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Risk of cervical cancer among female autoworkers exposed to metalworking fluids

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Objectives Cervical cancer is caused by human papilloma virus (HPV). However, only a small proportion of women infected with HPV, progress to cervical cancer. Other co-factors must therefore be necessary to cause cervical cancer. We examined cervical cancer in relation to occupational exposure to metalworking fluids (MWF), which are complex mixtures containing several known carcinogens.

Methods A cohort of 4374 female autoworkers was followed from 1985–2004 for cancer diagnosis. Based on an elevated standardized incidence rate (SIR), we focused on cervical cancer in an internal analysis. Pooled logistic regression was used to model the relationship between exposure to three different types of MWF, selected constituents, and incidence of cervical cancer.

Results Based on 40 cases, the SIR was statistically significantly elevated for both race specific subgroups: 3.30 and 2.43, respectively for Caucasian and African American women. The standard mortality ratio (SMR) was also statistically significantly elevated for Caucasian women (3.44) based on seven observed deaths. There was no association with oil-based straight fluid. Relative risks for soluble and synthetic MWF and nitrosamines were modestly elevated but not statistically significant.

Conclusions Water-based MWF may play a role in the etiology of cervical cancer. Further studies in larger cohorts of women are needed to clearly establish this relationship.

Key terms nitrosamine; occupation; soluble metalworking fluid; SIR; standardized incidence ratio; straight metalworking fluid; synthetic metalworking fluid; women.

Although much remains unknown about the etiology of cervical cancer, human papilloma virus (HPV) infection has been established as a necessary precondition (1). There are hundreds of different HPV types, but a vaccine against the high risk strains 6, 11, 16, and 18 has been developed and is currently being used among children and adults (12–26 years of age) (2). Studies have also shown that HPV infection is not sufficient to cause cervical cancer, since a large percentage of the population is HPV infected, but only a small percentage develops cervical cancer. Therefore, it is posited that other factors may be necessary in combination with a high risk HPV infection to cause cervical cancer (1).

Socioeconomic status, multiparity, early sexual debut, smoking, and other environmental determinants such as degree of urbanization have been associated with cervical cancer (3, 4). There have been a limited number of studies that explore the relationship between occupation and cervical cancer; many of these studies were unable to control for the confounding effects of "number of sexual partners" or "HPV infection status", both of which were likely to be related to both cervical cancer and occupation (5) .

Occupational exposure to industrial chemicals in relation to cervical cancer has received limited attention. Metalworking fluids (MWF) are used in manufacturing to reduce friction and remove chips and residues in metal machining and grinding operations (6). MWF have been associated with a multitude of cancers including malignant melanoma, bladder, laryngeal, prostate and rectal cancers (7–11) and can be classified into three categories (straight, soluble, and synthetic). Both straight and soluble MWF are oil-based and can contain polycyclic aromatic hydrocarbons (PAH), which are thought to be the primary carcinogenic component. Nitrosamines, formed by the interaction of ethanolamine

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and nitrates is one of several compounds in water-based soluble and synthetic MWF that may have carcinogenic effects (12–14).

The relationship between occupation and cervical cancer is complicated, as evidenced by inconsistent findings. Several studies found positive correlations between occupation and cervical cancer, but did not explore the relationship with specific workplace exposures. The following occupations have been reported to have increased mortality or incidence of cervical cancer: apparel manufacturing; building caretaking; stone, clay, and glass manufacturing; electrical equipment manufacturing; lumber and wood production; textile production; transportation manufacturing, and motor vehicle production (15, 16). By contrast, an occupational study of women in British Columbia did not find an increased standardized mortality ratio (SMR) for cervical cancer, but incidence rates were not studied (17). Incidence is a better measure of cervical cancer than mortality, because of the excellent survival rates in industrialized nations (1).

Increased odds of cervical cancer were reported for both metalworkers and industrial workers in a study that controlled for confounding due to smoking, age at first sexual intercourse, number of sexual partners, history of non-specific genital infection, and years since last Pap smear screening in the analysis (5). Manufacturing was associated with higher SMR due to cervical cancer in another study; socioeconomic status alone could not account for the elevated SMR, and excess risk therefore was likely due to specific occupational exposures (18).

