Exhibit 309

Cancer Incidence Among Women in the Workplace: A Study of the Association Between Occupation and Industry and 11 Cancer Sites

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Few studies of the occupational etiology of cancer have focused upon the risks that women experience in the workplace. In this case-referent study of 11 cancer sites (lung, colon, rectum, bladder, esophagus, liver, salivary gland, stomach, eye, melanoma of the skin, mesothelioma), 7686 women in the Detroit area were interviewed to obtain lifetime histories of employment, tobacco use, and adult health, as well as demographic information. The results provide both methodologic and substantive leads for future investigations of the association between women's employment and their risk of cancer. We found that 63% of respondents had a usual occupation of housewife. Methodologic issues are discussed about the implications of this finding for sample size and statistical analysis when conducting such studies. New observations that merit further investigation include an association between salivary gland cancer and employment in hairdressing shops, esophageal cancer and employment in restaurants, and bladder cancer and employment in computer manufacturing. Further research is needed to understand the occupational etiology of cancer among women; such studies must consider specific methodologic issues.

The study of occupation and its relationship to cancer incidence is often restricted to men and, more often than not, to white men. Women initially included in cohorts of workers are subsequently excluded from analysis because of insufficient numbers. As more women enter the workforce, especially jobs held traditionally by men, studies are needed to assess the relationship between occupational exposures and cancer development in women.

The number of studies concentrating on occupational risk factors for cancer in women is small. Most of them have been mortality studies.[1–12] Mortality studies are limited by single entries regarding occupation and industry and by lack of information on other critical risk factors such as smoking. This article, which presents results from a case-referent study conducted in the Detroit metropolitan area investigating occupational risk factors for 11 cancer sites, is concerned with workplace risks observed among female study subjects.[13]

Methods

The Occupational Cancer Incidence Surveillance Study (OCISS) is a population-based, case-referent investigation of occupational risk factors for selected cancers diagnosed from 1984 through 1991 among residents of the Detroit metropolitan area. Study subjects were identified through the Metropolitan Detroit Cancer Surveillance System, a participant in the Surveillance, Epidemi-

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ology, and End Results (SEER) program of the National Cancer Institute. The 11 cancer sites included in OCISS are lung, colon, esophagus, bladder, rectum, liver, salivary gland, stomach, eye, melanoma of the skin, and mesothelioma. Black and white men and women between the ages of 40 and 84 diagnosed with cancer at any of the study sites were enrolled in the study. Population controls were selected using random-digit dialing.[14] Potential controls were contacted using lists of randomly generated telephone numbers. Once interviewers contacted a working residential number, they recorded the age, gender, and race of all eligible adults in the household. One subject from the household was selected at random to be interviewed. Controls were frequency matched to cases by age (within 5 years), race, and gender.

Subjects or their surrogates were interviewed by telephone. The interview gathered information on lifetime occupational history, smoking history, medical history, residential history, and demographics. Occupation and industry data were coded using the three-digit 1980 US Census Bureau classification codes.[15] Grouped codes were created by combining three-digit codes for occupations or industries with similar work exposures. Usual occupation and industry were defined by summing the total number of months a person was employed in a specific occupation or industry over the entire work history, and then selecting the occupation or industry for which the person had accumulated the greatest number of months of employment. The unexposed group of occupations and industries was defined as those with the least potential for exposure to carcinogenic agents.[13]

This analysis reports the association between occurrence of the 11 cancer sites studied among women and (*a*) their usual occupation and industry, and (*b*) occupations and industries in which they were ever employed. All analyses were adjusted for the confounding effects of age, race, and pack-years of smoking. Pack-years of cigarette smoking were divided into five categories: 0; 1–29; 30–59; 60–89; 90+. Max-

TABLE 1
Participants in the Detroit Metropolitan Area, 1984–1991, by Subject Category and Race

