

Original Contributions

CERVIX CANCER AND CIGARETTE SMOKING: A CASE-CONTROL STUDY¹

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Stellman, S. D. (American Health Foundation, 320 E. 43rd Street, New York, NY 10017), H. Austin, and E. L. Wynder. Cervix cancer and cigarette smoking: A case-control study. *Am J Epidemiol* 111:383-388, 1980.

The association between cervix cancer and cigarette smoking was examined among 332 white cases and 1725 white controls. Cases were of lower socioeconomic status (SES) and smoked more than controls. After adjustment for both age and SES, no significant association was observed between cervix cancer and cigarette smoking. Many variables related both to cigarette smoking and to known risk factors for cervix cancer are sources of confounding and inadequate control for these variables may cause an overestimation of the effect of smoking.

biometry; cervix neoplasms; smoking

Although cervical cancer is not generally thought to be caused by cigarette smoking, a number of studies have suggested an association between cervix cancer risk and cigarette smoking (1-5). Renewed speculation concerning the possible causality of this association was prompted by two unexpected observations from the Third National Cancer Survey (TNCS): 1) the odds ratio for cervix cancer appears to increase with increasing consumption of cigarettes (5), and 2) the incidence rates for lung cancer in men and cervix cancer in women appear to be correlated in the TNCS regions (6). Winkelstein (7) has suggested that the common factor linking the two diseases may be the

histologic type: predominantly squamous epithelial tissue.

Since cervix cancer risk is inversely related to socioeconomic status (SES) (8, 9), which may itself be related to cigarette smoking in women (10), the association between cervix cancer risk and cigarette smoking may be confounded. We present below evidence that confounding accounts for some of the association.

METHODS AND MATERIALS

Cases and controls were extracted from the records of a case-control study of smoking and health (11), conducted at Memorial Hospital in New York City and other hospitals in the cities of New York, Birmingham, Alabama, Los Angeles and San Francisco, California, and Philadelphia, Pennsylvania, from 1974 through 1977. In the master study, cases were patients with cancer of the lung, larynx, esophagus, mouth, or bladder. Controls were patients hospitalized for non-tobacco-related diseases who were matched to the index case on age, sex, race, hospital, and hospital status (semi-

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Abbreviations: RR, risk ratio; SES, socioeconomic status; TNCS, Third National Cancer Survey.

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private vs. ward). Diagnoses of neoplastic disease were histologically confirmed. Patients with cardiovascular disease or chronic obstructive pulmonary disease were specifically excluded (11).

For the present analysis, cases were white women with cancer of the cervix. These women had formerly been controls in the master study. The controls were white women hospitalized for non-neoplastic diseases. The analysis was restricted to women who had ever been married and who had either never smoked regularly or were current smokers and had smoked for at least 10 years. Ex-smokers were excluded.

To classify a woman according to SES, her education, occupation, and husband's occupation were considered and her SES was defined as the highest of these three variables. For this purpose, four educational levels (below high school graduate, high school graduate, some college, and college graduate) and four occupational levels (unskilled, semiskilled, skilled, and professional) were used to classify both men and women.

To control potential confounding, summary risk ratio estimates and tests of statistical significance were obtained by the Mantel-Haenszel method (12). In addition, various log-linear models were fitted to the data to test for the single and joint effects of different variables on disease status (13). The Kullback-Cornfield analysis of information approach (14) was used to test for statistical significance between smoking and disease, after control for other variables had been secured. In this method, the logit of cell probabilities is predicted by successive models, each model containing additional terms. The difference of the likelihood ratio goodness of fit statistic between two successive models is the criterion for the assessment of the statistical association between the new variable and disease status. A large difference (as measured by a chi-square test with appropriate degrees of freedom)

indicates that the variable just added contains significant "information" not already present in the preceding model. This process is analogous to a stepwise regression for continuous variables and secures control of potentially confounding variables.

RESULTS

Age, SES, and smoking. A total of 332 cases and 1725 controls were included in the study. The distributions of age, SES, and cigarette consumption among cases and controls are displayed in tables 1 and 2 and in figure 1. The mean age of cases and controls was 51 and 53 years, respectively. A higher proportion of cases than controls was in the two lowest SES categories ($p < 0.001$). A higher proportion of cases than controls smoked at each level above one-half pack per day ($p < 0.001$). Thus, cases were younger, of lower SES, and heavier cigarette smokers than the controls.

Risk ratio estimates. Risk ratio (RR) estimates and 95 per cent confidence intervals at each level of smoking are dis-

TABLE 1
Distribution of age among cervix cancer cases and controls

Age	Cases (%) (N = 332)	Controls (%) (N = 1725)
20-39	21.7	21.7
40-49	31.0	19.1
50-59	20.8	23.8
60-69	18.4	20.3
70-89	8.1	15.1

TABLE 2
Distribution of socioeconomic status among cervix cancer cases and controls

Socioeconomic status*	Cases (%) (N = 332)	Controls (%) (N = 1725)
1 (lowest)	19.6	13.2
2	30.7	17.1
3	41.6	50.8
4 (highest)	8.1	18.8

* See text for definition of categories.

