Etiologic Heterogeneity for Cervical Carcinoma by Histopathologic Type, Using Comparative Age-Period-Cohort Models

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Abstract

Background: **Cervical carcinomas comprise two main histopathologic types, squamous cell carcinomas and adenocarcinomas. Human papillomavirus (HPV) infections are causative for both types but the respective tumors may have different carcinogenic pathways.**
Methods: **To assess potential etiologic heterogeneity of cervical cancer by histopathologic type, we examined invasive squamous cell carcinomas and adenocarcinoma cervical cancer incidence rates in the National Cancer Institute's Surveillance, Epidemiology, and End Results database. We complemented standard descriptive epidemiology with comparative age-period-cohort (APC) models fitted to each histopathologic type.**
Results: **Squamous cell tumors (n = 25,219) were nearly 5-fold more common than adenocarcinomas (n = 5,451). Age-adjusted incidence trends decreased for squamous cell carcinomas but increased for adenocarcinomas. Cross-sectional age-specific incidence rates increased more rapidly for squamous cell carcinomas than adenocarcinomas in adolescents and young adults then leveled off for both types. APC models confirmed that secular trends and age-specific rates differed for the two types (P = 0 for the null hypothesis of no difference). For squamous cell carcinoma, the APC "fitted" age-at-onset rate curve peaked before age 40 years then declined; for adenocarcinoma, the fitted curve increased rapidly until age 40 years then rose more slowly.**
Conclusions: **Despite the necessary role of HPV infection in both squamous cell carcinomas and adenocarcinomas of the cervix, secular trends and age-related natural histories differed for the two tumor types, consistent with etiologic heterogeneity. Future analytic and clinical studies should consider the interaction (effect modification) of HPV infection and other cervical carcinoma risk factors by histopathologic type, time, and age.** (Cancer Epidemiol Biomarkers Prev 2009;18(3):792–800)

Introduction

Carcinomas of the uterine cervix fall in two major histopathologic types, squamous cell carcinoma and adenocarcinoma (glandular), accounting for ~99% of cervical carcinomas. Although the human papillomavirus (HPV) is causative for both, epidemiologic studies suggest that these two histopathologic types may differ by risk factor profiles (1-5), patterns of detection by screening (6, 7), incidence rate trends (8-10), clinical characteristics (11), and outcomes (12-14). Therefore, to evaluate further potential etiologic differences by histopathologic type, we systematically examined incidence rate patterns for invasive squamous cell carcinomas and adenocarcinomas in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

We complemented standard descriptive epidemiology with age-period-cohort (APC) models, which simultaneously adjusted incidence rates for age at diagnosis, year of diagnosis (calendar period), and year of birth (birth cohort). In brief, divergent age-specific effects for squamous cell carcinomas and adenocarcinomas would suggest that age-associated carcinogenic events and/or exposures differ by the two tumor types. Differential calendar period effects would imply different patterns of case ascertainment due to screening and/or changing diagnostic patterns, while differential birth cohort effects would suggest that risk factor profiles vary from one generation to the next.

Standard APC models have been widely used to model trends for individual sets of data (15). For this study, we formally compared the incidence rates for the two types of cervical cancers using a comparative APC approach with tests for the statistical significance of differential time trends and age at onset curves.

Materials and Methods

We obtained invasive cervical carcinoma cases from the National Cancer Institute's SEER 9 Registries database,

Received 10/11/08; revised 12/19/08; accepted 1/12/09; published OnlineFirst 3/3/09.
Grant support: Intramural Research Program of the NIH, National Cancer Institute. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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doi:10.1158/1055-9965.EPI-08-0965

newly diagnosed during the years 1976 to 2005 (SEER 9; 1976-2005) and covering ~10% of the U.S. population (16). The 9 Registries of SEER are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Demographic and tumor characteristics included histopathologic type, year of diagnosis, age at diagnosis, Black and White race, and SEER historic stage A. Histopathologic tumor types were defined using the International Classification of Diseases for Oncology 3rd edition (ICD-O 3) of the WHO (17). More than 98% of all cervical carcinomas in SEER were microscopically confirmed. Data were stratified by the two main histopathologic types for cervical carcinoma, squamous cell carcinoma (ICD-O 3 codes 8050-8130) and adenocarcinoma (ICD-O 3 codes 8140-8490; refs. 18, 19). We excluded other histopathologic types from this analysis (n = 4,406 of 35,076 cervical cancers overall; Table 1). Age at diagnosis included fourteen 5-year age groups (ages 15-19, 20-24, ... 80-84 y). Year of diagnosis was stratified into six 5-y time periods (1976-80, 1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005). The historic stage A of SEER classified local disease as confined to the cervix uteri, regional disease as a direct extension to nearby surrounding areas, and distant disease as systemic metastases.

Statistical Methods. Age-adjusted (2,000 US standard population) incidence rates were calculated per 100,000 woman-years (or women per year). Relative risks were expressed as incidence rate ratios, where squamous cell carcinomas were compared with adenocarcinomas with an assigned incidence rate ratio of 1.0. Incidence rate ratios were tested for statistical significance at the 95% confidence level; all tests were two sided. Percentage changes (%CH) in incidence were calculated from the first 5-year time-period (1976-1980) to the last time-period (2001-20005) and tested for statistical significance at the 95% confidence level using the δ method (20).

