Occupational Exposure to Metalworking Fluids and Risk of Breast Cancer Among Female Autoworkers

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Background *Metalworking fluids (MWF) are used for lubrication during metal manufacturing. Previous studies have observed increased risks of several cancers among MWF-exposed workers. We hypothesized that MWF may be associated with risk of breast cancer because they can contain carcinogenic or endocrine-disrupting chemicals.*
Methods *We conducted a case-control study nested in a cohort of 4,680 female automobile workers employed for at least 3 years between 1/1/41 and 1/1/85, with follow-up through 1994. Cases were identified using the National Death Index (NDI), Michigan cancer registries, and company records. Detailed quantitative MWF exposure data were available for each subject, although data on known breast cancer risk factors were not.*
Results *Ninety-nine cases of breast cancer and 626 matched controls were identified. There was a weak positive association between lifetime cumulative exposure to soluble MWF and breast cancer risk, but no evidence of association with either straight or synthetic fluids. When exposure was divided into time-windows, the association was strongest for soluble MWF in the decade preceding diagnosis. Controlling for earlier exposures, there was an odds ratio of 1.18 (95% CI = 1.02–1.35) per mg/m^3-year of cumulative exposure to soluble MWF in this 10-year period.*
Conclusion *This hypothesis-generating study provides some preliminary evidence for an association between exposure to soluble MWF and increased risk of breast cancer. Additional studies of MWF and breast cancer, with data on known breast cancer risk factors, are warranted.* Am. J. Ind. Med. 47:153–160, 2005. *© 2005 Wiley-Liss, Inc.*

KEY WORDS: breast cancer; epidemiology; metalworking fluids; occupational exposure; female workers; pre-menopausal

INTRODUCTION

Breast cancer is the most common female cancer in the United States, other than skin cancer, and the second leading cause of death among American women [ACS, 2004]. Projections are for two hundred and sixteen thousand new cases of invasive breast cancer and for more than forty thousand deaths in the United States in 2004 [ACS, 2004]. More than two million American women are currently living with breast cancer [ACS, 2004]. During the last several decades, the incidence rate for breast cancer has risen gradually worldwide [Richie and Swanson, 2003] suggesting

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that there may be new unidentified risk factors or that the prevalence of known risk factors may be changing [Feuer et al., 1993; Feigelson et al., 2004].

Intensive research efforts during the last several decades have identified risk factors that account for approximately 40% of etiology [Brinton, 2000]. Almost all established risk factors for breast cancer have been linked to hormonal activity. A substantial body of research supports the premise that the number of ovulatory cycles a woman experiences during her lifetime, mediated by reproductive events such as pregnancy, can affect her risk [Hall et al., 2002; Feigelson et al., 2004].

The only two well-established environmental risks for breast cancer are ionizing radiation and alcohol consumption, although mechanisms have been proposed by which solvents [Labreche and Goldberg, 1997], petroleum [Petralia et al., 1999; Reutman et al., 2002], and a variety of other synthetic organic chemicals [Krieger, 1989; Morris and Seifter, 1992] might increase breast cancer risk. Thus, large well-designed studies of occupational exposures and risk of breast cancer are needed [Zahm et al., 1994; Goldberg and Labreche, 1996; Kreiger et al., 2003].

We conducted a hypothesis-generating study of occupational risk factors in a sizeable industrial cohort of women with exposure to metalworking fluids (MWF) and long-term mortality follow-up. In a cohort of 46,000 automobile manufacturing workers, more than 10% were women, and quantitative estimates of cumulative exposure to MWF were available for each subject [Eisen et al., 2001].