In this study of a cohort of female auto-manufacturing workers in Michigan, the relationship between time-varying exposure to the three types of MWF and a diagnosis of cervical cancer was explored. To our knowledge this is the first study that addresses the relationship between exposure to MWF and cervical cancer.

Methods

Study population

The original cohort included more than 46 000 autoworkers from Michigan hired prior to 1982 and employed for least three years at three Michigan manufacturing plants (19). This report is restricted to the 4374 females still alive as of 1 January 1985 . The sub-cohort was linked to the Michigan Cancer Registry (MCR) to identify incident cancers diagnosed between 1 January 1985 and 31 December 2004. Information on mortality provided by the National Death Index was analyzed for the same 20-year period. Death rates in Michigan due to cervical cancer were ascertained using the World Health Organization's International Classification of Disease (ICD-9) code 180 before 1999 and ICD-10 code C53 after 1999 from the US Center for Disease Control (CDC) "wonder" database (7). An internal analysis of cervical cancer was based on ICD-O code 180, excluding 9590-9989 histologies.

Exposure assessment

Quantitative levels of exposure to each MWF class were estimated over time as described elsewhere (7). Time-varying exposure was assessed by combining air sampling of total particulate matter with individual work histories. Cumulative exposure to each type of MWF was lagged by ten years allowing for a latency period until cervical cancer diagnosis. Due to the small number of cases, cumulative exposures to each type of fluid were treated as "ever" versus "never" exposed in the exposure–response models. The cohort for the exposure–response analysis was restricted to women with <50% of their work history missing (N=4322).

Statistical analysis

Standardized incidence ratios (SIR) were calculated using the MCR's statewide incident rates to compute expected numbers of cases. SMR were calculated using Michigan-specific mortality rates from the CDC "wonder" website. Person-time was stratified by calendar year (5-year increments), gender, age (5-year increments), and race. The person-years in each strata were multiplied by the Michigan-specific rates and then summed over strata to calculate a total expected number. Observed numbers were then divided by expected numbers to produce resulting ratios (SIR and SMR) and used to calculate 95% confidence intervals (95% CI).

Pooled logistic regression was used to estimate the effect of cumulative exposure to straight, soluble, and synthetic fluids lagged by ten years, as measured by dichotomous ever/never exposed variables, on cervical cancer incidence in each person-year. Pooled logistic regression has been shown to be equivalent to a Cox proportional hazards model when the unit of person time is small enough that the outcome occurs with small probability (20). In addition, duration of exposure to selected constituents (biocides and nitrosamines) was also examined. Nitrosamine exposure, defined as the co-presence of nitrates and ethanolamine, was only present in synthetic fluids in this work environment. Age, exposure to other types of MWF, plant, and race were considered as possible confounders in the analysis (age and exposure were treated as time-varying covariates). All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

The Office for the Protection of Human Subjects at the University of California, Berkeley, approved all research protocols.

Results

Demographic characteristics for the female cohort (N=4322) and the cervical cancer cases (N=40) are presented in table 1. The mean age of cases at diagnosis was consistent with a median age of cervical cancer diagnosis of 48 years of age in the US population (21). The year of birth, year of hire and years employed at the start of follow-up were all smaller among the cases than the entire cohort. Note, the race distribution of African American and Caucasian workers among cases reflected the distribution in the cohort as a whole (67.5% versus 71.9% Caucasian). Overall, 44, 72, and 29 percent of the cohort had ever been exposed to straight, soluble and synthetic MWF, respectively. The exposed cases had lower median exposure than the cohort as a whole. There was a slight deficit in the incidence rate of all cancers combined (table 2), and significant deficits for cancer of the breast, rectum, and uterus. The SIR was elevated for lung, non-Hodgkin's lymphoma, pancreatic, stomach, and cervical cancers, and significantly elevated only for lung (SIR=1.29) and cervical cancer (SIR=2.71). All further analyses were restricted to cervical cancer.

The SIR for cervical cancer among female autoworkers was also statistically significantly elevated when stratified by race: 2.43 and 3.30 for African American and Caucasian women, respectively (table 3). There were a total of 7 deaths due to cervical cancer during the 20 years of follow-up. Of these 7 cases, 6 were captured as incident cases. The median time from diagnosis to death was two years and the only death not also reported as an incident case died early on during follow-up (1986), making it likely that her diagnosis occurred before the start of follow-up. The SMR due to cervical cancer was 3.44 (95% CI 1.38–7.09) among Caucasian women (table 3). There were no observed deaths among African American women from cervical cancer.