Subject Category	Total Number	% Black	% White
Cases			
Lung	2,015	19.4	80.6
Colon	1,558	19.7	80.3
Bladder	627	14.1	85.9
Rectum	383	15.3	84.7
Stomach	292	26.7	73.3
Esophagus	289	42.4	57.6
Skin, melanoma	218	1.4	98.6
Liver	157	28.9	71.1
Salivary gland	83	14.3	85.7
Eye	62	—	100.0
Mesothelioma	30	15.4	84.6
Controls	1,972	21.7	78.3

TABLE 2
Response Rate of Participants in the Detroit Metropolitan Area, 1984–1991, by Respondent Type and Subject Category

Subject Category	Total Response Rate	% by Respondent Type		
		Subject	Surrogate for Ill Subject	Surrogate for Deceased Subject
Cases				
Lung	95.3	52.9	10.8	36.3
Colon	95.6	75.8	11.5	12.7
Bladder	96.0	75.7	13.5	10.8
Rectum	95.8	80.6	12.3	7.1
Stomach	94.8	58.5	13.4	28.2
Esophagus	95.5	49.6	19.2	31.2
Skin, melanoma	97.7	88.3	8.4	3.3
Liver	90.4	30.3	9.1	60.6
Salivary gland	92.8	85.7	7.8	6.5
Eye	88.7	76.4	3.6	20.0
Mesothelioma	86.7	38.5	15.4	46.1
Controls	98.6	96.7	3.2	0.1

TABLE 3
Participants in the Detroit Metropolitan Area, 1984–1991, by Subject Category and Usual Occupation of Housewife

Subject Category	% with Usual Occupation-of Housewife
Cases	
Lung	63.7
Colon	64.4
Bladder	66.0
Rectum	65.8
Stomach	63.4
Esophagus	63.7
Skin, melanoma	60.6
Liver	67.5
Salivary gland	54.2
Eye	75.8
Mesothelioma	66.7
Controls	62.6

imum likelihood estimates of the odds ratio (OR) for occupations and industries were obtained using unconditional logistic regression.[16] ORs and their respective 95% confidence intervals were calculated for occupation and industry groups that included at least five cases. Data presented are restricted to those categories of occupations and industries with ORs that were significantly elevated (ie, the CI did not include 1.0) or at least 2.0.

Results

A total of 5714 cancer cases and 1972 population controls among women were included in the analysis. Table 1 presents the frequency of study participants by subject category and race. Black women constitute more than 25% of subjects for just three cancer sites: esophagus, liver, and stomach.

The overall study response rate was 93%. In Table 2, response rates for each subject category are shown, as are the proportion of interviews by respondent type. Response rates for women experiencing cancer range from 86.7% among women diagnosed with mesothelioma to 97.7% among women with diagnoses of melanoma of the skin. Controls have the highest response rate (98.6%). The majority of control interviews occurred with the subject herself, whereas the percentage of subject interviews varied by cancer site. Cancer sites with higher mortality—lung, esophagus, liver, mesothelioma—had a higher percentage of interviews provided by surrogate respondents. More than 85% of the surrogate respondents were spouses or children of the subject.

The most frequent usual occupation among women was housewife, regardless of subject category (Table 3). Subjects reporting housewife as usual occupation varied from 54.2% for women diagnosed with salivary gland cancers to 75.8% for women diagnosed with malignant eye tumors. Analyses were performed to determine whether housewives were overrepresented in any of the cancer case categories, when compared with controls. Because no elevated ORs occurred, these data are not shown.

