Active and Passive Cigarette Smoking and the Risk of Cervical Neoplasia

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OBJECTIVE: Evidence links active cigarette smoking to cervical neoplasia, but much less is known about the role of passive smoking. Using a prospective cohort design, we examined personal cigarette smoking and household passive smoke exposure in relation to the risk of cervical neoplasia.

METHODS: Cohorts were established based on data collected on the smoking status of all household members during private censuses of Washington County, Maryland in 1963 (n = 24,792) and 1975 (n = 26,381). Using the Washington County Cancer Registry, the occurrence of cervical neoplasia in the two cohorts was ascertained from 1963–1978 and from 1975–1994. Poisson regression models were fitted to estimate the relative risk of developing cervical neoplasia associated with active and passive smoking in both cohorts. The referent category for all comparisons was never smokers not exposed to passive smoking.

RESULTS: The adjusted relative risk and 95% confidence limits for passive smoking was 2.1 (1.3, 3.3) in the 1963 cohort and 1.4 (0.8, 2.4) in the 1975 cohort. The adjusted relative risk and 95% confidence limits for current smoking were 2.6 (1.7, 4.1) and 1.7 (1.1, 2.6) in the 1963 and 1975 cohort, respectively.

CONCLUSION: The associations were in the direction of increased risk for both passive smoking and current active smoking in both the 1963 and 1975 cohorts, but were stronger in the 1963 cohort. The results of this long-term, prospective cohort study corroborate the association between active cigarette smoking and cervical neoplasia and provide evidence that passive smoking is a risk factor for cervical neoplasia. (Obstet Gynecol 2005;105:174–81. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: II-2

A consistent association between cigarette smoking and cervical cancer has been noted in numerous studies conducted since the 1960s, reviewed in Winkelstein[1] and Kuper et al.[2] Until recently, this evidence was considered insufficient to fulfill established epidemiologic criteria for causality, because the observed associations may have been due to the possibility that smokers have higher-risk sexual histories than nonsmokers. The identification of the critical role of human papillomavirus (HPV) infection in the causation of cervical cancer has raised the possibility that cigarette smoking could act as a cofactor that promotes progression of cervical carcinogenesis.[3,4] The evidence has now matured to the point that the United States Surgeon General[5] and International Agency for Research on Cancer[6] have judged that active cigarette smoking is causally associated with cervical cancer.

Less attention has been paid to the potential link between passive smoking and the development of cervical neoplasia. Given the association between active smoking and cervical cancer, passive exposure to cigarette smoke could plausibly contribute to cervical carcinogenesis. Cotinine, a nicotine metabolite, is present in measurable concentrations in the cervical mucus of active cigarette smokers.[7,8] The presence of cotinine in cervical mucus of nonsmoking women who are passively exposed to smoke from cigarettes make it reasonable to postulate that passive smoking can contribute to carcinogenesis through the same potential pathways as active smoking, including genotoxic and immunomodulatory effects.[9,10] These effects could be manifested, for example, through tobacco-specific N-nitrosamines,[10] altered local cervical cytokine profiles,[11] and altered immune

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cell infiltrates in the cervix of women with cervical dysplasia.[12,13]

Determining whether passive smoking contributes to the risk of cervical cancer will provide a more complete picture of the potential role of cigarette smoke in cervical carcinogenesis. Exposure to passive cigarette smoke is potentially modifiable, and hence this may have implications for strategies to prevent cervical cancer. The results of several case-control and cross-sectional studies indicate that women married to smokers experience a higher risk of cervical neoplasia than women married to nonsmokers.[14–18] However, there has been a notable lack of evidence concerning the potential association between passive smoking and cervical cancer from prospective cohort studies. In a prospective cohort study in Japanese women who never smoked, the relative risk of cervical cancer in those who were married to a smoker compared with those who were married to a nonsmoker was 1.1, with wide 95% confidence limits (0.3, 4.5), because this result was based on only 9 cases of cervical cancer.[19] To address this paucity of evidence, we evaluated the joint influence of active and passive cigarette smoking on the risk of developing cervical neoplasia in a community-based prospective cohort study implemented in Washington County, Maryland.