Metalworking Fluids (MWF)

Previous studies in this cohort have observed increased risk of several cancers among workers exposed to MWF [Eisen et al., 1992, 1994, 2001; Bardin et al., 1997; Schroeder et al., 1997; Sullivan et al., 1998]. Standardized mortality ratio (SMR) studies suggested elevated risk for several cancers (e.g., stomach, esophagus, rectum, intestine, pancreas, lung, and larynx) [Eisen et al., 1992, 2001], and a series of nested case-control studies were conducted to follow-up on the elevated SMRs [Eisen et al., 1994; Bardin et al., 1997; Schroeder et al., 1997; Sullivan et al., 1998]. Results from these studies included elevated risk of esophageal and pancreatic cancers associated with synthetic fluids generated during grinding [Bardin et al., 1997; Sullivan et al., 1998] and elevated risk of laryngeal cancer associated with straight MWF [Eisen et al., 1994; Bardin et al., 1997; Schroeder et al., 1997; Sullivan et al., 1998; Zeka et al., 2004].

MWF facilitate the working of metals by serving as a lubricant between tool and metal, dissipating heat, carrying away metal chips, and protecting against rust formation. NIOSH estimates that more than 1.6 million workers are exposed to MWF annually in the United States and 6 million more to its components throughout the world [NIOSH, 1996, 1998]. Until the middle of the 20th century, direct skin contact was thought to be the primary route of occupational exposure to MWF. Skin cancers of the hand, forearm, and scrotum were reported with exposure to oils in numerous studies [NIOSH, 1998]. With the introduction of high-speed machinery in the late 1900s, concern shifted to the inhalation of MWF mist, aerosol, and particulate [Woskie et al., 1994a,b].

There are three principal classes of MWF in use: straight oils, soluble fluids, and synthetic fluids [Childers, 1994]. Straight MWF are complex mixtures of straight and branched-chain paraffins refined from mineral oil with the final mixture dependent on the refining process and source. Soluble fluids consist of oils emulsified in water and have greater coolant properties than straight MWF. Synthetic fluids are man-made, water-based fluids created from inorganic and organic salts and contain no mineral oil. There is tremendous diversity in the composition of MWF in the workplace today, with individual plants generally purchasing unique formulas of MWF to meet specific performance criteria.

Toxic components of MWF include polyaromatic hydrocarbons (PAH), chlorinated paraffins, sulfur, nitrosamines, biocides, 12–14 carbon chains, and metals. In 1983, the International Agency for Research on Cancer (IARC) found sufficient evidence to classify mineral oils found in straight and soluble MWF as an animal and human skin carcinogen due to the PAH content [IARC, 1978, 1984]. Since the 1980s, changes in refining have greatly reduced the PAH content of straight and soluble fluids, although small quantities may still occur.

Other potentially toxic components of MWF include ethanolamines and nitrites added to soluble and synthetic MWF to inhibit corrosion and adjust pH. The interaction of these chemicals can form nitrosamines such as N-nitrosodiethanolamine (NDELA). NDELA has been classified as a Group 2B carcinogen by IARC. Twelve- to 14-length carbon chains and sulfur, both found in trace amounts in MWF, may be promoters or co-carcinogens. Chlorinated paraffins have tested positive in bioassays for carcinogenicity in breast cells [Davis et al., 1993; Wolff et al., 1993; Wolff and Toniolo, 1995].

A recent cohort mortality study [Delzell et al., 1994] of women in the automotive industry, but a different population from the one studied here, reported an SMR of 0.68 (95% CI 0.48–0.92) for breast cancer. The SMR for breast cancer among the female cohort from which the present case-control study was drawn was also 0.68 (95% CI 0.43–1.02), based on 23 deceased cases (data not shown). Although deficits in SMRs for breast cancer were reported in both of these mortality studies of female autoworkers, we pursued the question further. Taking advantage of quantitative exposure information available on the cohort, we evaluated incidence, considering those living with the disease, as well as mortality, in order to reduce misclassification of disease outcome.

Here we report results from a nested case-control study of breast cancer in relation to MWF exposure in time-windows preceding tumor detection. This study used incident cases to supplement the original set of deceased cases and took advantage of quantitative lifetime MWF exposure data to produce exposure-risk estimates with internal comparisons.