Table 4 presents analyses of usual occupation and of occupations in which women were ever employed. Among the 11 cancer sites, elevated

TABLE 4
Occupational Cancer Risk Among Women in the Detroit Metropolitan Area, 1984–1991, by Usual Occupation, Ever Employed in Occupation, and Cancer Site*

Cancer Site and Occupation	Cases	Controls	Odds Ratio	95% Confidence Interval
Usual occupation				
Bladder				
Private household services	16	49	2.0	0.9–4.8
Machine operators	7	11	2.5	0.9–6.9
Dry cleaning	6	16	2.0	0.7–6.2
Rectum				
Food workers	8	21	2.0	0.8–5.2
Ever employed in occupation				
Stomach				
Electrical workers	2	5	8.5	0.7–100.0
Dancing/sports	2	5	2.4	0.4–15.6
Precision workers	2	3	4.5	0.5–40.2
Salivary gland				
Tool-and-die workers	2	5	8.5	0.7–100.0

* Adjusted for age at interview, race, and cigarette smoking.

TABLE 5
Cancer Risk Among Women in the Detroit Metropolitan Area, 1984–1991, by Usual Industry and Cancer Site*

Cancer Site and Usual Industry	Cases	Controls	Odds Ratio	95% Confidence Interval
Lung				
Fabricated metal manufacturing	10	4	3.9	0.9–15.8
Computer manufacturing	9	4	2.5	0.6–10.1
Ferrous metals manufacturing	5	2	3.1	0.5–20.8
Clay products manufacturing	5	1	3.7	0.3–43.6
Rubber-plastics manufacturing	8	2	2.2	0.4–10.8
Clubs (membership organizations)	5	1	3.9	0.3–46.2
Colon				
Fabricated metals manufacturing	8	4	2.4	0.7–8.0
Rubber-plastics manufacturing	5	2	3.3	0.6–17.1
Utilities	6	2	4.1	0.8–20.6
Bladder				
Computer manufacturing	5	4	4.2	1.1–16.1†
Stomach				
Food stores	7	24	2.7	1.1–6.6†
Restaurants	10	34	1.9	0.9–4.1
Esophagus				
Restaurants	13	34	2.4	1.2–4.9†

* Adjusted for age at interview, race, and cigarette smoking.
† Significant at $P < .05$.

ORs of 2.0 or greater were observed only for women diagnosed with cancers of the bladder and rectum for usual occupation, and for stomach or salivary gland for any occupation. Numbers are very small, and none of the elevated ORs were statistically significant. Most notable is the greater than eightfold increase in salivary gland cancers among women ever employed as tool-and-die workers. Additionally, the twofold excess of women with usual occupation of private household service worker and 2.5-fold elevation of women with usual occupation of machine operators diagnosed with bladder cancer approached significance.

Tables 5 and 6 present results of the analyses of usual industry groups and of industries in which women were ever employed. For usual industry, significant excesses were observed for women employed in the computer manufacturing industry who were diagnosed with bladder cancer (OR = 4.2, 95% CI = 1.1–16.1), for women employed in the food store industry who were diagnosed with stomach cancer (OR = 2.7, 95% CI = 1.1–6.6), and for women employed in the restaurant industry who were diagnosed with cancer of the esophagus (OR = 2.4, 95% CI = 1.2–4.9). Elevated risk of cancers of the lung, colon, bladder, rectum, esophagus, liver, salivary gland, eye, or with mesothelioma were seen among women ever employed in certain industries. Significant excesses were observed among women employed in the beverage manufacturing industry (OR = 8.2, 95% CI = 1.4–47.0) and in the rubber-plastic manufacturing industry (OR = 2.0, 95% CI = 1.1–3.7) who were diagnosed with bladder cancer. An OR of 3.9 (95% CI = 1.5–10.2) was observed for women in the miscellaneous manufacturing industry who were diagnosed with cancers of the esophagus. Women working in hairdressing shops were at excess risk for salivary gland cancers (OR = 3.0, 95% CI = 1.3–7.2). Two industry groups were significantly elevated among women diagnosed with cancers of the eye: bus and truck services (OR = 4.6, 95% CI = 1.2–17.9) and military service (OR = 4.4, 95% CI = 1.5–13.4).