MATERIALS AND METHODS

This study was carried out with approval from the Institutional Review Board of the Johns Hopkins University Bloomberg School of Public Health. The present study is based on 2 cohorts established when records were collected during 2 private censuses of the residents of Washington County, Maryland. The first census was conducted in 1963, and the second census was conducted in 1975. Briefly, the private censuses were carried out by the Johns Hopkins Training Center for Public Health Research as follows: During the summer of 1963, questionnaires were mailed to all residential addresses in the county, and enumerators went door-to-door to collect or to assist in completion of the questionnaires. Data were collected on all household members aged 16.5 years and older. The protocol was similar to the protocol of the U.S. Census Bureau. The data collection protocol for the 1975 census was similar to the protocol used for the 1963 census, except that information was collected on household residents aged 18 years and older. Approximately 98% of households (n = 91,909) in Washington County participated in the 1963 census, and 90% of the households (n = 90,225) participated in the 1975 census.

From among the total number of women ascertained in the 1963 census (n = 46,741), the analytic cohort of the present study was limited to the 24,792 women who were 25 years or older, had no prior cancer diagnosis, and were not missing information on age, gender, or smoking. Age, gender, or smoking status were missing for only 5.6% and 0.8% of otherwise eligible women in the two cohorts, respectively. After applying these eligibility criteria to the 1975 cohort, from the total of 46,577 women ascertained in the 1975 census, 26,381 women were included in the present study. These 2 cohorts were then followed up across time for first-time occurrences of cervical neoplasia by linking personal identifying information collected at baseline with the Washington County cancer registry, as described below.

During the 2 private censuses, tobacco use history was collected on household members aged 16.5 years or older in 1963 and 18 years or older in 1975. Measurement of cigarette smoking in 1963 consisted of assessing whether household members had ever or currently smoked cigarettes, along with age of initiation and the amount smoked per day. Individuals were classified as never, former, or current cigarette smokers. Current smokers were further classified according to the number of cigarettes smoked per day: less than 10, 11–20, and more than 20. The cigarette smoking history collected during the 1975 census was similar to that collected in 1963, except that the actual number of cigarettes per day was recorded and age of initiation of cigarette smoking was not. Additionally, questions concerning pipe and cigar smoking measured ever use in 1963 and current use in 1975.

The information on smoking habits of all household members allowed assessment of active cigarette smoking history plus household exposure to passive smoking. In never smokers, passive smoking exposure was classified as nonexposed if no other household members were active cigarette smokers and exposed if any other household member was a current cigarette smoker. Exposure to passive smoking was further differentiated according to whether the household smokers included the spouse or only someone other than the spouse. Additional information collected in both cohorts included age, gender, years of schooling, and marital status, and frequency of religious attendance was collected only in the 1963 cohort.

Among the women in these two cohorts, the occurrence of in situ (International Classification of Diseases, 8th Revision, code 234) or invasive cervical cancer (International Classification of Diseases, 8th Revision, codes 180.0–180.9) that occurred among women with no known prior personal history of cancer after the baseline data collection was ascertained by linkage to the Washington County Cancer Registry. This registry, established in 1948, ascertains cancer cases primarily through discharge records from the Washington County

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Hospital, the only general hospital in the county, and death certificates. Our cancer registrar collects these data, and accepts the diagnosis and code from the source (Washington County Hospital). If the diagnosis from a doctor's office or laboratory is unclear, they are queried until a definite and accurate code can be assigned. Washington County Hospital has an excellent cancer unit and tends to draw patients from the surrounding area. Even patients who go elsewhere are likely to be diagnosed in Washington County hospital and hence ascertained in the Washington County cancer registry. Since the Maryland Cancer Registry has been fully operational, on average the Washington County Cancer Registry identifies 1 or 2 more cervical cancer cases per year than the state registry. Similar comparisons with the Maryland State Cancer Registry indicate that the Washington County Cancer Registry ascertainment of cervical carcinoma in situ is approximately 91% complete.