Internal analyses compared risk between exposed and unexposed categories for straight, soluble, and synthetic MWF and nitrosamines, adjusted for confounding. The relative risk (RR) was elevated in relation to soluble MWF (RR=1.55), although it was not statistically significant (table 4). The RR for synthetic MWF exposure was modestly elevated (RR=1.14), as well as the RR for nitrosamine (RR=1.30), a constituent of synthetic fluid, with wide confidence intervals (95% CI 0.41–4.09). There was no evidence of any association between exposure to straight MWF and cervical cancer. Age, plant, and race were included in all models, but only age was a significant (inverse) predictor of the outcome.

Discussion

The deficit observed in the SIR for all cancers combined might be caused, in part, by the healthy worker effect, a downward bias that has been documented in female as well as male occupational cohorts (22). This downward bias arises when the general population is used as the reference, though this bias may be weaker for cancer than for chronic diseases (23). The overall cancer deficit may also reflect incomplete ascertainment of cases; only cases diagnosed within the state of Michigan were identified and the patterns of emigration might differ between the state as a whole and this industrial population. In the context of the overall deficit, the elevated SIR for cervical cancer was particularly striking. The elevations were statistically significant for both race groups, motivating an internal analysis based on MWF (24). This is the first study to suggest a possible association between exposure to MWF and cervical cancer incidence.

All workers in this unionized industry had relatively good access to health insurance over the study period, increasing the likelihood of regular Pap smear screen-

Table 1. Demographic and exposure characteristics of female autoworkers cohort and cervical cancer cases. [IQR=interquartile range]

	Cohort [a]						Cases [a]					
	N	%	Mean	Range	Median	IQR	N	%	Mean	Range	Median	IQR
Subjects	4322						40					
Person years	77 950						333					
Race (Caucasian)	3109	67.5					27	71.9				
Year of birth			1940	1894–1961					1945	1909–1959		
Year of hire			1969	1940–1982					1972	1943–1979		
Age (years) [b]			52.5	24.0–103.3					48.0	28.2–83.9		
Metalworking fluid (mg/m^3-years)												
Straight [c]					0.36	0.10–1.09					0.15	0.03–0.27
Soluble [c]					1.53	0.47–3.59					1.39	0.20–2.96
Synthetic [c]					0.24	0.07–0.81					0.09	0.02-0.10
Years employed [c]					21.3	15.2–28.3					18.5	13.3–24.5

[a] Follow-up period 1985–2004.
[b] At start of follow-up for cohort and at date of diagnosis for cases.
[c] Median and IQR among the exposed.

Table 2. Standardized incidence ratios (SIR) for the cohort of female autoworkers alive of as 1 January 1985 (N=4374). [ICD= International Classification of Disease; 95% CI=95% confidence interval].

Site [a]	ICD-O–3 code	Observed	Expected [b]	SIR	95 % CI
All sites	All	528	566	0.93	0.86–1.02
Bladder	670–679	13	13	0.97	0.52–1.66
Breast	500–509	148	183	0.81	0.68–0.95
Brain	700–729	6	6	0.93	0.34–2.03
Cervix	530–539	40	14	2.96	2.11–4.02
Colon	180–189, 260	51	52	0.99	0.74–1.30
Esophagus	150–159	3	4	0.83	0.17–2.43
Kidney	649– 659	8	13	0.63	0.27–1.25
Larynx	320–329	3	3	0.94	0.19–2.76
Leukemia [c]	All	9	13	0.70	0.32–1.33
Liver	220	1	3	0.31	0.00–1.75
Lung	340–349	104	81	1.29	1.05–1.56
Non-Hodgkin's lymphoma [d]	All	24	22	1.09	0.70–1.62
Ovary	569	16	22	0.73	0.42–1.19
Pancreas	250–259	16	14	1.12	0.64–1.82
Rectum	199–218	9	18	0.50	0.23–0.95
Skin	440–449	10	11	0.88	0.42–1.63
Stomach	160–169	9	7	1.26	0.58–2.40
Uterus	540–549	19	35	0.54	0.32–0.84

[a] All site-specific cancers exclude 9590-9989 histologies.
[b] Expected values rounded to whole numbers.
[c] Histologies 9733, 9742, 9800–9948, 9951, 9963–9964.
[d] Histologies 9590–9642, 9670–9729.

