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SMOKING AND CERVICAL CANCER—CURRENT STATUS: A REVIEW

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Editor's note: *For a discussion of this paper, see page 958.*

It is four years since the evidence for an association between smoking and cervical cancer was reviewed (1). At that time, 18 studies provided relevant data (2–19). Fifteen studies supported the hypothesis that cigarette smoking and cervical cancer are associated and three studies did not. Of the three negative studies, one included smoking-related diseases among the controls (3), the second accepted the null hypothesis on the basis of a p value of 0.06 and has been criticized for its method of selecting controls and data analysis (10, 20), and the third was conducted in a township in Lesotho, in southern Africa (18), and provided insufficient information to evaluate the validity of ascertainment of possible risk factors in cases and controls. Of the 15 positive studies, four studies were cohort investigations (5, 6, 8, 19), one study (the first to report an association between cigarette smoking and cervical cancer) was cross sectional (2), and 10 studies were case-control designs (4, 7, 9, 11–17). Only three case-control studies controlled for lifetime numbers of sexual partners (12, 14, 15). One of these demonstrated a dose-response relation between amount smoked and cervical cancer after adjusting for age, numbers of sexual partners, age at first intercourse, socioeconomic status, and oral contraceptive use (15). Smoking dose was measured by pack-years smoked with six categories. Only two of the 15 studies were specifically designed to test for a smoking-cervical cancer association (14, 15). In both, an interaction between age and risk from smoking was demonstrated with younger cases, with a stronger association shown than for older cases. The 1986 review (1) also included consideration of the biologic plausibility of a smoking-cervical cancer association (21–27) and of the possible effects of unknown confounders on associations demonstrated in epidemiologic studies (22).

Despite the extensive epidemiologic and other evidence in support of the hypothesis of an association between smoking and cer-

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vical cancer available by 1986, the interpretation of the association has remained equivocal (28–32). Neither the International Agency for Research on Cancer (28) nor the US Public Health Service (29) list cervical cancer as smoking related. Nevertheless, in 1983, in a signed editorial in the *Journal of the American Medical Association*, Austin (31) concluded that the evidence at that time warranted a causal interpretation. A similar view has appeared in a British journal (32).

This paper will consider the 15 epidemiologic studies of cervical cancer and smoking that have been published since the last review (33–47). Two important studies of multiple primary cancers (48, 49), which bear on the biologic plausibility of the smoking-cervical cancer association and were missed previously, will then be reviewed. Selected recent studies that bear on the question of the biologic plausibility of an association between cervical cancer and smoking will also be considered (50–63).

Epidemiologic studies

In table 1, the 15 epidemiologic studies are listed according to study populations, confounding variables accounted for, maximum unadjusted and adjusted odds ratios, and presence or absence of dose response. All 15 studies were case-control in design. Table 1 is divided into two parts; in the upper portion, the four studies which do not support the smoking-cervical cancer hypothesis are tabulated (34, 36, 39, 43) and in the lower portion, the 11 studies which support the hypothesis are shown (33, 35, 37, 38, 40–42, 44–47).

In the first of the negative studies, controls were obtained by asking cases to name four female friends within 5 years of their own age (34). Such a selection procedure could easily produce a bias toward the selection of controls with similar social and behavioral characteristics, including smoking habits. In the second, a small study among Hispanic women (36), which included 39 cases of in situ and invasive cervical cancer and 39 controls, only six cases and two controls had ever smoked as many as 10 cigarettes per day. Although the odds ratio for smoking in this study was 2.3, the small numbers preclude considering it to be supportive of the hypothesis. In the third negative study, smoking status was unavailable for 37 percent of the cases and 66 percent of the controls (39). In the fourth, controls were also obtained by case nomination from among neighbors and friends (43).