The analyses of the 1963 cohort are based on 47 cases of invasive cervical carcinoma and 184 cases of cervical carcinoma in situ that occurred between 1963 and 1978. The analyses of the 1975 cohort are based on 47 cases of invasive cervical carcinoma and 71 cases of cervical carcinoma in situ that occurred between 1975 and 1994. Deaths were ascertained from Maryland State Death Certificates.

Person-time of follow-up was estimated based on randomly sampling 5% of each cohort at the midpoint of the follow-up interval to identify characteristics associated with likelihood of remaining in the county. Specifically, a 5% random sample of each cohort was surveyed 8 (1963 cohort) or 10 (1975 cohort) years after the baseline data were collected to determine factors associated with the probability of remaining alive and in Washington County. The follow-up survey for the 1963 cohort took place in July, 1971 and the follow-up survey for the 1975 cohort was implemented in July, 1985. The follow-up survey results indicated that 76% of the cohort was still alive and living in Washington County at the halfway point of the follow-up. The results of each survey were analyzed to assess the probability of remaining a Washington County resident according to age, gender, marital status, education, and smoking status. Factors associated with emigration and death, such as age, gender, marital status, education, and smoking status were included in a linear regression model to assign the probability of remaining a resident in the county.[20]

The probability factor calculated for each individual from this regression model was then multiplied by the maximal possible duration of follow-up for each cohort (15 years for the 1963 cohort and 19 years for the 1975 cohort) to estimate person-time, correcting for the potential for emigration as determined by individual characteristics (age, marital status, education, smoking status). The maximal dates of follow-up were taken to be July 15, 1978, for the 1963 cohort and July 15, 1994, for the 1975 cohort. The rationale for truncating the follow-up time at these dates was to keep within a period that the follow-up survey information could reasonably be expected to retain validity, by taking the follow-up survey date as the midpoint of the maximal month of follow-up. For example, in the 1963 cohort, each woman's follow-up time from baseline (July 15, 1963) was estimated by multiplying the probability of residing in the county by 15 years, the maximal duration of follow-up. For a diagnosis of cervical neoplasia to contribute to the numerator of the incidence rate, the diagnosis had to occur within the woman's estimated follow-up time. To avoid introducing selection bias, this method was applied uniformly to the entire cohorts, regardless of whether a woman's specific survival information was actually known.

The 1963 and 1975 cohorts were analyzed separately. Poisson regression models[21] were employed to estimate the relative risk of developing cervical neoplasia. For the modeling of incidence rates of cervical neoplasia during the follow-up period according to tobacco exposure, Poisson regression is the appropriate statistical model because the dependent variable is expressed as counts of cases per person-time. For our study design and follow-up, the Poisson regression model is more appropriate than the logistic regression model, for which the outcome is usually a dichotomous (disease compared with no disease) variable measured at some point in time.

All relative risks presented were at least age-adjusted, and "fully-adjusted" relative risks were also adjusted for education and marital status. In the 1963 cohort, responses to a question concerning frequency of attendance at religious services were incorporated into the analyses, because Kinsey and colleagues observed that religious devoutness, as measured by regularly attending religious services and actively participating in religious activities, was inversely correlated with extramarital coitus.[22]

Models for the total cohorts first dealt with the joint active and passive smoking variables. Analyses were then limited to never smokers to evaluate the associations between household exposure to passive smoking and cervical neoplasia by spouse compared with nonspouse exposure.