Age-adjusted temporal trends were plotted on a log y and linear x scale by six 5-year time-periods, such that an angle of 10 degrees portrayed a rate change of 1% per year (21). Using a similar aspect ratio, age-specific incidence rates were plotted on a log-linear scale by 5-y age groups. We used Poisson regression models to examine trend and age interactions by histopathologic type on cervical cancer incidence rates, as previously described (22). For example, under the null hypothesis of no age interaction by histopathologic type, the age-specific incidence rate curves for squamous cell and adenocarcinomas would be parallel on the log-log scale or proportional on the absolute scale. Statistically significant trend or age interactions implied nonproportional incidence rates by histopathologic type over time or across age, respectively, consistent with cancer etiologic heterogeneity.

APC models were used to simultaneously adjust incidence rates for age, period, and cohort effects by histopathologic type. Given the APC relationship, (year of birth or birth cohort) = (year of diagnosis or calendar period) − (age at diagnosis), we had a maximum of nineteen 5-y birth cohorts calculated from our six 5-y calendar periods and fourteen 5-y age groups. Because the APC variables are collinear, it is impossible to determine the independent or separate effects for age, calendar period, or birth cohort, producing the so-called ''nonidentifiability'' problem of APC models. Notwithstanding this well-established nonidentifiability issue, certain APC parameters can be estimated if the age,

Table 1. Invasive squamous cell and adenocarcinoma of the cervix from SEER 9 Registry Database, 1976 to 2005

	Overall	Squamous cell	Adenocarcinoma
Total n	35,076	25,219	5,451
% of total cases	100%	72%	16%
Rate	9.70	6.98	1.52
Mean age (SE)	50.9 (0.09)	50.9 (0.10)	51.2 (0.23)
Median age	48.0	49.0	48.0

	Overall			Squamous			Adenocarcinoma			Squamous/Adenocarcinoma		
											95% CI	
Variable	n	Rate	SE	n	Rate	SE	n	Rate	SE	IRR	LL	UL
Age (y)												
<20	94	0.09	0.01	34	0.03	0.01	17	0.02	0.00	2.00	1.09	3.81
20-39	10,467	9.36	0.09	7,459	6.67	0.08	1,563	1.42	0.04	4.71	4.46	4.98
40-59	13,603	15.79	0.14	9,911	11.50	0.12	2,194	2.56	0.06	4.50	4.29	4.71
60+	10,912	17.19	0.17	7,815	12.32	0.14	1,677	2.65	0.07	4.65	4.41	4.91
Race												
White	26,349	8.96	0.06	18,658	6.34	0.05	4,417	1.52	0.02	4.18	4.05	4.33
Black	5,336	15.77	0.22	4,138	12.10	0.19	465	1.47	0.07	8.22	7.45	9.09
Other/unknown	3,391	11.14	0.19	2,423	7.98	0.17	569	1.85	0.08	4.31	3.93	4.74
SEER stage												
Localized	18,278	5.03	0.04	13,075	3.59	0.03	3,228	0.90	0.02	3.97	3.82	4.13
Regional	11,290	3.16	0.03	8,938	2.50	0.03	1,383	0.39	0.01	6.48	6.13	6.87
Distant	2,972	0.83	0.02	1,965	0.55	0.01	505	0.14	0.01	3.95	3.58	4.37
Other/Unknown	2,536	0.69	0.01	1,241	0.34	0.01	335	0.09	0.01	3.68	3.26	4.17

NOTE: Rates are per 100,000 and age-adjusted to the 2000 US standard population (single ages to 84-Census P25-1130) standard; confidence intervals (Tiwari mod) are 95% for ratios.
Abbreviations: IRR, incidence rate ratio; LL, lower limit; UL, upper limit.

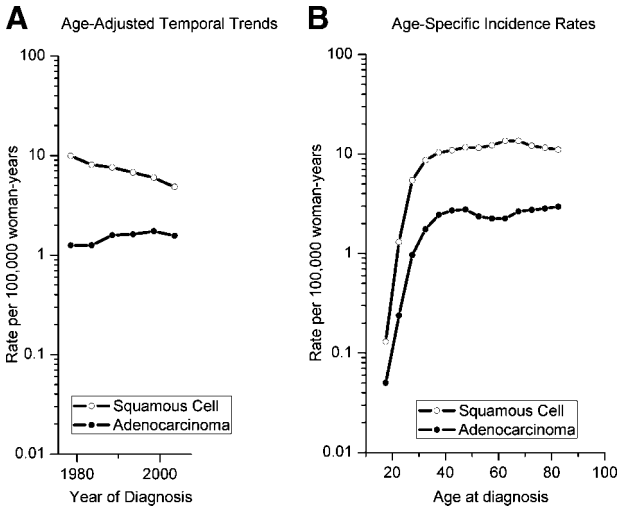

Figure 1. Incidence rates by histopathologic type (*SEER 9; 1976-2005*). **A.** Age-adjusted temporal trends among squamous cell carcinomas and adenocarcinomas, P value of <0.001 for trend interaction by histopathologic type. **B.** Age-specific incidence rates among squamous cell carcinomas and adenocarcinomas, P value of <0.001 for age interaction by histopathologic type.

calendar period, and birth cohort trends are orthogonally decomposed into their linear and nonlinear components, following Holford (15). The estimable APC parameters included ''drifts'' (23), ''deviations'' (24), ''curvatures'' (25), and ''slope contrasts'' (26).