Table 3. Observed and expected numbers of cancer cases and deaths, standardized incidence ratios (SIR), and standardized mortality ratios (SMR) among female autoworkers in the period 1985–2004, stratified by race. [95% CI=95%confidence interval]

Population	Observed deaths	Expected [a] deaths	SMR	95% CI	Observed incident cases	Expected [a] incident cases	SIR	95% CI
All females	7	3	2.02	0.81–4.15	40	14	2.96	2.11–4.02
Caucasian	7	2	3.44	1.38–7.09	27	8	3.30	2.18–4.80
African American	0	1			13	5	2.43	1.29–4.15

[a] Expected values rounded to whole numbers.

ing. It is possible that increased screening could explain some of the excess in cervical cancer as compared to the general population. If detected in the early stages, cervical cancer is easily treated and has one of the best recovery and survival rates after diagnosis (1). The elevated SMR due to cervical cancer in this cohort, therefore suggests that increased access to regular Pap smears may not explain the excess incidence. Additionally, routine screening is actually thought to help decrease the number of cervical cancer diagnoses by finding and treating pre-cancerous lesions (25). Interestingly, we found higher SIR and SMR for Caucasian women, whereas higher rates of both incidence and mortality of cervical cancer have been reported among African American women in the Detroit area (26).

There are several limitations of this study. First is the lack of information concerning several potential confounders, including: last Pap smear, number of sexual partners, parity, smoking, amongst others. However, modeling was performed using internal comparison groups based on exposure, and it is unlikely that any of these risk factors differ by exposure status. Second, given the small number of cervical cancer cases, exposure had to be dichotomized; even so the power was not sufficient to detect a modest statistically significant elevation in RR. However, the RR were positive and elevated for both the soluble and synthetic MWF, as well as for nitrosamines, suggesting that exposure to chemicals or microbial contaminants in water-based MWF may be related to cervical cancer.

Soluble and synthetic MWF are both water-based MWF; soluble fluids contain both water and oil components and synthetics contain only water-based chemicals. The exact ratio of water to oil in soluble MWF varied widely over the study period (27). Therefore, synthetics and straight MWF are the two more reliable surrogates for the main carcinogenic constituents (nitrosamines and PAH) respectively.

Table 4. Relative risks (RR) for cervical cancer incidence and cumulative exposure to each type of metalworking fluid (MWF), adjusted for exposure to other types of MWF, race, plant, and age in pooled logistic regression models. [95% CI=95% confidence interval.]

MWF exposure type	Cases	Person-years	RR	95% CI
Straight MWF				
Unexposed reference	22	43 730	1.00	..
Exposed	18	33 718	1.00	0.46–2.19
Soluble MWF				
Unexposed reference	9	21 796	1.00	..
Exposed	31	55 652	1.55	0.66–3.61
Synthetics MWF				
Unexposed reference	27	54 814	1.00	..
Exposed	13	22 634	1.14	0.50–2.60

A relationship between MWF and cervical cancer is biologically plausible given other studies of cervical cancer and other chemical agents, such as tobacco (28). It has been hypothesized that while HPV infection is a necessary precondition for cervical cancer to develop, there are other initiating events that must occur in addition to HPV infection to cause neoplastic change of cervical tissue (29). Several studies have found that tobacco use is associated with higher rates of cervical cancer even when HPV infection status is adjusted for in analyses (4, 30). Both lesion size and efficacy of treatment of cervical cancer are associated with tobacco use (31–32). Tobacco contains many of the same chemical compounds found in synthetic and oil-based MWF, such as nitrosamines and PAH, and thus MWF may act similarly to maintain cervical lesions after HPV infection. In fact, nitrosamines have been found in cervical tissue and may thus exert a localized effect (33).

This study adds valuable information on a possible association between cervical cancer and exposure to MWF. The results of the study suggest a possible association, but the possible chemical constituent and the mechanism of action are unknown. Results should be replicated in another study population exposed to water-based MWF with a larger number of cervical cancer cases.

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