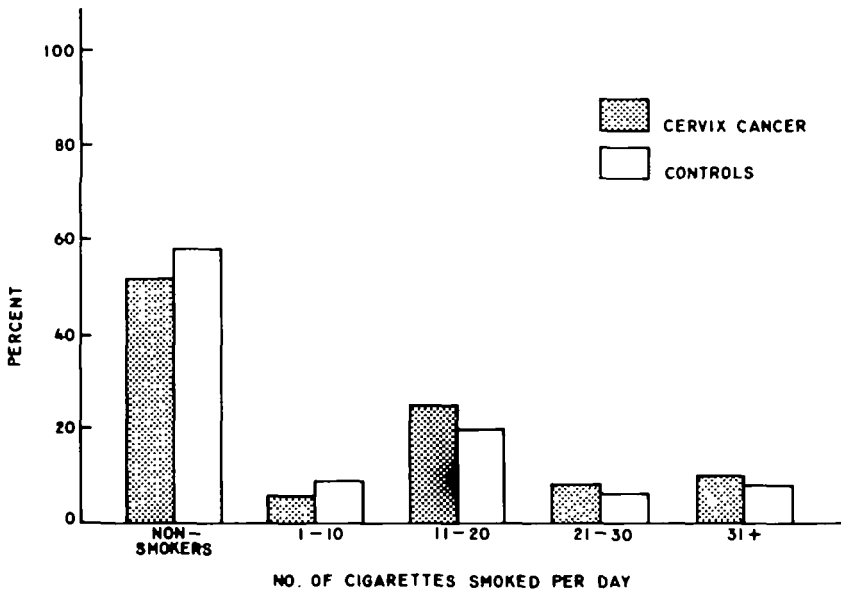


FIGURE 1. Distribution of cigarette consumption among 332 cervix cancer cases and 1725 controls.

played in figure 2 (referent non-smokers). Both the unadjusted estimates and estimates adjusted individually for age and SES, and jointly for both, are shown. The unadjusted estimates ranged from 1.4–1.6 for smokers of more than one-half pack per day. After Mantel-Haenszel adjustment for age and SES, the RRs ranged from 1.2–1.3. This represents a 50 per cent reduction in the estimated excess risk due to smoking.

The data were also analyzed by fitting successive log-linear models to the data and the results are displayed in table 3. SES was significantly associated with disease status after controlling for age ($G^2 = 41.1$, $df = 3$, $p < 0.001$). However, after controlling for both age and SES, smoking was not associated at the 5 per cent level of statistical significance ($G^2 = 8.6$, $df = 4$, $p = 0.06$).

DISCUSSION

The results reported here are similar to those obtained in the TNCS interview study in which an RR of 1.3 and 0.9 was found for whites and blacks, respectively. The TNCS estimates were adjusted for

age but not SES. (Our RRs for 143 black cases and 585 black controls were all below 1.0, ranging from 0.5–0.7. These estimates were not statistically significant, and increased towards 1.0 after Mantel-Haenszel adjustment.) The results of the TNCS study also confirmed the association between cervix cancer and low SES, which remained after adjustment for smoking (see reference 5, tables 7A and 11A). However, we did not observe a dose-response relationship for cigarette smoking as TNCS did, even though our results are based on 160 white women who were current smokers of at least 10 years' duration, while the TNCS results were based on 126 cases of all races and included ex-smokers who are more likely to be in higher SES groups (10).

Other factors

In the present study, SES may be a "marker" for sexually related variables which are of more direct etiologic importance and which may confound the association between cervix cancer and cigarette smoking. For example, our data set did not contain information on sexual ac-