TABLE 6
Cancer Risk Among Women in the Detroit Metropolitan Area, 1984–1991, by Industry Group in Which Ever Employed and Cancer Site*

Cancer Site and Industry Group	Cases	Controls	Odds Ratio	95% Confidence Interval
Lung				
Beverage manufacturing	5	2	2.3	0.3,15.5
Miscellaneous manufacturing	41	18	2.1	1.0,4.3
Colon				
Beverage manufacturing	6	2	2.6	0.5,13.8
Bladder				
Beverage manufacturing	5	2	8.2	1.4,47.0†
Paper manufacturing	8	10	2.5	0.9,6.7
Rubber-plastic manufacturing	23	40	2.0	1.1,3.7†
Computer manufacturing	10	18	2.0	0.8,5.1
Lumber sales	5	12	2.3	0.7,7.0
Car sales	14	20	2.1	1.0,4.7
Clubs (membership organizations)	8	9	2.8	1.0,7.9
Rectum				
Miscellaneous manufacturing	9	18	1.9	0.8,4.8
Esophagus				
Miscellaneous manufacturing	7	18	3.9	1.5,10.2†
Liver				
Rubber-plastics manufacturing	10	40	1.9	0.7,4.7
Toys manufacturing	4	18	2.4	0.8,7.5
Salivary Gland				
Clay products manufacturing	2	15	4.1	0.8,19.9
Printing	4	51	2.5	0.8,7.6
Computer manufacturing	2	18	3.8	0.8,18.4
Utilities	2	18	2.0	0.2,16.2
Hairdressing shops	14	70	3.0	1.3,7.2†
Eye				
Fabricated metal products manufacturing	5	83	2.9	1.0,8.6
Bus and truck services	5	23	4.6	1.2,17.9†
Postal service	2	23	5.1	1.0,25.8
Laundry/dry cleaning services	4	109	3.2	1.0,10.5
Military service	9	45	4.4	1.5,13.4†
Mesothelioma				
Miscellaneous manufacturing	2	18	3.9	05,33.2

* Adjusted for age at interview, race, and cigarette smoking.
† Significant at $P < .05$.

One of the critical methodological problems encountered in conducting studies of occupational cancer risks among women is selecting a sample of subjects that is large enough to perform analyses by specific occupations and industries. This study includes nearly 6000 cases and 2000 controls, making it one of the largest studies focused upon occupational cancer risks among women. However, Table 7 shows that there were few categories with 10 or more sub-

jects per occupation or industry group, and almost none having 50 or more subjects. Even for the more common cancer (eg, lung, colon, bladder), only 4 to 14 occupation or industry groups had at least 10 subjects.

Discussion

The results of our analysis highlight some of the methodological dilemmas associated with investigating of occupational cancer risk factors in women. The two major problems are (*a*) the large proportion of women with a usual occupation of housewife, and (*b*) the small number of women employed in any single occupation or industry category. When 65% of the subjects in a study are in the category of housewife, few subjects remain in other occupations and industries of concern.

Our study exemplifies these problems. The total number of subjects in the study was very large, including nearly 6000 cancer cases and 2000 population controls. First, the majority of women had a usual occupation of housewife. Second, even for cancer sites with large numbers of cases (more than 2000 for lung cancer, about 1500 for colon cancer, and over 600 for bladder cancer), the number of occupation or industry categories that encompassed 10 or more subjects never exceeded 14, and the number of categories with at least 50 subjects was three or less. Although women in the age groups with highest cancer risk (60+) were less likely to have been employed jobs outside the home, 30–40% had a usual workplace other than the home, and 80% had at some time during their lives held a job other than housewife.

Notwithstanding these difficulties, this study has identified occupations and industries in which women who were cancer patients were more likely to have been employed than women who constituted the population-based referent group. The OCISS study has several strengths. First, a complete work history was obtained by interview. Using lifetime work history, it was possible to assess cancer risk for all occupations and industries in which subjects had ever been employed. A second strength of the study is that the outcome measure is cancer incidence rather than mortality, allowing for a more specific and accurate assignment to a case category. Third, the interview data include history of tobacco use, enabling evaluation of occupational risk factors in the context of cigarette smoking status.