Of the 11 studies in which a positive association between smoking and cervical cancer was demonstrated, six took account of both major confounders, lifetime number of sexual partners, generally accepted as the "proxy" for an infectious etiology and age at first intercourse, usually considered indicative of increased susceptibility at younger ages (37, 38, 41, 44–46). In three additional studies, only lifetime numbers of sexual partners were controlled (35, 42, 47). In all but one of these nine studies, the association remained after adjustment for confounders (44). The maximum adjusted odds ratios for the six studies which controlled for both major confounders varied between 2.6 (38) and 4.3 (46). Other confounders most frequently accounted for included education, frequency of Papanicolaou smears, and age.

Of the 11 studies that supported the hypothesis, eight reported a dose-response relation for the smoking-cervical cancer association (35, 37, 38, 40, 42, 45–47). Dose was measured variously; packs per day or cigarettes per day (35, 37, 42, 45–47), years smoked (35, 37, 38, 42), and pack-years (40, 47). One study reported no dose-response relation (41), and two studies did not report an investigation of this issue (33, 44). Five of the 11 studies provided data to compare odds ratios for ex-smokers with current smokers (35, 38, 41, 46, 47). In each, unadjusted odds ratios for ex-smokers were intermediate between nonsmokers and current smokers. Two studies provided odds ratios for ex-smokers and current smokers

after adjustment for major confounders (46, 47). In these two studies, by Brisson et al. (46) and Slattery et al. (47), ex-smokers had odds ratios of 1.9 and 1.4 and current smokers had odds ratios of 3.5 and 3.4, respectively.

Five of the 11 studies utilized cases of invasive cancer of the cervix exclusively (37, 40, 42, 44, 45). Four included both in-situ and invasive cancer (33, 35, 38, 47). Two studies included only in-situ cases (41, 46). The association with smoking was observed to be equally strong with dose-response effects for both in-situ and invasive cancer.

The most recently published study of the smoking-cervical cancer hypothesis reported increased risk among women exposed to passive smoke (47). Women exposed to ≥3 hours of passive smoke per day compared with women unexposed to passive smoke had an adjusted odds ratio of 3.0 (numbers of cigarettes smoked by exposed women adjusted to distribution of

TABLE 1

Selected results of epidemiologic studies of smoking and cervical cancer, 1984–1989

Ref. no.	Study population	Confounders controlled		Maximum odds ratio†		Dose-response relation
		Major*	Other	Unadjusted	Adjusted	
	Studies not supporting the smoking-cervical cancer hypothesis					
34	156 Cases 299 Controls			1.3		
36	39 Cases 39 Controls			2.3		
39	126 Cases 1,914 Controls	A, B	6	1.0		No
43	153 Cases 153 Controls	B	3		1.0	No
	Studies supporting the smoking-cervical cancer hypothesis					
33	165 Cases 2,788 Controls			2.8		
35	210 Cases 317 Controls	A	3	2.5	3.7	Yes
37	200 Cases 200 Controls	A, B	5	3.7	($p < 0.001$)	Yes
38	413 Cases 413 Controls	A, B	5	3.2	2.6	Yes
40	1,174 Cases 2,128 Controls		4	1.8	1.8	Yes
41	140 Cases 280 Controls	A, B	1	4.7	($p < 0.0003$)	No
42	481 Cases 801 Controls	A	6	2.6	1.9	Yes
44	46 Cases 51 Controls	A, B	2	2.9	($p > 0.05$)	
45	225 Cases 435 Controls	A, B	4	2.9	2.7	Yes
46	247 Cases 137 Controls	A, B	1	5.7	4.3	Yes
47	266 Cases 408 Controls	A	3	10.1	3.4	Yes

* A, lifetime number of sexual partners; B, age at first sexual intercourse.

† For certain studies (37, 41, 44), adjusted odds ratios were not reported. For these, the p value of the regression coefficient is tabulated.

unexposed). The odds ratio for nonsmokers was slightly higher than for smokers, 3.4 and 2.6, respectively. Because no other studies have evaluated the association of passive smoking and cervical cancer, this issue will not be given further consideration in this review.

