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HHS Public Access

Author manuscript

Am J Ind Med. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Am J Ind Med. 2020 January ; 63(1): 44–50. doi:10.1002/ajim.23067.

Occupational exposure to disinfectants and asthma incidence in US nurses: a prospective cohort study

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Abstract

Background: Exposure to disinfectants among healthcare workers has been associated with respiratory health effects, in particular asthma. However, most studies are cross-sectional and the role of disinfectant exposures in asthma development requires longitudinal studies. We

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Institutions at which the work was performed: INSERM, U1168, VIMA (Villejuif, France) and Channing Division of Network Medicine (Boston, USA)

Authors' contributions: OD contributed to the study conception, the acquisition, analysis and interpretation of the data, and primary manuscript preparation. RV and NLM contributed to the study conception, data interpretation and critical revision of the manuscript. CQ, JPZ and PKH were involved in the data interpretation and critical revision of the manuscript. KMB and FES contributed to the acquisition and interpretation of the data and critical revision of the manuscript. CAC participated in the study conception, acquisition of the data, data interpretation and critical revision of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Institution and Ethics approval and informed consent: This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital, (Boston, MA).

Disclosure (Authors): The authors declare no conflicts of interest.

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investigated the association between occupational exposure to disinfectants and incident asthma in a large cohort of US female nurses.

Methods: The Nurses' Health Study II is a prospective cohort of 116,429 female nurses enrolled in 1989. Analyses included 61,539 participants who were still in a nursing job and with no history of asthma in 2009 (baseline; mean age: 55 years). During 277,744 person-years of follow-up (2009–2015), 370 nurses reported incident physician-diagnosed asthma. Occupational exposure was evaluated by questionnaire and a Job-Task-Exposure Matrix (JTEM). We examined the association between disinfectant exposure and subsequent asthma development, adjusted for age, race, ethnicity, smoking status, and body mass index.

Results: Weekly use of disinfectants to clean surfaces only (23% exposed) or to clean medical instruments (19% exposed) was not associated with incident asthma (adjusted hazard ratio [95%CI] for surfaces, 1.12 [0.87–1.43]; for instruments, 1.13 [0.87–1.48]). No association was observed between high level exposure to specific disinfectants/cleaning products evaluated by the JTEM (formaldehyde, glutaraldehyde, bleach, hydrogen peroxide, alcohol quats or enzymatic cleaners) and asthma incidence.

Conclusions: In a population of late career nurses, we observed no significant association between exposure to disinfectants and asthma incidence. A potential role of disinfectant exposures in asthma development warrants further study among healthcare workers at earlier career stage to limit the healthy worker effect.

Keywords

Asthma; cleaning products; disinfection; healthcare workers; occupational asthma

INTRODUCTION

Occupational exposures may cause one in six cases of adult-onset asthma.[1] Exposure to asthmagens is common in many workplaces and hundreds of asthma-causing agents have been identified.[2,3] In the last decades, a growing proportion of work-related asthma cases has been observed in the healthcare industry,[4,5] raising concerns about the role of exposure to cleaning products and disinfectants, especially in women.[6,7]

Exposure to cleaning products and disinfectants has been associated with increased risk of asthma symptoms and exacerbations.[6–11] Although evidence for adverse respiratory effects is accumulating, it is still mostly based on cross-sectional studies.[8–11] Only three longitudinal studies have examined the association between occupational exposure to cleaning products and asthma development.[12–14] All were European population-based studies, with limited information regarding exposure to specific agents. The need for additional large-scale longitudinal studies has been emphasized in recent literature reviews,[6,7] and cohorts of highly exposed workers, such as healthcare workers, are of particular interest.