MATERIALS AND METHODS

Exposure Assessment

The exposure assessment for this cohort has been described previously [Hallock et al., 1994; Woskie, 2000; Woskie et al., 2003]. In short, a team of experienced industrial hygienists developed historical estimates of exposure based on company records, including plant purchasing and industrial hygiene information, interviews with long-term employees, departmental and job histories, material safety data sheets, 800 personal and area industrial hygiene measurements, and laboratory analyses.

Using all sources of information, scale factors were developed to account for changes in production over time, and exposure was estimated for each job/department/plant/calendar period to create a job-exposure matrix. The job-exposure matrix was then combined with individual employment histories for every person in the cohort to estimate cumulative exposure (mg/m^3-years) to straight oils, soluble oils, and synthetic fluids. To investigate cancer latency, cumulative exposure was divided into three time-windows: 1–10, 11–20 years, and 21 or more years preceding diagnosis.

Cohort Study Population

The cohort of 46,000 [Eisen et al., 1992, 2001] included 4,680 female hourly automobile production workers employed for at least 3 years between January 1, 1941 and January 1, 1985 in three large manufacturing plants. Study members entered the cohort at hire or 1941 (whichever occurred later) and were followed until death or the end of follow-up on December 31, 1994.

National Death Index (NDI) records, death certificates, social security data, and plant employment records were used to determine vital status and cause of death through December 31, 1994 [Eisen et al., 2001]. Death certificates were coded by a professional nosologist, according to the 8th Revision of the International Classification of Diseases. This case-control study was approved by the Institutional Review Board of the University of Massachusetts at Lowell.

Nested Case-Control Study

The Karmanos Cancer Registry was used to identify cases in the metropolitan Detroit area between 1973 and 1984. Two of the three manufacturing plants were located in metropolitan Detroit and the third in another Michigan city. The statewide Michigan Cancer Registry, begun in 1984, identified cases in all of Michigan between 1985 and 1996. Incident (registry) cases were supplemented with deceased cases identified during two cohort follow-up periods (1940–1984, 1985–1994). Follow-ups were based on union and social security records as well as the NDI. The NDI was searched again for cases who died in 1995 and 1996. Combining all sources of data, a total of 110 cases of breast cancer were located. Ninety-five cases were identified through the registries; 64 of these cases were deceased. Thirteen cases had died before the registries began so their dates of diagnosis were unknown. Death certificates were obtained for all but one deceased case.

Pre- and post-menopausal breast cancer are frequently studied separately because of epidemiologic and clinical evidence that these disease processes differ. In the absence of information on date of onset of menopause, we stratified cases on age of diagnosis before or after age 51, to approximate menopausal status. For this section of analysis, 13 cases, identified solely from death certificates, were excluded.

Controls were selected 6:1 from the cohort using incidence density sampling. Matching was performed on date of birth (+/− 5 years), race, and being alive at the date of diagnosis of the case. Matching was not performed on vital status. For those 13 cases who had died before the registries began, we estimated a diagnosis date using the mean time from diagnosis to death in our cohort, among cases for whom both dates were known (pre- and post-menopausal cases were treated separately). For pre-menopausal cases, mean survival time was 2 years before death, for post-menopausal cases, 5 years.

Statistical Analysis

Conditional logistic regression was used to estimate the strength of the association between breast cancer and exposure to MWF using continuous exposure variables. Odds ratios therefore quantify the relative risk of disease associated with each mg/m^3-year of exposure during a particular window of time prior to diagnosis. Alternative parameterizations of cumulative exposure were investigated, including categorical models with two, three, and four levels; cut-points were based on the exposure-distribution of cases. Cumulative exposure was also transformed with its natural logarithm to check for excessive influence of high values. The final models used continuous measures of cumulative exposure and represent a balance between goodness-of-fit and simplicity. Results with all of the other parameterizations were broadly consistent with the final results shown here. Exposure–response associations were estimated in separate models for exposure to each fluid during each of the three time-windows preceding diagnosis: 1–10, 11–20 years, and 21 or more years. To adjust for potential confounding of exposure in one time-period by subsequent exposure in other time-periods, all three exposure-windows were included together in a single model. For these analyses, no information was available for individual risk factors that might possibly confound any observed associations with MWF–reproductive events, alcohol consumption, or family history of breast cancer, for example.