To more clearly demonstrate the strength of the smoking-cervical cancer association, data from a recently published study by Brisson et al. (46) have been tabulated in table 2. Brisson et al. (46) were interested in examining the associations between established risk factors for cervical cancer and their possible associations with cervical condylomata, because both may be etiologically dependent on infection by human papillomaviruses (56). Only data relevant to in-situ cancer have been included in table 2. The dose-response association between current numbers of cigarettes smoked and the odds ratios adjusted for numbers of sexual partners and age at first intercourse are clearly shown. The adjusted odds ratio for ex-smokers is also elevated, although less so than for current smokers of <20 cigarettes/day. To provide an indication of the amount of confounding generated by age at first intercourse and numbers of sexual partners, crude odds ratios were calculated for the published data and are shown in table 2. The differences between the crude and adjusted odds ratios indicate that confounding was not a major contributor to the observed associations. The smoking-adjusted odds ratios of 2.4 and 2.2 for 2–3 and ≥4 lifetime numbers of sexual partners and 1.6, 1.6, and 1.9 for ages 19–20, 17–18, and ≤16 years at first intercourse were both strongly, and independently, associated with cervical cancer in this study.

As indicated above, the association between numbers of sexual partners and risk of developing cervical cancer is usually interpreted as evidence for an etiologic role of an infectious agent, presumably a virus. The positive association between cigarette smoking and cervical cancer is usually interpreted as evidence for an etiologic role for a chemical carcinogen. The possible interaction of chemical and viral agents in carcinogenesis was first demonstrated by Rous and Kidd (23) in their classical study published in 1938. These investigators showed that the coal tar-induced benign skin lesions of rabbits were rapidly converted into malignant tumors when rabbit papillomavirus was injected into the blood stream of the experimental animals. Herpesviruses and papillomaviruses have been proposed as viral carcinogens for cervical cancer (56). However, only one epidemiologic study, that of Mayberry (35), has directly addressed the possibility of a biologic interaction between viral infection, smoking, and cervical cancer.

Mayberry (35) investigated 204 cases and 313 controls who had previously participated in a seroepidemiologic investigation of herpesvirus type 2, chlamydia trachomatis infections, and cervical cancer devel-

TABLE 2

*Crude and adjusted odds ratios (and 95 percent confidence intervals) for cigarette smoking and intraepithelial cancer of the cervix**

Variable category	No. observed		Crude odds ratio	Adjusted† odds ratio	95% confidence interval
	Cases	Controls			
Nonsmoker	50	71	1.0	1.0	
Ex-smoker	26	13	2.8	1.9	0.9–4.3
Current smokers (cigarettes/day)					
<20	55	24	3.2	2.6	1.4–4.8
≥20	116	29	5.7	4.3	2.4–7.7

* Adapted from Brisson et al. (46).

† Adjusted for age, age at first intercourse, and lifetime number of sexual partners.

opment. Most of the cases were cervical dysplasia although 19 were classified as in-situ or invasive carcinoma. No association was found between herpesvirus type 2 infection and cervical abnormalities, while a strong association was revealed with smoking. In a multiple logistic regression analysis, these associations were adjusted for age, education, and lifetime numbers of sexual partners. The analysis revealed no interactions (multiplicative or additive) between any of the associated variables. Compared with nonsmokers, past smokers had an adjusted odds ratio of 1.9 and current smokers had an adjusted odds ratio of 3.7 (odds ratios were adjusted for age, education, lifetime number of sexual partners, and serostatus for herpesvirus type 2).

A valuable measure of association which depends on both the relative risk of an etiologic factor and its prevalence in the population is the attributable risk proportion. The attributable risk proportion is the proportion of the incidence of a disease which is due to some particular risk factor or etiologic agent. Presumably, removal of exposure to such a factor would reduce the incidence of the disease accordingly. Only one of the 26 reported epidemiologic studies which have supported the smoking-cervical cancer hypothesis contains an estimate of the attributable risk proportion for cigarette smoking (37). Seven factors were found to contribute significantly to risk. The highest adjusted odds ratios were 7.2 for years since last Papanicolaou smear, 4.2 for smoking, and 3.2 for sexual partners before age 20 years. The adjusted population attributable risk proportions for these independent variables were 55.3 percent, 45.9 percent, and 28.6 percent, respectively. Each of these adjusted population attributable risk proportions can be interpreted as the proportion of disease that could be eliminated if all subjects were exposed to the factor at some "no risk" level. The seven variables accounted for more than 90 percent of the risk.