APC deviations reflected the nonlinear departures from their respective linear trends. Net drift is the linear trend in the logarithm of the age-specific rates over time and is equal to the summation of the period and cohort slopes, i.e., $(\pi_L + \gamma_L)$, where π_L and γ_L are the linear trends for calendar period and birth cohort, respectively. The net drift parameter is estimable (identifiable), although the constituent components π_L and γ_L are not. Therefore, differences in the net drifts by histopathologic types assessed differential secular trends between squamous cell and adenocarcinomas, controlling for cohort and period deviations. Another type of drift parameter is the longitudinal age trend. The longitudinal age trend is the linear trend in the logarithm of the age-specific rates across age and is equal to the summation of the age and period slopes, i.e., $(\alpha_L + \pi_L)$, where α_L and π_L are the linear trends for age and period, respectively. Similar to net drift, the longitudinal age trend is identifiable, although the constituent components α_L and π_L are not. Differences in the longitudinal age trends were used to test for differential age-related effects for the study period.

Another useful APC function is the ''fitted'' age-at-onset curve, as recently introduced (27):

$$\hat{\rho}_i = \mu(\alpha_L + \pi_L)(i - \bar{i}) + \tilde{\alpha}_i$$

The parameter $\hat{\rho}_i$ reflects the age-specific incidence rate curve after adjustment for calendar period and birth cohort deviations, and approximates the true age-specific incidence rate curve devoid of period and/or cohort effects. In this model, μ is the intercept term, $(\alpha_L + \pi_L)$ is the longitudinal age trend, and $\tilde{\alpha}_i$ is the age deviation over interval i.

Results

Descriptive Statistics. Mean and median ages at diagnoses were nearly identical for squamous cell carcinomas and adenocarcinomas, Table 1 ($P_{\text{difference}}$ = 0.137). Overall incidence rates were 5-fold more common for squamous cell tumors (n = 25,219) than for adenocarcinomas (n = 5,451). In fact, rates were greater for squamous cell carcinomas than adenocarcinomas for all demographic and tumor characteristics (incidence rate ratio$_{SA}$, >1.0). For both histopathologic types, the majority of cases were either local or regional stage. Incidence rates for squamous cell tumors were approximately twice as high for Blacks than Whites (12.10 versus 6.34 per 100,000 woman-years), whereas adenocarcinoma incidence rates were roughly equal for Blacks and Whites (1.47 and 1.52 per 100,000 woman-years, respectively).

Age-adjusted temporal trends decreased for squamous cell carcinoma but increased for adenocarcinoma with a statistically significant trend interaction by histopathologic type (P < 0.001 for trend interaction by histopathologic type; Fig. 1A). Consequently, squamous cell carcinoma incidence rates declined 51% [95% confidence interval (95% CI), −54% to −49%] from 1976-1980 to 2001-2005 (Table 2A). By comparison, incidence rates for adenocarcinoma increased 25% (95% CI, 23–27%) during the same time period (Table 2B). Adenocarcinoma rates rose for all demographic and tumor characteristics, with exception of ages 60+ years (−10%CH; 95% CI, −12% to −9%) and Black race (−6%CH; 95% CI: −7% to −5%).

We also observed differential age-specific incidence rates by histopathologic type (P < 0.001 for age interaction by histopathologic type; Fig. 1B). For example, incidence rates rose rapidly for squamous cell tumors prior than age 40 years then flattened, whereas rates for adenocarcinomas rose more slowly before flattening. Given the statistically significant interactions over time (Fig. 1A) and across age (Fig. 1B), we used APC models to further assess the secular and age-related effects by histopathologic type.

APC Models. The APC summary results for squamous cell carcinoma and adenocarcinoma are shown in Fig. 2A to E. There were significant age, period, and cohort deviations for both squamous cell carcinomas and adenocarcinomas (Fig. 2B, C, and E, respectively). However, highly statistically significant differences between the deviations for the 2 histopathologic types were detected only for age ($P = 2.82 \times 10^{-6}$). There was less difference for the period deviations (P = 0.05) and birth cohort (P = 0.01) deviations. In addition to significant differences between age, period, and cohort deviations, there was striking heterogeneity for the longitudinal age trends and net drifts (Fig. 2A and D, respectively).