To assess the extent to which correcting the person-time of follow-up for individual characteristics (age, marital status, education, smoking status) influenced the study inferences, ancillary analyses were conducted without accounting for the probability of remaining a Washington County resident. In these analyses follow-up times were assigned based on dates of cancer diagnoses or death, with follow-up time assumed to be

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Table 1. Characteristics of Women in the 1963 and 1975 Cohorts, Washington County, Maryland

	1963 Cohort		1975 Cohort	
	N	%	N	%
Total	24,792	100.0	26,381	100.0
Age (y)				
25–34	5,377	21.7	6,134	23.3
35–44	6,221	25.1	5,008	19.0
45–54	5,199	21.0	5,391	20.4
55–64	3,846	15.5	4,584	17.4
> 65	4,149	16.7	5,264	20.0
Years of school				
< 11	14,469	58.4	11,681	44.3
> 12	9,811	39.6	14,378	54.5
Missing	512	2.1	322	1.2
Marital status				
Married	18,181	73.3	18,895	71.6
Widowed	3,653	14.7	4,227	16.0
Divorced/separated	1,278	5.2	1,739	6.6
Single	1,605	6.5	1,489	5.6
Missing	75	0.3	31	0.1
Cigarette smoking				
Never smoker, no passive	8,538	34.4	10,907	41.3
Passive smoking only	6,184	24.9	4,071	15.4
Former smoker	2,190	8.8	3,830	14.5
Current smoker	7,880	31.8	7,573	28.7
Religious attendance*				
Never	2,434	9.8		
< 2 times per year	1,726	7.0		
2–12 times per year	4,442	17.9		
> Once per month	2,877	11.6		
Once per week	9,265	37.4		
> Once per week	2,319	9.4		
Missing	1,729	7.0		

* Data available for 1963 only.

complete for women not known to have been diagnosed with cancer or to have died. Because the results of these analyses were not materially different from the corrected estimates, the results of these ancillary analyses are not presented. All statistical analyses were performed using SAS (SAS Institute Inc, Cary, NC).

RESULTS

The characteristics of the 1963 and 1975 cohorts are summarized in Table 1. Reflecting the population of Washington County, almost all of the participants in each cohort were white. The cohorts were similar in most respects, except that the average years of schooling increased from 10 in 1963 to 11 in 1975. The average age was 48 years in the 1963 cohort and 49 years in the 1975 cohort. The percentage of women who were never smokers and did not live with a smoker and the prevalence of current smokers was similar in 1963 and 1975, but a major shift in exposure occurring between the two time points was that the percentage of women who never smoked but lived with someone who smoked dropped from 25% in 1963 to 15% in 1975 (Table 1). Conversely, the percentage of women who were former smokers increased over time, from 9% to 15% (Table 1).

Education and marital status both showed some evidence of being associated with cervical neoplasia risk in both cohorts. The age-adjusted relative risk (RR) of cervical neoplasia for women with greater than or equal to 12 years compared with less than 12 years of schooling was 0.6 (95% confidence limit [CL] 0.4, 0.8) in 1963 and 0.6 (95% CL 0.4, 0.9) in 1975. Compared with women who were married, women who were separated or divorced had a significantly increased risk of developing cervical neoplasia (age-adjusted RR 1.6, 95% CL 1.0, 2.6 in 1963 and 2.0, 95% CL 1.0, 3.3 in 1975). Compared with women who attended less regularly, women who attended religious services at least once per week had a nonsignificantly lower risk of developing cervical neoplasia (RR 0.8, 95% CL 0.5, 1.2).

Table 2 summarizes the baseline characteristics of the women in the 1963 and 1975 cohorts according to active and passive cigarette smoking status. In the 1963 cohort,

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Table 2. Frequency Distribution of Active and Passive Cigarette Smoking Status by Demographic Characteristics of the 1963 and 1975 Cohorts (Row Percentages)