The original hypothesis of an association between cigarette smoking and cervical cancer was partially based on the observation that most, if not all, smoking-related cancers were predominantly of squamous cell histology (64). Of the 26 studies that have supported the hypothesis, only the study by Brinton et al. (42) has addressed this issue. In a multicenter case-control study of 481 invasive cervical cancer patients and 801 population controls, Brinton et al. (42) evaluated risk factors according to the histologic type of the cancers. Substantial differences in risk factors were reported between cancers of various cell types. The epidemiology of squamous and adenosquamous cell cancers resembled that found in other studies and adenocarcinomas followed a different pattern. For cigarette smoking, only squamous cell carcinomas showed a statistically significant association with smoking.

Multiple primary cancers

When the smoking-cervical cancer hypothesis was proposed, one of the reasons advanced was the observation of a strong geographic correlation between cancer of the lung in males and cancer of the cervix in females (65). It was reasoned that cancers that share a common geographic distribution might also share common etiologies. Similarly, one might expect a clustering in individuals of cancers etiologically related to some particular exposure. Two large studies of multiple primary cancers provide relevant data (48, 49). Bailar (48) followed up 3,008 women with cervical cancer registered in the Connecticut Tumor Registry between 1935 and 1951; 91 patients had subsequent nonuterine primary cancers. Strict criteria were used to rule out metastatic tumors. Expected numbers of subsequent site-specific primary tumors were calculated from the age-sex-specific incidence rates for nonuterine sites in the Connecticut Tumor Registry experience for the period 1935–1951. Newell et al. (49) drew their cases from the Charity Hospital of Louisiana at New Orleans Tumor Registry. These investigators followed up 4,871 cases of cervical cancer and identified 230

subsequent primary cancers of nonuterine sites. They too used stringent criteria to rule out metastatic secondary tumors. Their expected numbers of site-specific second cancers were based on the experience of the Charity Hospital Tumor Registry.

Data from the two studies are shown in table 3, which has two parts. In the upper part of the table, data regarding numbers of patients, person-years of observation, and second primary cancers are shown for the two studies. In the lower portion of the table, observed and expected numbers and rates of second primary cancers are shown according to whether or not the second primary cancer sites are listed as smoking related in the latest International Agency for Research on Cancer report on smoking and cancer (28).

Although the rate of second primary cancers, based on person-years of follow-up, was slightly higher in the Charity Hospital Tumor Registry data (7.3/1,000 person-years) than in the Connecticut Tumor Registry data (6.3/1,000 person-years), the observed to expected ratios for the various secondary sites were fairly similar in the two cohorts. The higher overall incidence rate in the Charity Hospital cohort may be attributable to the lower economic status of that hospital's clientele, more than half of whom were black, compared with the predominantly white middle class population of Connecticut.

The observed to expected ratios for second cancers at three of the four sites designated by the International Agency for Research on Cancer as caused by smoking were greater than 2.0 in both cohorts. Second primary cancers of the pancreas did not exceed an observed to expected ratio of 1.0 in either cohort. Second primary can-

TABLE 3

*Selected data from two studies of subsequent primary cancers of nonuterine sites in women with an initial cancer of the uterine cervix**