On a logarithmic scale (Fig. 2D), net drift decreased a negative 0.033 per year of calendar-time (95% CI, −0.040 to −0.025) for squamous cell carcinomas but rose 0.013

Table 2. Invasive cervical carcinoma by histopathological type

A. Invasive squamous cell carcinoma of the cervix incidence, SEER 9 Registries 1976-2005

Time period	1976-1980			1981-1985			1986-1990			1991-1995			1996-2000			2001-2005			1976-1980 to 2001-2005		
Variable	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	%CH	LL	UL
Total cases	4,822	9.93	0.147	4,274	8.07	0.127	4,374	7.60	0.117	4,248	6.77	0.105	4,042	5.99	0.095	3,459	4.84	0.083	−51%	−54%	−49%
Age (y)																					
<20	5	0.03	0.012	8	0.05	0.016	5	0.03	0.014	6	0.04	0.016	9	0.05	0.018	1	0.01	0.005	−81%	−120%	−54%
20-39	1,257	8.42	0.246	1,304	7.43	0.21	1,415	7.31	0.196	1,338	6.56	0.18	1,188	5.88	0.171	957	4.98	0.161	−41%	−44%	−38%
40-59	1,834	16.03	0.383	1,527	13.26	0.345	1,550	12.56	0.321	1,649	11.40	0.282	1,771	10.35	0.246	1,580	8.13	0.205	−49%	−54%	−45%
60+	1,726	19.93	0.484	1,435	14.77	0.392	1,404	13.32	0.356	1,255	11.36	0.321	1,074	9.50	0.291	921	7.72	0.256	−61%	−70%	−54%
Race																					
White	3,664	8.74	0.148	3,221	7.16	0.13	3,295	6.89	0.123	3,156	6.19	0.111	2,879	5.43	0.102	2,443	4.48	0.091	−49%	−51%	−46%
Black	835	21.82	0.796	726	16.32	0.632	667	13.17	0.527	639	10.60	0.432	676	9.77	0.386	595	7.55	0.316	−65%	−82%	−52%
Other/unknown	323	—	0.734	327	—	0.554	412	—	0.491	453	—	0.409	487	—	0.337	421	—	0.256	—	—	—
SEER																					
Localized	2,643	5.42	0.109	2,126	3.98	0.089	2,221	3.78	0.082	2,225	3.48	0.074	2,202	3.24	0.069	1,658	2.35	0.058	−57%	−60%	−53%
Regional	1,596	3.32	0.085	1,525	2.92	0.076	1,546	2.76	0.071	1,490	2.44	0.064	1,399	2.10	0.056	1,382	1.91	0.052	−42%	−45%	−40%
Distant	368	0.75	0.04	391	0.74	0.038	341	0.61	0.034	277	0.45	0.027	257	0.39	0.024	331	0.45	0.025	−39%	−43%	−37%
Other/unknown	215	—	0.031	232	—	0.029	266	—	0.028	256	—	0.025	184	—	0.02	88	—	0.013	—	~	~

B. Invasive adenocarcinoma of the cervix incidence, SEER 9 Registries 1976-2005

Time period	1976-1980			1981-1985			1986-1990			1991-1995			1996-2000			2001-2005			1976-1980 to 2001-2005		
Variable	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	*n*	Rate	SE	%CH	LL	UL
Total cases	599	1.25	0.052	650	1.26	0.051	897	1.59	0.054	1,009	1.62	0.051	1,176	1.74	0.051	1,120	1.57	0.047	25%	23%	27%
Age (y)																					
<20	2	0.01	0.007	3	0.02	0.01	3	0.02	0.011	2	0.01	0.009	3	0.02	0.01	4	0.02	0.011	100%	14%	713%
20-39	159	1.10	0.09	179	1.05	0.08	273	1.45	0.089	289	1.44	0.085	335	1.67	0.091	328	1.71	0.095	56%	46%	68%
40-59	206	1.82	0.13	230	2.05	0.137	352	2.82	0.151	402	2.78	0.139	513	2.99	0.132	491	2.52	0.114	38%	33%	44%
60+	232	2.76	0.183	238	2.49	0.162	269	2.57	0.157	316	2.85	0.16	325	2.84	0.158	297	2.47	0.144	−10%	−12%	−9%
Race																					
White	511	1.23	0.056	536	1.22	0.054	741	1.59	0.059	800	1.58	0.056	950	1.78	0.058	879	1.61	0.055	31%	28%	34%
Black	48	1.41	0.213	69	1.72	0.214	78	1.59	0.186	88	1.62	0.178	85	1.35	0.149	97	1.33	0.138	−6%	−7%	−5%
Other/unknown	40	—	0.251	45	—	0.197	78	—	0.212	121	—	0.21	141	—	0.174	144	—	0.148	—	—	—
SEER																					
Localized	347	0.73	0.04	361	0.71	0.038	532	0.94	0.041	616	0.98	0.04	716	1.06	0.04	656	0.93	0.036	27%	24%	30%
Regional	153	0.31	0.026	203	0.38	0.028	239	0.43	0.028	220	0.36	0.024	267	0.40	0.024	301	0.41	0.024	31%	27%	36%
Distant	68	0.14	0.017	53	0.10	0.014	71	0.12	0.015	80	0.13	0.015	114	0.17	0.016	119	0.17	0.015	23%	18%	28%
Other/unknown	31	—	0.013	33	—	0.011	55	—	0.013	93	—	0.015	79	~v	0.013	44	—	0.009	—	—	—

NOTE: Rates are per 100,000 and age-adjusted to the 2000 US standard population (single ages to 84-Census P25-1130) standard; confidence intervals (Δ method) are 95% for %CH, percentage change.