	1963 Cohort				1975 Cohort			
Characteristic	Never Smoker/No Passive Smoking (n = 8,538)	Passive Smoking Only (n = 6,184)	Former Smoker (n = 2,190)	Current Smoker (n = 7,880)	Never Smoker/No Passive Smoking (n = 10,907)	Passive Smoking Only (n = 4,071)	Former Smoker (n = 3,830)	Current Smoker (n = 7,573)
Age								
25–34	24.7	21.9	11.3	42.1	34.0	16.5	15.8	33.7
35–44	23.7	23.6	10.5	42.2	32.2	17.2	15.8	34.8
45–54	27.6	26.7	10.2	35.6	33.3	16.0	15.2	35.5
55–64	44.8	26.9	6.8	21.6	43.9	13.0	15.3	27.8
≥ 65	62.1	26.9	3.5	7.5	64.6	14.1	10.4	10.9
Years of school								
≤ 11	36.2	27.5	7.3	29.0	43.4	16.0	11.4	29.2
≥ 12	31.3	21.1	11.3	36.4	39.7	14.8	17.2	28.3
Marital status								
Married	29.4	26.7	9.8	34.0	37.3	17.2	15.8	29.8
Widowed	53.7	23.5	5.4	17.4	57.7	12.0	10.8	19.5
Divorced/separated	26.1	13.9	9.2	50.9	31.6	6.4	14.4	47.6
Single	54.1	16.8	5.3	23.8	58.4	12.4	9.6	19.6
Religious attendance (1963 only)								
Never	24.6	27.6	6.3	41.6				
< 2 times per year	19.0	23.9	8.9	48.2				
2–12 times per year	23.4	24.9	8.7	43.0				
> Once per month	57.4	21.3	10.5	10.5				
Once per week	41.2	25.8	8.9	24.1				
> Once per week	30.4	23.8	10.1	35.7				

the percentage of current smoking was inversely associated with age; stated conversely, the percentage of never smoking increased with age. In contrast, the proportion of never smokers who were exposed to passive smoking remained relatively constant between 22% to 27% across the age groups. This pattern of cigarette smoke exposure by age was similar in the 1975 cohort, with trends that were slightly less pronounced. Compared with the 1963 cohort, the percentage of never smokers in the 1975 cohort increased in age groups less than 55 years, whereas the percentage of exposure to passive smoking decreased in all age groups. There was relatively little variation in cigarette smoke exposure according to years of school in either cohort, but there was marked variation by marital status. Compared with married women, the percentage of current smoking was highest in women who were divorced or separated (approximately 50% in both cohorts) and lowest in women who were single or widowed. The probability of exposure to passive smoking in the home did not vary considerably according to attendance at religious services, but the proportion of current active smoking was notably lower among women who attended religious services at least once per month.

The women-years of follow-up in the 1963 and 1975 cohorts were 290,955 and 377,695, respectively. The number of cervical neoplasia cases, person-years of follow-up, and relative risks according to smoking status are summarized in Table 3. The nonexposed comparison group for all the analyses of cigarette smoke exposure was composed of women who never smoked cigarettes and who did not reside with any cigarette smokers (Table 3). The risk of developing cervical neoplasia was statistically significantly higher among women who were current cigarette active smokers in both cohorts, with fully adjusted relative risks (aRR) of 2.6 in the 1963 cohort and 1.7 in the 1975 cohort (Table 3). In both cohorts, passive smoking was also associated with increased risk of developing cervical neoplasia. The association with passive smoking was stronger in the 1963 cohort (aRR 2.1, 95% CL 1.3, 3.3) than the 1975 cohort (aRR 1.4, 95% CL 0.8, 2.4) and was statistically significant only in the 1963 cohort. The association between passive smoking and cervical neoplasia was relatively uniform regardless of whether of source of exposure was the spouse or solely from other persons in the household who smoked (Table 3). Former smokers did not have a statistically significantly elevated risk of cervical neopla-

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Table 3. Relative Risk (and 95% Confidence Limits) of Developing In Situ or Invasive Cervical Cancer According to Active and Passive Smoking Status, Washington County, Maryland, 1963–1978 and 1975–1994