RESULTS

The initial study group numbered 766 (not all cases could be matched to six controls). Eleven cases and 30 controls were dropped from the study due to missing or incomplete exposure information, reducing the study population to 725 (99 cases and 626 controls). The final study group was composed of—73 1:6 case:control sets, 21 1:5 case:control sets, 5 1:4 case:control sets, a single 1:8 case:control set, and a single 1:2 case:control set. Fifty-two unmatched controls were included in unconditional analyses.

Study subjects tended to be hired in their early thirties and frequently left work before the age of 50 (Table I). On average, participants were born in 1929, stopped work in 1978, and were diagnosed with breast cancer in 1986. Thirty-eight cases were diagnosed before age 51. Forty-eight cases were either still working or within a year of leaving work when diagnosed (dates are precise to the nearest year).

Because race was not routinely recorded in the early years of plant operation, race for nearly one-third of study

TABLE I. Characteristics of Breast Cancer Cases and Controls Nested in a Cohort of Female Automobile Workers Exposed to Metalworking Fluids; Michigan

	Study subjects			
	Cases (99)		Controls (626)	
	Mean (SD)		Mean (SD)	
Descriptors				
Year of birth[c]	1929 (13)		1929 (13)	
Year began work	1961 (13)		1963 (13)	
Year stopped work	1978 (16)		1979 (15)	
Risk year[a,c]	1986 (9)		1986 (9)	
Age started work	32 (8)		34 (8)	
Age stopped work	49 (10)		50 (11)	
Risk age[b,c,d]	57 (12)		57 (12)	
Exposure years	10 (8)		8 (3)	
Race[c]				
% White	51%		51%	
% Black	21%		20%	
% Missing	28%		29%	
Vital status				
% Alive	55%		88%	
% Dead	45%		12%	
Ever exposed				
% Straight MWF	55%		57%	
% Soluble MWF	87%		85%	
% Synthetic MWF	36%		35%	
Quantitative exposure (mg/m^3-year)	Mean, median	SD (range)	Mean, median	SD (range)
Cumulative straight	2.0, 0.0	6.2 (0–43.0)	1.1, 0.1	4.0 (0–40.4)
Cumulative soluble	5.9, 2.2	14.9 (0–123.7)	4.0, 1.7	7.8 (0–79.4)
Cumulative synthetic	1.7, 0.5	2.9 (0–11.9)	2.0, 0.4	3.9 (0–26.9)

[a]Risk year is the year a case was diagnosed with breast cancer; for controls, it is the risk year of the matched case.
[b]Risk age is the age a case was diagnosed with breast cancer; for controls, it is the risk age of the matched case.
[c]Matching variable.
[d]For those 13 cases identified only at death, risk age (age at diagnosis) was defined as 2 years before death for pre-menopausal cases and 5 years before death for post-menopausal cases (see text).

members was unknown. At least 20% of the cohort was Black. In general, cases and controls were alike in work patterns in the factories (age started and ended work, number of years worked) (Table I).

Overall, the prevalence of exposure to each MWF type was similar between cases and controls (Table I). Cases, however, had nearly twice the lifetime cumulative exposure to straight MWF and almost 50% more exposure to soluble fluids than controls (Table I). Cases had slightly less average cumulative exposure to synthetic fluid than controls.

Using conditional logistic regression, the odds ratios for univariate associations between breast cancer and lifetime exposure to straight and soluble MWF were 1.04 (95% CI 0.99–1.08) and 1.02 (95% CI 1.00–1.04) per mg/m^3-year, respectively (Table II). When all three fluids were included in a single model, the association with straight MWF became essentially null, and the confidence interval for the association with soluble MWF widened substantially to 0.89–1.14 (Table II).