Characteristic	Connecticut Tumor Registry (48)			Charity Hospital Tumor Registry (49)		
No. of patients followed	3,008			4,871		
Person-years	14,461			31,332		
Average follow-up (years)	4.8			6.4		
No. with 2nd primary	91			230		
2nd primary/1,000 person-years	6.3			7.3		
2nd primary cancer site	Observed	Expected	Observed/ Expected	Observed	Expected	Observed/ Expected
Smoking-related 2nd primary sites†						
Oral cavity and esophagus	3	1.1	2.7	8	3.6	2.2
Lung	7	1.9	3.7	22	4 1	5.4
Bladder	4	1.5	2.7	13	5.8	2.2
Pancreas	0	2.2		3	4.6	0.7
Total	14	6.7	2.1	46	18.1	2.5
Non-smoking-related 2nd primary sites						
Stomach	4	6.6	0 6	5	8.8	0.6
Large intestine	10	9.4	1.1	9	15.0	0.6
Ano-rectum	7	4.8	1.4	14	10.3	1.4
Breast	17	19.9	0.8	43	41.2	1.0
Central nervous sytem	1	0.8	1.2	5	1.7	2.9
Skin	18	5.5	3 3	24	12.5	1.9
Total	57	47.2	1.2	100	89.5	1.1

* Adapted from Bailar (48) and Newell et al. (49).

† Smoking-related second primary sites as listed by the International Agency for Research on Cancer (28).

cers of the lung had the highest observed to expected ratios in each cohort, 3.7 in the Connecticut Tumor Registry and 5.4 in the Charity Hospital Tumor Registry. The combined observed to expected ratios for the smoking-related cancers were 2.1 in the Connecticut Tumor Registry data and 2.5 in the Charity Hospital Tumor Registry data.

The International Agency for Research on Cancer does not provide an explicit list of cancers which are not considered to be causally related to smoking. In the latest report, data regarding smoking and cancers of the stomach, liver, cervix, endometrium, and breast are reviewed and a causal association is rejected for all. Table 3 includes, therefore, all second primary cancers of nonuterine sites reported from both the Connecticut and Charity Hospital Tumor Registries that are not listed as causally associated with smoking by the International Agency for Research on Cancer. Four of the six second primary cancers listed—stomach, large intestine, ano-rectum, and breast—have observed to expected ratios less than 1.5 in both studies. Second primary cancers of the central nervous system have an observed to expected ratio in the Charity Hospital data of 2.9 although the observed to expected ratio in the Connecticut data, at 1.2, is not elevated. It should be noted that the expected numbers of central nervous system cancers in the two cohorts are very small, 1.7 and 0.8, respectively (smallest for any of the non-smoking-related second primary sites). In both the Connecticut and Charity Hospital cohorts, second primary cancers of the skin have elevated observed to expected ratios—3.3 and 1.9, respectively. However, there is a strong possibility, suggested by Bailar (48) that skin cancers are underreported in registries and overreported in follow-up data, producing a biased observed to expected ratio. For the six cancers not listed as smoking-related by the International Agency for Research on Cancer, the combined observed to expected ratios were 1.2 for the Connecticut Tumor Registry and 1.1 for the Charity Hospital Tumor Registry.

Biologic plausibility

In previous reviews of studies regarding the smoking-cervical cancer hypothesis, three types of evidence have been considered in support of the biologic plausibility of the hypothesis. First, evidence that most smoking-related cancers are predominantly of squamous cell histology (the histologic makeup of most cervical cancers) has been examined (21, 22). Second, the phenomenon of co-carcinogenesis (see above) has been considered (23). Third, extensive evidence indicating that chemicals present in cigarette smoke, including established carcinogens, can be absorbed in the lungs and transported to distant sites by the blood has been presented (24–27). Recently, more direct evidence that agents absorbed from cigarette smoke may have an effect on cervical mucosa has become available (50–55). Additionally, nutritional studies indicating that susceptibility to carcinogenic agents may be influenced by host levels of vitamin A and its precursor beta-carotene have been reported (57–63).