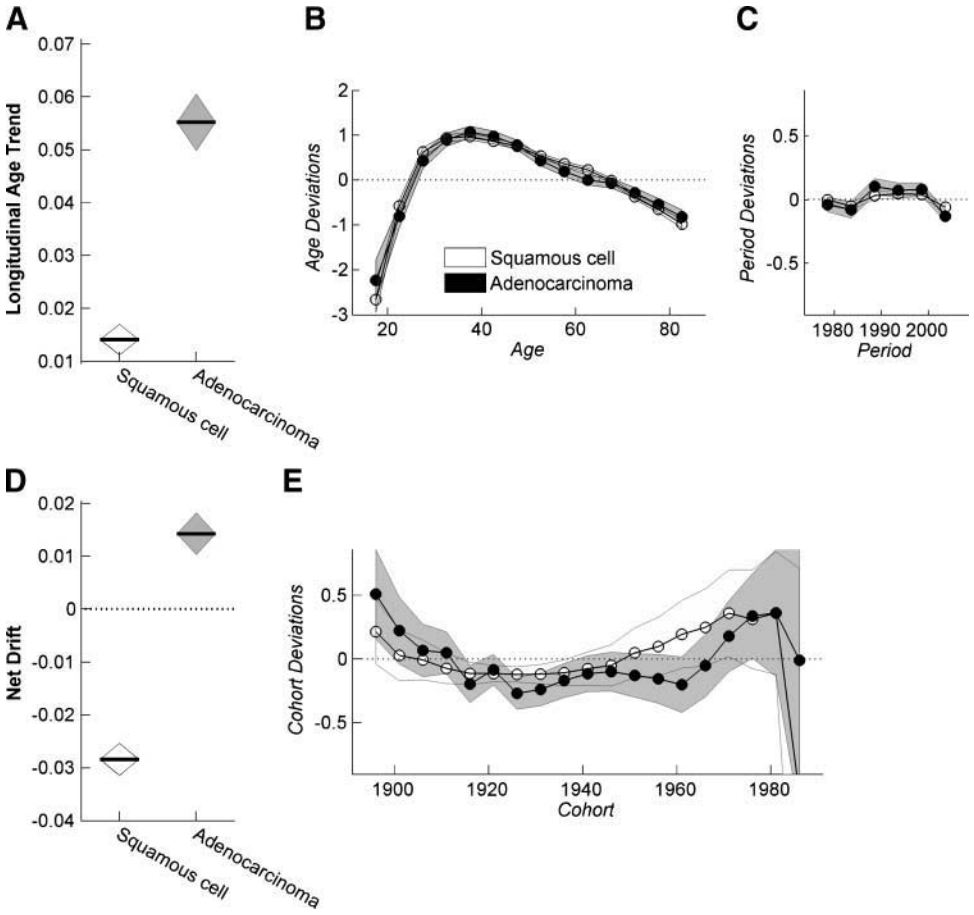

Figure 2. APC summary models by histopathologic type (*SEER 9; 1976-2005*). **A.** Longitudinal age trend with point estimates (midlines) and 95% CIs. Point estimates are expressed in log rates per 100,000 woman-years and correspond to the linear trend for the summation of the age + period effects ($\alpha_L + \pi_L$), see text for details. **B.** Age deviations with point estimates and 95% CIs for squamous cell (*open circles*) and adenocarcinomas (*closed circles*). Point estimates are expressed as age effects. **C.** Period deviations with point estimates and 95% CIs for squamous cell (*open circles*) and adenocarcinomas (*closed circles*). Point estimates are expressed as calendar period effects. **D.** Net drifts with point estimates (*midlines*) and 95% CIs. Point estimates are expressed in log rates per 100,000 woman-years and correspond to the linear trend for the summation of the period + cohort effects ($\pi_L + \gamma_L$), see text for details. **E.** Cohort deviations with point estimates and 95% CIs for squamous cell (*open circles*) and adenocarcinomas (*closed circles*). Point estimates are expressed as birth cohort effects.

per year (95% CI, 0.007-0.019) for adenocarcinomas. On a linear scale, net drift for squamous cell carcinomas decreased at an average rate of 3.20% per year of calendar time. Conversely, the incidence for adenocarcinomas rose at a rate of 1.29% per year. The corresponding Wald test for net drift was highly significant ($\times^2 = 87.7$, $P = 0$ for the null hypothesis of no difference), suggesting nonproportional (heterogeneous) secular trends by histopathologic type.

