use do not support that hypothesis. However, the positive association for unopposed estrogen use and null association for combined estrogen–progestin regimens indicate a potential similarity between endometrial carcinoma and cervical adenocarcinomas. We reasoned that hormones might be especially associated with the endometrioid histologic type of adenocarcinomas, but only 2 of the 13 exposed adenocarcinoma cases were diagnosed as such.

There is biologic plausibility for an association between noncontraceptive hormones and cervical carcinomas. *In vitro* systems demonstrate HPV viral oncogene activation in the presence of steroid hormones [17–19], and *in vivo* data offer evidence that HPV-related cervical lesions contain estrogen and progesterone receptors [3]. Their role in cervical adenocarcinomas, however, is unclear [20, 21].

Few data exist on noncontraceptive hormones and risk of cervical carcinomas. A case–control study of 645 women with invasive cervical carcinomas (57% squamous cell carcinomas, 18% adenocarcinomas, 25% undefined) and 749 hospital-based controls noted a significantly decreased risk of all cervical cancers combined among hormone replacement therapy (HRT) users; histology-specific associations were not presented [9]. Longer use and 10 or more years since last use were associated with the greatest reductions even after adjustment for confounding by screening, but HPV data were not available. A Swedish cohort study observed fewer than expected invasive cervical carcinomas among HRT users, but the study design did not allow for assessment of confounding or address potential differences in adenocarcinomas vs squamous carcinomas [10]. Our negative associations with squamous carcinomas agree with these studies.

A major limitation of this study was the small numbers that limited our ability to assess detailed associations with exposure

and to remove confounding by HPV, Pap smears, or other factors. The analyses restricted to the HPV-positive controls in theory provide the most valid risk estimates, but also encountered the problem of small numbers of exposed women. The nature of most hormone use in this population—one-time or short-term use before menopause—suggests that constellations of gynecologic symptoms or medical concerns that prompt hormone use, rather than the use itself, may be associated with adenocarcinomas. We did not ascertain individual reasons for each exposure and were therefore unable to address this possibility.

Our panel of three pathologists reviewed histologic slides from potential cases to reduce misclassification [22] of the diagnosis of adenocarcinoma, a rare and clinically heterogeneous tumor [23]. Selection of controls from the same geographic region should have decreased referral bias, but selection bias was possible if the 21% of eligible adenocarcinoma cases, 26% of squamous carcinoma cases, and 27% of controls who had died, were in poor health, or chose not to participate differed from participants on menopausal status or use of noncontraceptive hormones. The squamous carcinoma cases were included in this study to allow a comparison of the distribution of cervical cancer risk factors in adenocarcinoma cases and squamous carcinoma cases, and absence of positive associations in squamous carcinoma cases suggests, but does not guarantee, that information bias due to study design or collection of exposure information likely does not account for the associations with adenocarcinomas.

In conclusion, we observed opposite associations for squamous carcinomas and adenocarcinomas. Negative associations for squamous carcinomas are consistent with the two published studies on this topic. Adenocarcinomas are increasingly diagnosed at younger ages and in premenopausal women and, therefore, relative risks of 2.0 associated with noncontraceptive hormones would generate a low attributable fraction. Nonetheless, these results are somewhat consistent with the theory that adenocarcinomas may resemble endometrial carcinomas. Irregular bleeding usually implies endometrial carcinoma, but our results suggest that clinicians who examine women who use unopposed estrogens and experience irregular bleeding should consider a complete evaluation of both the endometrium and the endocervix.

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