Recent collaborative studies (50, 51) have confirmed that a high degree of sensitivity and specificity (>95 percent) can be achieved in distinguishing smokers from nonsmokers by a radioimmunoassay of cotinine in cervical flushes. Furthermore, in one study (50), quantitative levels of cotinine reflected recent smoking intensity. In a subsequent study, some of the same investigators (51) showed that, in women with in-situ cancer of the cervix, cotinine and nicotine were actually more concentrated in cervical mucus than in serum. Previously, it had been shown that, in smokers, nicotine concentrations in cervical mucosa were much greater than in serum and it was suggested that other hydrophylic constituents of tobacco smoke might be selectively accumulated as local carcinogens in the cervix (27).

Several investigators have now shown

reductions in numbers of Langerhans' cells in the cervical epithelium of women with in-situ cancer which might influence local cellular immunity and susceptibility (52, 53). Langerhans' cells are epithelial cells derived from bone-marrow which are important in presenting antigen to T lymphocytes and are considered to play a role in immune surveillance and response to neoplastic transformation (54). Reductions in numbers of Langerhans' cells in the cervical epithelium of smokers have also been observed and these changes have been shown to be independent of similar changes associated with infection by human papillomaviruses, the current principal viral etiologic candidate (56). Barton et al. (55) studied associations between both cigarette smoking and papillomavirus infection and Langerhans' cell counts in normal cervical epithelium and in the cervical epithelium of women with both in-situ cancer and papillomavirus infection. Selected data from that study are shown in table 4. They show that numbers of Langerhans' cells in the normal or neoplastic cervical epithelium of smokers are substantially lower than in the epithelium of nonsmokers or former smokers. Furthermore, the numbers of Langerhans' cells in neoplastic epithelium are lower than in normal epithelium in strata formed by smoking status.

Recently, the possibility that a deficiency of dietary vitamin A may be etiologically related to epithelial cancer has received considerable attention (57). Several studies of cervical cancer have addressed this issue and have shown a protective effect for consumption of foods containing high vitamin A and beta-carotene content (17, 58). However, studies in which serum levels of retinol and beta-carotene were measured have yielded varying results. In two studies (59, 60), lower levels of retinol and/or beta-carotene were associated with risk of cervical cancer compared with controls. In two other studies (61, 62), no differences in risk were observed. More recently, the issue has been reinvestigated with particular attention to the possible association of smoking with serum levels of retinol and beta-carotene (63).

In a study of 38 in-situ and 32 invasive cases of cervical cancer, each age-matched with two controls, Harris et al. (63) found no difference in serum retinol between the cases at any stage and the controls. However, the in-situ cases had significantly lower mean levels of beta-carotene than controls after adjustment for current smoking status, current oral contraceptive use, number of lifetime sexual partners, and social class. The adjusted geometric mean values were 213.1 μg/liter for cases and 291.6 μg/liter for controls. Smokers who were not current users of oral contraceptives had increased levels of serum retinol compared with controls (means, 564.8 and 509.8 μl/liter, respectively) and decreased levels of beta-carotene (means, 229.6 and 367.3 μg/liter, respectively). Among current oral contraceptive users, there was no dif-

TABLE 4

*Median numbers of Langerhans' cells in cervical epithelium according to cigarette smoking, histology, and human papillomavirus (HPV) infection**

Smoking status	Normal epithelium		In-situ cancer and HPV	
	No. observed	Cell count†	No. observed	Cell count
Never	18	137.8	11	44.5
Former	3	115.7	10	37.0
Current	15	45.4	34	21.6
Test for trend	$p = 0.004$		$p = 0.02$	

* Adapted from Barton et al. (55).

† Langerhans' cells identified by immunocytochemical staining for T6 (CD1) antigen and reported as median number cells/mm^2.

ference between serum levels of retinol in cases and controls, and the difference between levels of beta-carotene was reduced.