Similarly, we observed substantially different longitudinal age trends by histopathology (Fig. 2A). On a logarithmic scale, the longitudinal age trend rose 0.014 per year of attained age (95% CI, 0.011-0.017) for squamous cell carcinomas and 0.055 (95% CI, 0.050-0.060) for adenocarcinomas. The difference between these trends was highly significant (Wald test $\times^2 = 175.5$; $P = 0$), consistent with differential natural histories described by nonproportional age at onset curves for the two tumor types.

Overall, these results strongly posit that squamous cell carcinoma and adenocarcinoma were nonproportional (heterogeneous or different) over time and age, as further highlighted by the joint net drifts and longitudinal age trends (Fig. 3). Both longitudinal age trends and net drifts were less for squamous cell carcinomas than adenocarcinomas in Fig. 3A, consistent with Fig. 2A and D. We saw similar patterns, by histopathologic type within race and stage (Fig. 3B and C, respectively). That is, both longitudinal age trends and net drifts were less for squamous cell carcinomas than adenocarcinomas irrespective of race (Fig. 3B) or stage (Fig. 3C).

Distinctly different age-specific effects and secular trends also were shown by the APC fitted age-at-onset curves and by the APC fitted age-specific temporal trends (Fig. 4A-C). The fitted age-specific incidence rates for squamous cell tumors that were adjusted for period and cohort effects peaked near age 40 years then fell

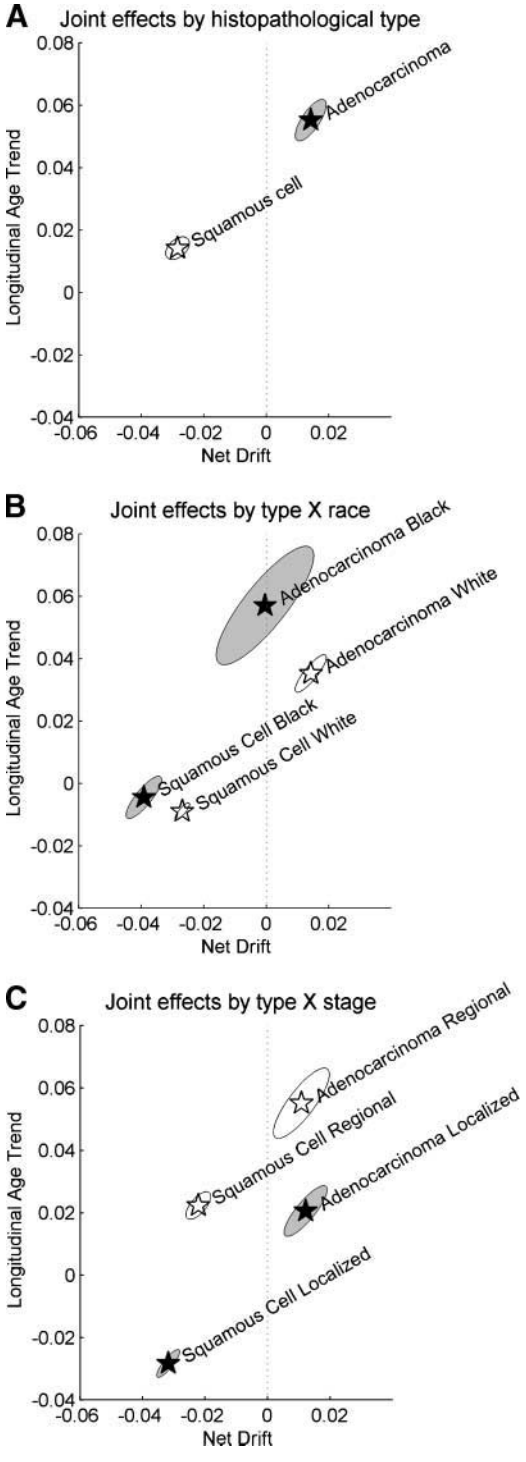

Figure 3. Joint effects for the longitudinal age trends and net drifts by histopathologic type, race, and stage (*SEER 9; 1976-2005*). **A.** Joint effects by squamous cell carcinoma and adenocarcinoma with point estimates (*stars*) and 95% CIs (*circles*). **B.** Joint effects by histopathologic type and race with point estimates (*stars*) and 95% CIs (*circles*). **C.** Joint effects by histopathologic type and stage with point estimates (*stars*) and 95% CIs (*circles*).

steadily (Fig. 4A), whereas the fitted age-at-onset curve rose continuously for adenocarcinomas, albeit at a slower rate after age 40 years. Decreasing age-specific incidence rates for squamous cell carcinomas and rising rates of adenocarcinomas eventually converged near age 80 years. Squamous cell carcinoma incidence rates declined over time for all age groups (Fig. 4B). In contrast, adenocarcinoma incidence rates increased or were stable for all age groups (Fig. 4C).

Discussion

Standard descriptive techniques and comparative APC analysis showed distinct secular and age-related patterns in cervical carcinoma incidence according to histopathologic type. Differential secular trends are concisely quantified by the divergent net drifts (Fig. 2D), and also manifested in the age-specific temporal trends (Fig. 4B-C). Indeed, whereas standard APC models often focus on period and cohort deviations (Fig. 2C and E), this comparative APC analysis identified far more striking and statistically significant differences in the linear trends for period and cohort (i.e., net drifts).