The associations between breast cancer risk and cumulative MWF exposure were estimated for 10-year windows preceding diagnosis by each fluid (Table III). There was no evidence of association for either straight or synthetic fluids, but soluble MWF exposure in the 10 years preceding diagnosis was associated with breast cancer risk. The odds ratio for this association was about the same whether modeled separately (Model 4), or when controlled for exposure by the other two time-windows (Models 5 and 6). In the model controlling for earlier exposures, there was an odds ratio of about 1.2, indicating a 20% increase in risk per mg/m^3-year of cumulative exposure to soluble MWF in the 10 years preceding diagnosis.

The association between exposure to soluble MWF in the 10 years before diagnosis and risk of disease was evaluated separately for those diagnosed before and after age 51 (Table IV). Risk appeared to be concentrated among the younger cases for whom the odds ratio was again

TABLE II. Breast Cancer Risk and Exposure to Straight, Soluble, and Synthetic Metalworking Fluids: Cases and Controls Nested in a Cohort of Female Automobile Workers; Michigan

		Cumulative exposure (mg/m^3-year)	
	Type of fluid	Odds ratio[a,b,c,d]	95% CI
Univariate			
Model 1	Straight	1.04	(0.99–1.08)
Model 2	Soluble	1.02	(1.00–1.04)
Model 3	Synthetic	0.93	(0.78–1.11)
Multivariate			
Model 4	Straight	0.81	(0.36–1.83)
	Soluble	1.01	(0.89–1.14)
	Synthetic	0.93	(0.78–1.10)

[a]Odds ratios estimated in conditional logistic regression models.
[b]Increase in breast cancer risk per mg/m^3-year of MWF exposure.
[c]Six hundred sixty-two observations in Models 1 and 2, 104 observations in Models 3 and 4.
[d]Cases and controls matched on date of birth (+/− 5 years) and race.

TABLE III. Breast Cancer Risk and Exposure to Straight, Soluble, and Synthetic Metalworking Fluids in Time Windows Prior to Diagnosis: Cases and Controls Nested in a Cohort of Female Automobile Workers[a,d]; Michigan

	1–10 years before risk[b]		11–20 years before risk		20+ years before risk	
	OR[c]	95% CI	OR	95% CI	OR	95% CI
Straight						
Model 1	1.05	(0.97–1.14)				
Model 2	1.05	(0.97–1.14)	1.01	(0.93–1.10)		
Model 3	1.05	(0.97–1.14)	1.01	(0.93–1.11)	1.04	(0.98–1.11)
Soluble						
Model 4	1.11	(1.01–1.22)				
Model 5	1.16	(1.01–1.32)	0.95	(0.86–1.05)		
Model 6	1.18	(1.02–1.35)	0.93	(0.84–1.04)	1.03	(0.99–1.06)
Synthetic						
Model 7	0.90	(0.63–1.30)				
Model 8	0.90	(0.62–1.30)	1.01	(0.84–1.21)		
Model 9	0.90	(0.62–1.30)	1.01	(0.84–1.21)	1.00	(0.88–1.14)

[a]Each model includes those 662 observations with complete data for all three time windows.
[b]Windows are not exclusive; study subjects may contribute to more than one window.
[c]Odds ratios estimate increase in breast cancer risk per mg/m^3-year of MWF exposure in indicated window.
[d]Cases and controls matched on date of birth (+/− 5 years) and race.

TABLE IV. Soluble Metalworking Fluid Exposure and Breast Cancer Risk in Three Time Windows: Cases and Controls Nested in a Cohort of Female Automobile Workers[a,b,f]; Michigan

	1–10 years before risk[c]		11–20 years before risk		20+ years before risk	
	OR[d]	95% CI	OR	95% CI	OR	95% CI
Dx before 51[e]						
Model 1	1.12	(0.76–1.66)				
Model 2	1.24	(0.82–1.89)	0.66	(0.37–1.18)		
Model 3	1.24	(0.82–1.89)	0.66	(0.36–1.19)	1.00	(0.59–1.68)
Dx after 51						
Model 4	0.90	(0.67–1.22)				
Model 5	0.86	(0.61–1.21)	1.06	(0.89–1.26)		
Model 6	0.89	(0.63–1.24)	1.02	(0.84–1.23)	1.02	(0.99–1.06)