Discussion

No hypothesis is tenable if rigorous studies fail to provide supportive evidence. Thus, it is necessary to evaluate the validity of those studies which do not support the smoking-cervical cancer hypothesis before proceeding to consideration of the supportive studies. Four of the 15 epidemiologic studies reviewed here did not support the hypothesis. Three were designed to test hypotheses regarding the causal associations of other risk factors, viz., infection by papillomaviruses (34), sexual practices of spouses (36), and contraceptive use (43). Smoking practices in these studies were assessed incidentally and only one study (43) included smoking in a multivariate analysis to evaluate the independent contribution of various risk factors. The fourth negative study (39) was designed to evaluate risk factors, including smoking, for women under 20 years of age. It is quite possible that a smoking effect would require a greater latency than is available in such young cases. As indicated previously, all four of these studies have serious methodological shortcomings as well. Considered individually or together, these four studies do not provide substantial evidence to refute the smoking-cervical cancer hypothesis.

Of the 11 epidemiologic studies which supported the smoking-cervical cancer hypothesis, only two studies (33, 44) did not include smoking as one of the major risk factors under study. In one study (33), epidemiologic characteristics of cases and controls were evaluated in a nested case-control study derived from a large cohort study designed to evaluate the relation between herpesvirus type 2 infection and cervical neoplasia. In this study, no adjustment was made for possible confounding variables. In the second, the primary objective was the evaluation of human papillomavirus and cervical cancer (44). Of the remaining nine, all were designed to evaluate the risk conferred by cigarette smoking for cervical neoplasia.

Although this review does not include studies of smoking and cervical dysplasia, generally considered a precursor of cancer, one case-control study examined the association of smoking and certain other putative risk factors in women with cervical dysplasia (66). In that study, smoking remained a strong risk factor after adjustment for both numbers of sexual partners and age at first sexual intercourse (both strongly associated with risk of cervical dysplasia).

In evaluating the validity of associations demonstrated in epidemiologic investigations, three issues are of primary importance, i.e., the control of confounding variables, the presence or absence of a dose-response relation of the independent variable to the outcome, and the biologic plausibility of the association. As already noted, the most important potential confounding variables for the smoking-cervical cancer association are number of sexual partners, a proxy for an infectious agent, and age at first sexual intercourse, an indicator of increased susceptibility at younger ages. Five of the six studies (37, 38, 41, 45, 46) that controlled for both of these variables found the association to persist after adjustment by logistic regression. Three of the five studies (38, 45, 46) reported adjusted odds ratios (two reported only adjusted p values, both $p < 0.001$), and, in each, adjustment lowered the maximum values slightly, 3.2 to 2.6, 2.9 to 2.7, and 5.7 to 4.3. A reduction in the adjusted odds ratio is to be expected if there is any interaction or colinearity between the confounders and the variable under examination. One to five additional variables were also adjusted for in each of these three studies.

A persistent problem in evaluating the role of confounding variables is the possibility that an association may be due to a variable which was not measured or controlled in the particular investigation. This question was raised in one of the publica-

tions previously reviewed (8). This issue has been examined by several investigators (22, 67, 68) and has been reviewed by Schlesselman (69). The consensus of these investigators is that large values for relative risks (or odds ratios) are unlikely to be explained by some unknown confounder. One group of investigators (22) provided a simple method for estimating the relative risk (odds ratio) required of an unknown confounder to explain an observed association, viz., double the relative risk to be explained and then subtract 0.5. Thus, to explain the adjusted odds ratio estimate of the relative risk of 4.3 for smokers of more than 20 cigarettes per day observed in the study by Brisson et al. (46), the odds ratio of an unknown confounder would have to be 8.1. This estimation procedure also requires that the unknown confounder have a prevalence greater than the high level prevalence of the observed risk factor.

Eight of the nine studies with data on dose found a dose-response relation (35, 37, 38, 40, 42, 45–47). All five studies which included an analysis of risk among exsmokers found that their risks were higher than those of nonsmokers but lower than for current smokers (35, 38, 41, 46, 47). This pattern has been observed for other smoking-cancer associations which have been judged causal (70). The consistency of the dose-response relation between smoking and cervical cancer provides considerable support for a causal interpretation of the association.