	1963 Cohort				1975 Cohort			
Smoking Status	Cases	Person Years	Relative Risk*	Relative Risk†	Cases	Person Years	Relative Risk*	Relative Risk‡
Never smoker, no passive smoking§	30	97,118	1.0	1.0	35	162,130	1.0	1.0
Passive smoking only	64	73,491	2.5 (1.3, 3.3)	2.1 (1.3, 3.3)	20	61,194	1.3 (0.7, 2.3)	1.4 (0.8, 2.4)
Former smoker	19	26,235	1.7 (1.0, 3.1)	1.7 (0.9, 3.1)	14	51,844	1.1 (0.6, 2.0)	1.1 (0.6, 2.1)
Current smoker	118	94,110	2.9 (1.9, 4.4)	2.6 (1.7, 4.1)	49	102,527	1.8 (1.1, 2.7)	1.7 (1.1, 2.6)
≤ 10 cigarettes/day	29	27,511	2.6 (1.5, 4.3)	2.6 (1.5, 4.5)	3	13,619	0.9 (0.3, 2.8)	0.8 (0.3, 2.7)
11–19 cigarettes/day	62	47,967	3.0 (1.9, 4.6)	2.5 (1.5, 4.1)	34	63,189	2.1 (1.3, 3.3)	1.9 (1.2, 3.1)
≥ 20 cigarettes/day	26	17,565	3.3 (1.9, 5.6)	2.9 (1.6, 5.1)	12	23,068	1.9 (1.0, 3.6)	1.5 (0.8, 3.0)
Source of passive smoke exposure								
Never smoker, no passive smoking§	30	97,118	1.0	1.0	35	162,130	1.0	1.0
Other household member	13	22,309	2.6 (1.6, 4.0)	2.3 (1.1, 4.9)	6	18,101	1.3 (0.7, 2.5)	1.3 (0.6, 3.2)
Spouse	51	51,182	2.2 (1.2, 4.3)	2.0 (1.2, 3.3)	14	43,092	1.6 (0.7, 3.9)	1.6 (0.8, 3.2)

Values in parentheses are 95% confidence limits.
* Age-adjusted (age as a continuous variable).
† Adjusted for age, education, marital status, and religious attendance (as shown in Table 1).
‡ Adjusted for age, education, and marital status (as shown in Table 1).
§ Referent category.

sia in either cohort, although the RR was of borderline statistical significance in the 1963 cohort (age-adjusted RR 1.7, 95% CL 0.9, 3.1), but not in the 1975 cohort (age-adjusted RR 1.1, 95% CL 0.6, 2.1).

DISCUSSION

This long-term, community-based prospective cohort study to assess the joint influence of active and passive smoking on the risk of cervical neoplasia is unique in many important respects. Exposure to passive smoking was not a suspected risk factor in the 1960s, so it is rare for a cohort study initiated during that era to have the capacity to examine passive smoking. The statistical power to detect clinically relevant associations was enhanced by the large size of the cohorts in combination with follow-up periods of up to 19 years.

The fact that 2 private censuses established 2 cohorts also allowed us to examine the associations between tobacco smoke exposure and cervical neoplasia during 2 different periods, 1963–1978 and 1975–1994. The findings for these 2 points exhibited both similarities and differences. In both the 1963 and 1975 cohorts, current active cigarette smokers had a significantly increased risk of subsequently being diagnosed with cervical neoplasia. For passive smoking, the relative risks of developing cervical neoplasia were in the direction of increased risk in both cohorts, but the association was stronger in the 1963 cohort and statistically significant only for this period. The results for the 2 cohorts were somewhat discrepant in the former smokers, with former smokers showing some evidence of increased risk of cervical neoplasia in the 1963 cohort (aRR 1.7) but not in the 1975 cohort (aRR 1.1).