Some results provide new information about occupations and industries associated with occurrence of specific cancers, whereas other results confirm findings of earlier studies and of studies of male workers. The excess of bladder cancer in dry cleaners is similar to the observations of a mortality study conducted within a cohort of female dry cleaners in Wisconsin.[5] An important finding is the twofold excess of women ever employed in the rubber-plastic manufacturing industry group who were diagnosed with bladder cancer. Previous studies[17–20] have associated this particular industry with bladder cancer, but few have included women.[1,2,12] Two of the studies among women were mortality studies that found nonsignificant excesses of bladder cancer in the rubber industry.[1,2] The other study was a large national study of bladder cancer incidence in which a significant fourfold excess of women employed as rubber processing workers was observed among the bladder cancer cases.[12] Women employed in the restaurant industry who were diagnosed with cancer of the esophagus had elevated ORs. The association between cancer of the esophagus and employment in restaurants results from such numerous exposures as alcohol ingestion, passive smoking, or exhaust from kitchen appliances and equipment.

New findings of this study merit further investigation. These include elevated ORs for (*a*) women employed in the computer manufacturing industry who were diagnosed with bladder cancer, (*b*) women employed in hairdressing shops who were diagnosed with salivary gland cancer, (*c*) women employed in the beverage manufacturing industry who were diagnosed with bladder cancer, (*d*) women who worked in food stores and were diagnosed with stomach cancer, and (*e*) women em-

TABLE 7
Number of Usual Occupation and Industry Groups, by Number of Subjects and Subject Category, Detroit Metropolitan Area, 1984–1991

Subject Category	Number of Usual Occupation Groups with 10+ or 50+ Subjects		Number of Usual Industry Groups with 10+ or 50+ Subjects	
	with 10+ Subjects	with 50+ Subjects	with 10+ Subjects	with 50+ Subjects
Cases	14	1	12	3
Lung	12	1	6	2
Colon	4	1	4	0
Bladder	1	1	3	0
Rectum	2	1	2	0
Stomach	2	1	3	0
Esophagus	2	1	0	0
Skin, melanoma	1	1	0	0
Liver	1	1	0	0
Salivary gland	1	1	0	0
Eye	1	1	0	0
Mesothelioma	1	0	0	0
Controls	15	2	10	3

ployed in bus and truck services or military service who were diagnosed with eye cancer.

Potential explanations for some of these findings can be inferred. Women with eye cancer who were employed in the bus and truck industry or the military may have been exposed to exhaust from motor vehicles that contains carcinogenic compounds. The association between salivary gland cancer and employment in the hairdressing industry may be due to exposure to hair dyes and other chemicals. Previous studies of female beauticians have not shown any excess of salivary cancer.[7,8]

Among women ever employed as tool-and-die workers, a large increase (OR = 8.5) was observed for salivary gland cancer. This increase, although not statistically significant and based on only two cases, may still be worth pursuing, since little is known about risk factors for salivary gland cancer and its incidence is higher among women than men.

This study both provides leads that merit further investigation and identifies methodological issues to be addressed in future studies. An agenda for research into the occupational etiology of cancer in women must (*a*) include large samples of cases and controls; (*b*) utilize cancer incidence, rather than mortality, as the outcome measure; (*c*) obtain information about tobacco use; (*d*) obtain data on lifetime work history; (*e*) obtain exposure data, in addition to occupation or industry categories; and (*f*) identify exposures experienced by housewives that may be associated with elevated cancer risk. In addition, methods of statistical analysis that are more appropriate for small numbers, such as those observed for most occupation and industry groups in which women are employed, should be thoroughly explored.

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