With respect to the biologic plausibility of the smoking-cervical cancer association, this review has added several new dimensions to the previously cited mechanisms. Independent observations that three of four International Agency for Research on Cancer-designated smoking-related cancers occur as second primaries with significantly greater frequency than expected in women who have had a primary cancer of the uterine cervix is evidence supporting a common etiologic factor (48, 49). This inference is further strengthened by the observation, in these studies, that four major nonsmoking-related cancers did not occur as second primaries at greater than expected rates among women with primary cancer of the cervix. This clustering of smoking-related cancers in individuals is analogous to the previously reported geographic clustering of cervical and lung cancer (65).

The recently reported observations regarding the greater concentration of nicotine and cotinine in cervical mucus compared with serum in women with in-situ cancer indicates a more than passive response by the epithelial cells of the cervix to the blood-borne products of tobacco smoke absorbed in the lung (50, 51). Furthermore, the depression of Langerhans' cells in the cervical epithelium of smokers and women with in-situ cervical cancer provides a possible mechanism for the carcinogenic role of absorbed tobacco products either as initiating or promoting factors (52–55).

Although an etiologic role for a deficiency of dietary vitamin A, or more specifically its precursor, beta-carotene, has been proposed for epithelial cancers (57, 58), the evidence in support of the hypothesis remains equivocal. However, to the extent that a deficiency of beta-carotene is a risk factor for cervical cancer, it provides another biologic pathway through which smoking could exert an effect. As indicated in this review, current smokers have significantly lower serum beta-carotene levels than nonsmokers (57–63).

Conclusions

During the past 24 years, 33 epidemiologic studies have provided data relevant to an association between cigarette smoking and cancer of the uterine cervix, and 26 of these studies have shown a positive association. All four cohort studies have reported an association and two have demonstrated a dose-response effect. In the seven case-control studies that failed to show an association between smoking and cervical cancer, serious questions can be raised regarding the adequacy of the meth-

odologies employed to demonstrate associations. Studies of this association have been conducted in a variety of populations, sometimes using data collected for other purposes and sometimes using study designs specifically developed to address this issue. Of the last 11 studies showing an association, nine were designed to test the smoking-cervical cancer hypothesis.

Additional studies have examined the question of biologic plausibility and have provided substantial supporting evidence. The possibility that the association is due to confounding by an unknown factor has been investigated and found to be quite improbable. Thus, the evidence would seem to support the conclusion that the association between cigarette smoking and cervical cancer is causal and that a chemical carcinogen contained in tobacco smoke is responsible for a substantial proportion of the incidence of this disease. This conclusion does not, however, depreciate the importance of the established association between numbers of sexual partners and risk of cervical cancer, interpreted as evidence for an infectious causal agent. The evidence regarding the extent of biologic interaction between these causal agents remains equivocal as does the identity of the putative chemical carcinogen and specific virus (32, 71). Future epidemiologic research on cervical cancer should incorporate appropriate biochemical and virologic components in the investigations.

While proposing that the cumulative evidence regarding the association of cigarette smoking and cervical cancer supports a causal inference, I am not unaware of the current controversy regarding the use of epidemiology to establish causality (72). However, my purpose in reviewing the data regarding the association of cigarette smoking and cervical cancer is to determine whether public health action is indicated. This requires a pragmatic definition of causation, as proposed by Lilienfeld and Lilienfeld (73): "A causal relationship would be recognized to exist whenever evidence indicates that the factors form part of a complex of circumstances that increase the probability of the occurrence of disease and that a diminution of one or more of these factors decreases the frequency of that disease." The importance of recognizing cervical cancer as a smoking-related disease, as well as as a sexually transmitted disease, is no less today than it was seven years ago when Austin (31) published the first editorial on the causal nature of the smoking-cervical cancer association. The reasons for the delayed acceptance of this etiology are obscure. To what extent this has interfered with the control of this important cancer is also not known. What is apparent is that cervical cancer should be added to the list of smoking-related diseases. More importantly, strategies directed toward the control of cervical cancer should include appropriate consideration of the role played by cigarette smoking in contributing to risk for this major cancer.

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