The results of the present study thus corroborate previous evidence documenting an association between active smoking and cervical neoplasia.[5,6] Our results also point toward a role for passive cigarette smoking as a risk factor for cervical neoplasia. Although the risk estimates varied considerably between the 2 cohorts, even the weaker association observed in the 1975 cohort is of public health concern if it is genuine. The higher risk observed in the 1963 cohort compared with the 1975 cohort does not seem to be due to a greater intensity of exposure to passive smoking, because the median exposure level was greater in the 1975 cohort (20 cigarettes per day) than in the 1963 cohort (15 cigarettes per day). The risks associated with passive smoking were less than those observed for active cigarette smoking, as expected given the lower doses of exposure to carcinogens in cigarette smoke from passive as compared with active smoking. To give an indication of how the relative risks estimated in the present study contributed to the population burden of cervical neoplasia in these cohorts if the observed associations were causal, 37% of cervical neoplasia in the 1963 cohort could be attributed to active plus passive cigarette smoking, with 13% due to passive exposure to cigarette smoke. The corresponding figures for the 1975 cohort were 17% and 4%, respectively.

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The present investigation had several advantages that have been uncommon in previous investigations, including the population-based, prospective cohort study design. However, a number of limitations should be kept in mind when assessing the evidence provided by this study. A major deficiency was the lack of measurement of passive smoke exposure outside the home. The proportion of women working outside of the home increased during the study periods,[23] likely diminishing the importance of household passive smoke exposure with the passage of time. We lacked the information to account for some potential confounding variables, such as number of sexual partners, parity, and other sexually transmitted diseases that reflect potential exposure to and infection with oncogenic strains of human papillomavirus. In the absence of this information the findings were prone to overestimating risks because smokers are more likely to have high-risk sexual behavior profiles.[24] Hence, adjusting for sexual history would be expected to attenuate any observed association. However, this seems an unlikely explanation for the pattern of associations observed in the present study. Although more complete information would have been desirable, a measure of the study's internal validity is that the observed associations for education, marital status, and religious attendance were in the direction expected based on previous research. Being separated or divorced, completing fewer years of school, and attending religious services less frequently (1963 cohort only) were risk factors for cervical neoplasia. Furthermore, the prevalence of cigarette smoking at baseline followed the expected patterns according to marital status[25,26] and religious attendance.[27] As expected, statistically adjusting for these factors did attenuate the relative risks. We statistically corrected for factors associated with migration from the county to allay concerns about the passive follow-up of the study cohorts. This approach minimizes concerns about differential losses to follow-up introducing a major bias, but the possibility of some residual bias remains. To the extent that differential losses to follow-up were not completely accounted for, it is likely that the residual error would be in the direction that would bias our results toward the null. The present study investigated the associations of active and passive smoking with respect to invasive cervical carcinoma and cervical carcinoma in situ. To the extent that active and passive smoking are also associated with cervical intraepithelial neoplasia (CIN) II and CIN III, not accounting for women who developed CIN II/III and who did not progress to in situ or invasive disease could lead to RR estimates closer to the null value of 1 than may have otherwise been the case.

The results of the study provide prospective data suggesting that passive smoking is also associated with increased risk of cervical neoplasia. The evidence from the earlier 1963 cohort was stronger, but the evidence from the 1975 cohort was also compatible with the link between passive cigarette smoking and the risk of developing cervical neoplasia. Considered in total, the results of this large, community-based prospective cohort study strengthens previous evidence that implicates active cigarette smoking as a risk factor for cervical neoplasia. The results also add data from a prospective cohort study to a growing body of knowledge from case-control studies suggesting that passive exposure to cigarette smoke may also contribute to cervical neoplasia.