Additionally, the findings of differential longitudinal age trends and age deviations (Fig. 2A and B) support a differential age-related natural history for squamous cell carcinoma and adenocarcinoma. The APC fitted age-at-onset curve combines these two distinct parameters to reconstruct a ''natural history'' adjusted for period and cohort factors (Fig. 4A).

The sharp increase and decrease of the fitted age-at-onset curve for squamous cell tumors suggests an age-dependent risk factor profile because susceptibility increases with age then wanes. Incidence rates may increase initially due to increasing HPV exposure early in reproductive life, and rates may decline later in life due to age-related reductions in HPV exposure, increased immunity to HPV, cervical epithelial atrophy, hormonal changes, and other unknown factors. Studies in E6/E7-expressing transgenic mice have shown that estrogen is required for carcinogenesis in the cervicovaginal epithelium (28); estrogen-dependent carcinogenesis is consistent with the sharp decrease in the APC fitted age-at-onset curve for squamous cell carcinoma in postmenopausal women. In contrast to the age-dependent pattern for squamous cell carcinomas, adenocarcinomas incidence rates increase continuously with aging, consistent with a long-term multihit carcinogenic process (29).

However, an important caveat is that an APC fitted age-at-onset curve can only describe an ''apparent'' age-related natural history. In our analysis, the two type-specific curves differed primarily in the linear trends of the age-specific log rates more so than in the age deviations. Hence, it is theoretically possible that a portion of the difference between the fitted curves is the consequence of equal and opposite latent linear trends in calendar period effects. Such trends might reflect differential period trends in diagnostic specificity, case ascertainment, etc. We think that this is an unlikely scenario for cervical carcinomas. For example, although it is widely believed that older women are prone to false-negative and inadequate cytology screening (30), it is not clear that the effect of aging on cytology is differential

with respect to histopathologic type. Additionally, although the sensitivity for adenocarcinoma may have increased over time, we are aware of no data to suggest that the sensitivity for squamous cell carcinoma has decreased. Even if this were so, the opposing trends in sensitivity would have to be implausibly large to explain the 4.1% per year difference in the estimable longitudinal age trends (Fig. 2A), which reflect the sum of latent (but not identifiable) linear trends associated with age and period, respectively.

A study in Taiwan also reported distinct APC effects by histopathologic type (31). In contrast, two European studies showed similar birth cohort effects for squamous cell and adenocarcinomas, suggesting homogeneous etiologies (32, 33). Previous APC studies, however, mainly assessed the age, period, and cohort deviations. Notably, our results for the U.S. SEER population found the largest differences by contrasting the linear trends (i.e., net drifts and longitudinal age trends, $P = 0$), with smaller distinctions among the age, period, and/or cohort deviations. Further comparative APC studies across populations would be of interest to assess formally the heterogeneity.

As for most population-based registry studies, our analyses lacked information on individual risk factors, and had the potential of incomplete data collection. However, SEER rigorously assesses the quality and completeness of cancer information through Registry assessment, accountability, and education. Additionally, we did not take into account hysterectomy, removing women who have had a hysterectomy from our standard population would likely increase the incidence rates (34). The potential role of hysterectomy as a confounding factor of trends merits further analysis.

Despite these potential limitations, our results are consistent with a growing body of evidence suggesting etiologic differences for squamous cell carcinomas and adenocarcinomas of the cervix. For example, although both squamous cell and adenocarcinomas are caused by HPV infections, the distribution of carcinogenic HPV genotypes responsible for each differ somewhat. HPV16 causes 50% to 60% and HPV18 causes another 15% to 20% of squamous cell carcinomas (35, 36). By contrast, in adenocarcinoma, the prevalence of HPV16 and HPV18 are 33% and 37%, respectively (36). Unlike for squamous cell carcinoma, virtually nothing is known about the physical state of the virus, viral integration, expression, and viral productivity (viral load), in adenocarcinoma and its precursors. HPV gene expression and virion production are linked to epithelial differentiation in the squamous tissue but how the virus propagates in the glandular tissue is largely unknown. Further studies are needed to characterize the mechanism by which HPV promotes cancer in the two cancer types.

There also is some preliminary evidence to suggest that patterns of epigenetic changes, specifically hypermethylation of CpG islands, differ between histopathologic types. A few reports also have found *adenomatosis polyposis coli* (*APC*; refs. 37, 38), *Tissue inhibitor of metalloproteinases-3* (*TIMP-3*; refs. 38, 39), and *Ras association (RalGDS/AF-6) domain family 1* (*RASSF1A*; refs. 38, 40) genes are more commonly hypermethylated in adenocarcinoma versus squamous cell carcinoma. Another report found that the *chromodomain helicase DNA binding protein 1* gene (*CHD1*; ref. 39) was much more likely to be hypermethylated in squamous cell carcinoma compared with adenocarcinoma. There have been two reports of differential gene expression by