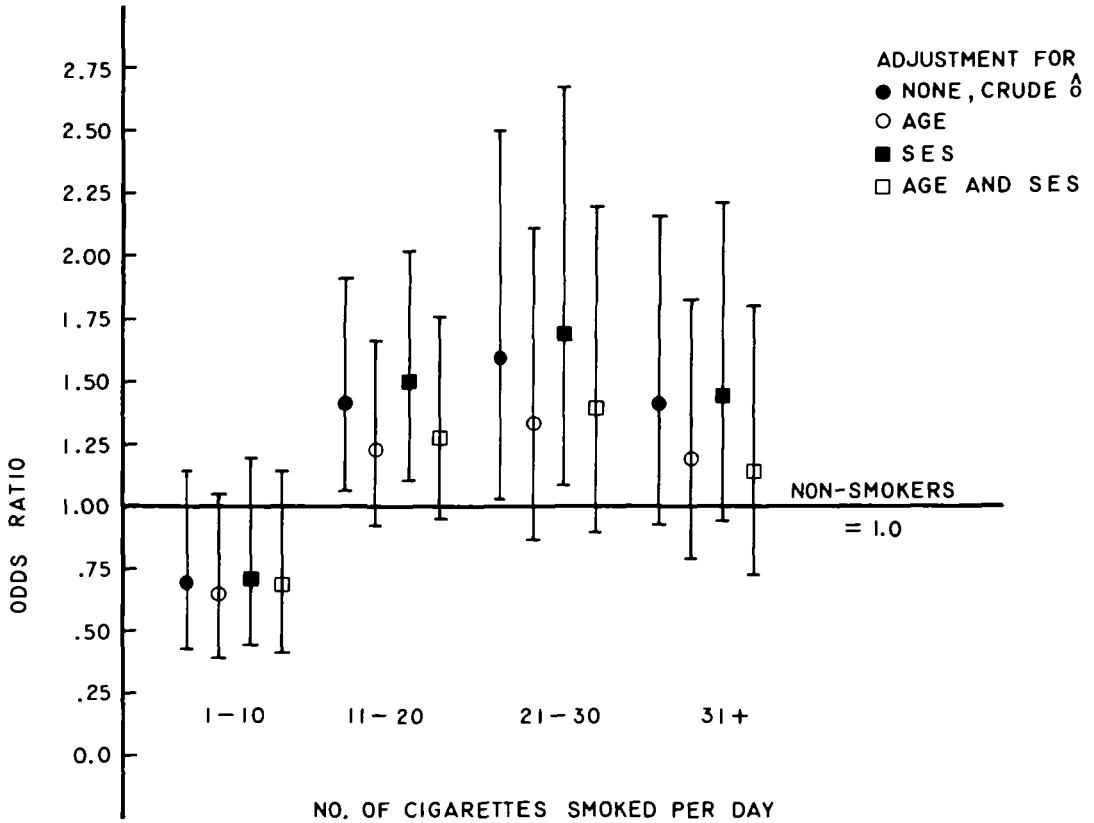


FIGURE 2. Risk ratio estimates for cervix cancer, relative to non-smokers, with 95 per cent confidence intervals. (SES, socioeconomic status.)

TABLE 3
Analysis of information for 332 cervix cancer cases and 1725 controls

Variables and levels				
A = cervix cancer (yes, no)				
B = smoking (0, 1-10, 11-20, 21-30, 31+ cigarettes/day)				
C = age (20-29, 30-39, 40-49, 50-59, 60-69, 70-89 years)				
D = socioeconomic status (SES) (1 = low; 2; 3; 4 = high)				
Model fitted*	Effect(s) tested	Incremental		
		G ²	df	p value
AC, BCD	SES (age already controlled)	41.1	3	<0.001
AC, AD, BCD	Smoking (age, SES already controlled)	8.6	4	= 0.06
AB, AC, AD, BCD				

* Notation is that of program BMDP3F, "Biomedical Computer Programs," University of California Press, 1977.

tivity, which is known to be a risk factor for cervix cancer (8, 9). Previous studies have shown that women with early sexual activity are more likely to smoke ciga-

rettes (2, 4). Thomas (2) estimated that the relative risk of "cervical pathology suggestive of neoplasia" in smokers (compared to non-smokers) was more than

twice as high among women who had conceived before marriage compared to those who had not. Thus, if we had been able to control for sexual variables, the apparent association between cervix cancer and cigarette smoking would probably have been reduced further. Furthermore, early sexual activity is also associated with frequency of oral contraceptive use which, in turn, has been associated with cigarette smoking (15, 16) as well as cervical dysplasia (17) and possibly cervical cancer (18). We have recently shown (19) that oral contraceptive use is dependent on age, SES, and other variables which are also related to cigarette smoking. Thus, the association between cervix cancer and cigarette smoking is probably confounded by many variables. Future studies of cervical cancer must address these issues.

Since this study was not designed to investigate the relationship between cigarette smoking and cervix cancer, there are some limitations in its interpretation. Specifically, cervix cancer "cases" were interviewed solely because they met criteria for inclusion as controls in the smoking and health study. They are therefore not representative of any readily identifiable population. However, for this reason, we are confident that the data are reasonably free of either response or interviewer bias and the possibility of a bias in the selection of the "cases" also seems unlikely.

CONCLUSIONS

Evidence for the causality of an association in an epidemiologic study is provided by the internal consistency of the data. While reduction of estimated RRs to just below the conventional level of statistical significance does not necessarily rule out a biologic association between cigarette smoking and cervix cancer, the lack of epidemiologic consistency within this data set does not support causation. To be specific, the associations found in our data

did not exhibit a dose-response relationship and were opposite in whites and blacks. Furthermore, there appear to be confounding variables which affect the association in an opposite manner in whites and blacks. In view of these results, a number of alternative conclusions regarding the association between cervix cancer and cigarette smoking can be considered:

- 1) The association is real, but its magnitude is small and therefore a consistent statistically significant association has not been found because of limitations in sample sizes and study designs.
- 2) The association is highly confounded.
- 3) There is no association and any observed is due to chance.

The results of this study seem to favor the second alternative and are not consistent with a causal hypothesis.

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