REFERENCES

1. Winkelstein W. Smoking and cervical cancer—current status: a review. Am J Epidemiol 1990;131:945–57.
2. Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. J Intern Med 2002; 252:206–24.
3. Ho GYF, Kadish AS, Burk RD, Basu J, Palan PR, Mikhail M, Romney SL. HPV 16 and cigarette smoking as risk factors for high-grade cervical intraepithelial neoplasia. Int J Cancer 1998;78:281–5.
4. Olsen AO, Dillner J, Skrondal A, Magnus P. Combined effect of smoking and human papillomavirus type 16 infection in cervical carcinogenesis. Epidemiology 1998;9: 346–9.
5. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Atlanta (GA): U.S.D.H.H.S., Centers for Disease Control and Prevention, Office on Smoking and Health; 2004.
6. International Agency for Research on Cancer. Tobacco smoking and involuntary smoking. IARC Monograph No. 83. Lyon: IARC Press; 2003.
7. McCann MF, Irwin DE, Walton LA, Hulka BS, Morton JL, Axelrad CM. Nicotine and cotinine in the cervical mucus of smokers, passive smokers, and nonsmokers. Cancer Epidemiol Biomarkers Prev 1992;1:125–9.
8. Poppe WA, Peeters R, Daenens P, Ide PS, Van Assche FA. Tobacco smoking and the uterine cervix: cotinine in blood, urine and cervical fluid. Gynecol Obstet Invest 1995;39:110–4.
9. Szarewski A, Jarvis MJ, Sasieni P, Anderson M, Edwards R, Steele SJ, Guillebaud J, et al. Effect of smoking cessation on cervical lesion size. Lancet 1996;347:941–3.
10. Prokopczyk B, Cox JE, Hoffmann D, Waggoner SE. Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers. J Natl Cancer Inst 1997;89:868–73.
11. Eppel W, Worda C, Frigo P, Manavi M, Czerwenka K. The influence of cotinine on interleukin 6 expression in smokers with cervical preneoplasia. Acta Obstet Gynecol Scand 2000;79:1105–11.

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12. Szarewski A, Maddox P, Royston P, Jarvis M, Anderson M, Guillebaud J, Cuzick J. The effect of stopping smoking on cervical Langerhans' cells and lymphocytes. BJOG 2001;108:295–303.
13. Poppe WAJ, Ide PS, Drijkoningen MPG, Lauweryns JM, Van Assche FA. Tobacco smoking impairs the local immunosurveillance in the uterine cervix. Gynecol Obstet Invest 1995;39:34–8.
14. Buckley JD, Harris RW, Doll R, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2: 1010–5.
15. Hellberg D, Valentin J, Nilsson S. Smoking and cervical intraepithelial neoplasia. Acta Obstet Gynecol Scand 1986; 65:625–31.
16. Slattery ML, Robison LM, Schuman KL, French TK, Abbott TM, Overall JC, et al. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. JAMA 1989;261:1593–8.
17. Coker AL, Bond SM, Williams A, Gerasimova T, Pirisi L. Active and passive smoking, high-risk human papillomaviruses and cervical neoplasia. Cancer Detect Prev 2002; 26:121–8.
18. Tay S-K, Tay K-J. Passive cigarette smoking is a risk factor for cervical neoplasia. Gynecol Oncol 2004;93:116–20.
19. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, et al. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Control 2001;12: 797–802.
20. Comstock GW, Tonascia JA. Education and mortality in Washington County, Maryland. J Health Soc Behav 1978; 18:54–61.
21. Breslow NE, Day NE. Statistical methods in cancer research. Volume II. The design and analysis of cohort studies. IARC Scientific Publication No. 82. Lyon: International Agency for Research on Cancer; 1987.
22. Kinsey AC. Sexual behavior in the human female. Philadelphia (PA): Saunders Company; 1953.
23. Vatter RH. Women in the labor force. Stat Bull Metrop Insur Co 1994;75:2–10.
24. Lam TH, Stewart SM, Ho LM. Smoking and high-risk sexual behavior among young adults in Hong Kong. J Behav Med 2001;24:503–18.
25. Waldron I, Lye D. Family roles and smoking. Am J Prev Med 1989;5:136–41.
26. Kiefe CI, Williams OD, Greenlund KJ, Ulene V, Gardin JM, Raczynski JM. Health care access and seven-year change in cigarette smoking: the CARDIA Study. Am J Prev Med 1998;15:146–50.
27. Spangler JG, Bell RA, Knick S, Michielutte R, Dignan MB, Summerson JH. Church-related correlates of tobacco use among Lumbee Indians in North Carolina. Ethn Dis 1998; 8:73–80.

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