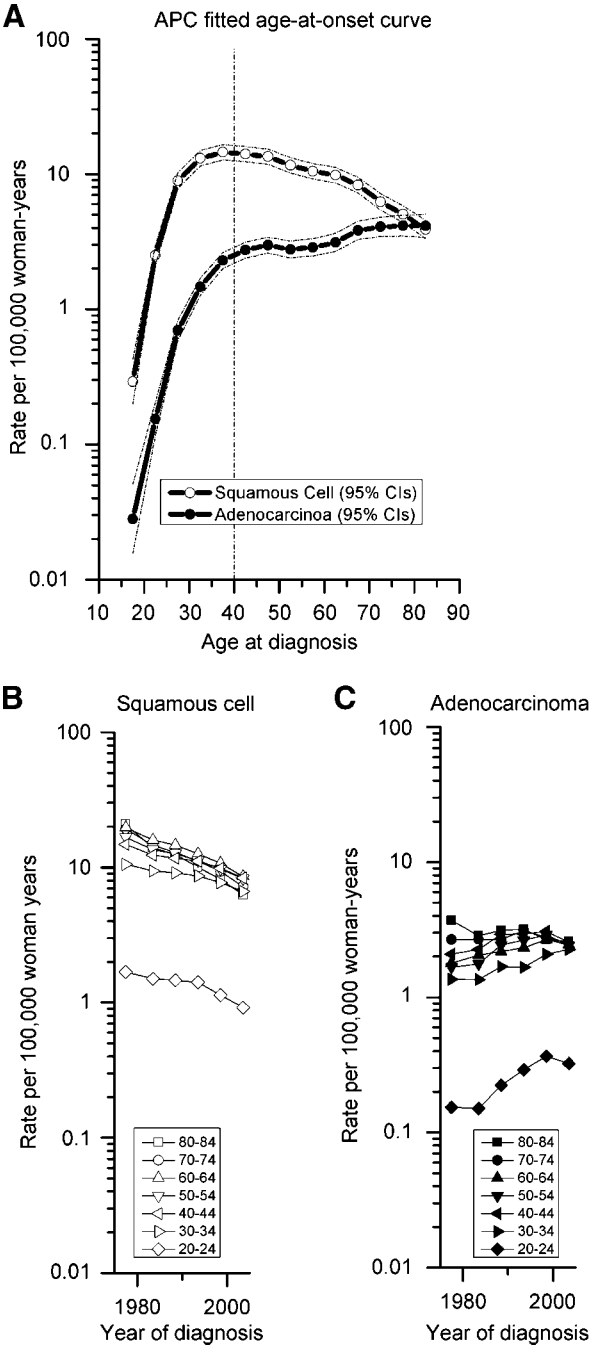

Figure 4. Fitted age-at-onset curve and fitted age-specific temporal trends by histopathologic type (*SEER 9; 1976-2005*). **A.** Fitted age-at-onset curves for cervical squamous cell carcinoma and adenocarcinoma on a log-linear scale with 95% CIs. **B.** Age-specific temporal trends for squamous cell carcinomas (*open symbols*). **C.** Age-specific temporal trends for adenocarcinomas (*closed symbols*).

histopathologic type (41, 42), but the two studies found different profiles of important distinguishing genes and there have been no follow-up, confirmatory studies.

Furthermore, secondary factors, HPV ''cofactors,'' may differ between squamous cell carcinoma and adenocarcinoma of the cervix. Although smoking has been consistently found to be associated with squamous cell carcinoma and its immediate precursor lesions (43-46), no association has been found with adenocarcinoma (2, 47, 48). Similarly, there are reports of serologic evidence of Chlamydial infections being associated with squamous cell carcinoma (49) but not with adenocarcinoma (2, 50), perhaps suggesting that inflammation contributes to development of squamous cell carcinoma but not adenocarcinoma. In one study, obesity and body fat distribution were associated more strongly with adenocarcinoma than with squamous cell carcinoma (4), perhaps suggesting an interaction of glandular cells with hormonal factors. However, it is unclear whether hormonally related exposures (e.g., parity, oral contraceptive use, and hormone replacement therapy) differentially influence by cell type the risk of cervical cancer (2, 48, 51, 52). Thus, the role of endogenous and exogenous hormonal factors and the risk of cancer by histopathologic type warrant further investigation.

In sum, our population data suggest that the two most common histopathologic types of cervical cancer are epidemiologically distinct despite the central role of HPV infection for both. Thus far, there is little insight into the mechanisms by which HPV and other risk factors contribute to distinct carcinogenic pathways. Our results suggest one possible model. Assuming that at least two genetic ''hits'' are required for both types, and assuming that HPV infection is often the first hit for both, subsequent events for squamous cell carcinoma may happen comparatively early in life, whereas those for adenocarcinoma happen comparatively late. Future analytic and clinical studies should consider the interaction (effect modification) of HPV infection and other cervical carcinoma risk factors by histopathologic type, time, and age.

Disclosure of Potential Conflicts of Interest

None of the coauthors has a financial conflict of interest that would have affected this research.

Acknowledgments

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We thank the reviewers for helpful comments that have improved the content of this manuscript.

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