[a]Models exclude 13 cases identified only from death certificates. When we imputed date-of-diagnosis (by subtracting mean survival time from year of death) and included the 13 preregistry cases, the odds ratio for exposure in the 1–10 years before risk in Models 2 and 3 was 1.33 (95% CI 1.05–1.67).
[b]One hundred ninety-one observations included in Models 1, 2, and 3. Three hundred eighty-two observations included in Models 4, 5, and 6.
[c]Windows are not mutually exclusive; study subjects may contribute to more than one window.
[d]Odds ratios estimate increase in breast cancer risk per mg/m^3-year of MWF exposure in indicated window.
[e]Twenty-eight cases had risk ages before their 51st birthday, 58 cases after their 51st birthday.
[f]Cases and controls were matched on date of birth (+/− 5 years) and race.

approximately 1.2 per mg/m^3-year, though the confidence interval was wide.

The models in Table IV were constructed excluding 13 cases identified from death certificates alone. When we imputed date-of-diagnosis (by subtracting mean survival time from year of death) and included these 13 deceased cases, the odds ratio for exposure in the decade before risk was somewhat stronger in both models 2 and 3: 1.33 (95% CI 1.05–1.67).

DISCUSSION

Studies based in the workplace have helped to elucidate mechanisms for many environmentally induced cancers [Siemiatycki, 1995]. Yet until recently, industrial cohorts have not included enough women to examine female cancer risks. The strengths of this study are the relatively large number of women in this industrial cohort and the extensive industrial hygiene exposure information [Woskie et al., 2003]. Despite the good exposure assessment for this cohort, it will always be difficult to identify particular toxic component(s) associated with risk because MWF are complex mixtures with compositions that change frequently to meet company requirements.

An important limitation of this study was the lack of data on some potential confounders, particularly reproductive history. On the other hand, confounding by reproductive risk factors is unlikely to have been serious because of the relative homogeneity of this unionized blue-collar population. It would be necessary to hypothesize that, for example, heavily MWF-exposed female autoworkers had later dates of first full-term pregnancy than less exposed members of the same population. While such a pattern cannot be ruled out, it seems improbable. In general, class-associated patterns of risk would not be expected to be important with the use of an internal analysis comparing risks within the cohort.

Matching on race was done to increase efficiency because of the relatively small number of non-White women in the cohort. Sensitivity analyses were performed omitting race from final models, and very little difference was observed in exposure risk estimates.

This preliminary investigation revealed weak evidence of an association between lifetime cumulative exposure to soluble MWF and breast cancer risk. The association was strengthened when restricted to the 10 years preceding diagnosis. There was some evidence that risk was limited to cases diagnosed before age 51, although stratifying on age of diagnosis resulted in small numbers and unstable risk estimates. The association with exposure in the 10 years preceding diagnosis did not appear to be confounded by exposures in earlier periods.

"Late stage" carcinogens—those appearing to act in the period just before diagnosis—are not commonly observed in epidemiologic studies; thus why this temporal pattern might have occurred is not clear. A relevant exception is the association between alcohol and breast cancer. Some, but not all, studies have found that recent alcohol consumption (5 or 10 years prior to diagnosis) is most strongly related to breast cancer [Longnecker et al., 1995; Swanson et al., 1997]. If alcohol acts at a late stage in breast cancer [Longnecker et al., 1995; Swanson et al., 1997], this would lend support to the possibility that some component of MWF may as well.

This is the first examination of the association between MWF and breast cancer risk that relied on quantitative individual exposure data. Because the exposure is widespread and the disease poorly understood, we believe the findings warrant further study. However, the lack of data on non-occupational risk factors and lack of strong a priori hypotheses suggest cautious interpretation of the results.

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