Clinical manifestations of airway diseases vary over the lifespan, with gender-related patterns.[15] In adulthood, asthma incidence rates are higher in women, but vary with age, partly in relation to hormonal factors.[16,17] Late-onset asthma has been described as a distinct

asthma phenotype, associated with higher morbidity.[18] Similarly, occupational asthma can develop at any time during the working life,[19,20] and older age at diagnosis has been associated with worse outcomes.[21] Nonetheless, few studies have investigated the impact of occupational exposures on respiratory health at later career stages. One cross-sectional study among women older than 55 years reported higher risk of asthma-like symptoms among nurses.[22]

The Nurses' Health Study II (NHSII) is a large, ongoing, prospective study of US female nurses. Detailed data on occupational exposure were collected in 2009, when nurses were at a late-career stage (age 45–65 years). Based on a cross-sectional analysis among nurses with asthma (mean age: 58 years), we recently reported that occupational exposure to cleaning products and disinfectants was associated with poor asthma control.[23,24] Here, we investigated the prospective association between occupational exposure to disinfectants and incident asthma in late-career nurses.

METHODS

Population

The NHSII began in 1989 when 116,429 female registered nurses from 14 U.S. states, aged 25–44 years, completed a questionnaire on their medical history and lifestyle characteristics.[25] Follow-up questionnaires have been sent every 2 years since. Information on occupational exposures was collected for the first time in 2009, which was defined as baseline for the current study. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital, (Boston, MA).

Occupational exposure to disinfectants

Information on nursing job types (education/administration, outpatient/other nurses, emergency room or inpatient unit, operating room) and general disinfection tasks was collected by questionnaire in 2009, 2011 and 2013.[26] The two questions regarding the frequency (days/week) of disinfection tasks were: "Thinking about your current job and the use of disinfectants (such as ethylene oxide, hydrogen peroxide, orthophthalaldehyde, formaldehyde, glutaraldehyde and bleach): (a) On how many days per week, on average, do you clean medical instruments with disinfectants? (b) On how many days per week, on average, do you clean surfaces (like floors, tables) at work with disinfectants?". A specific question was asked about the use of sprays: "In your current job, on how many days per week, on average, do you use spray or aerosol products?".

Exposure to seven major disinfectants/cleaning products (formaldehyde, glutaraldehyde, hypochlorite bleach, hydrogen peroxide, alcohol, quaternary ammonium compounds [quats], and enzymatic cleaners) was evaluated by a nurse-specific Job-Task-Exposure Matrix (JTEM), as described in detail elsewhere.[27] Briefly, it used the responses to the questions described above in a population of 9,073 nurses without asthma (2014–2015), drawn from the NHSII. We generated the JTEM based on the percentage of participants reporting exposure to a given disinfectant for a given nursing job and task category. The JTEM assigned exposure level (low, medium, or high) based on types of nursing jobs and general

disinfection tasks (24 possible combinations of 8 types of nursing jobs by 3 categories of weekly cleaning/disinfection tasks: surfaces only, at least instruments, none). Specific cut-offs were defined to classify exposure levels for each disinfectant in a given job-task combination. The JTEM was applied to evaluate occupational exposure in 2009, 2011 and 2013.

Asthma incidence

In biennial questionnaires, participants were asked to report any condition(s) with which they were diagnosed since the last questionnaire cycle, including asthma. Between 2014 and 2017, we sent a supplemental questionnaire on asthma to participants who reported a physician's diagnosis of asthma in any past biennial questionnaire (80% response rate[23]). Based on information collected on the supplemental questionnaire, we selected participants who reiterated that a physician had diagnosed her as having asthma and who reported use of any asthma medication in the past year. Age of diagnosis reported in the supplemental asthma questionnaire was used to further identify incident asthma cases. All women with a diagnosis of asthma before baseline (2009) were excluded from the analyses. Incident asthma with (or without) allergy was defined based on the report of ever having had (or not had) hay fever, seasonal allergies or allergic rhinitis on the supplemental questionnaire.

Statistical Analyses

Prospective associations between occupational exposures and asthma incidence were evaluated by Cox proportional hazard models. Disinfection tasks were studied using a dichotomous (weekly use of disinfectants to clean surfaces or medical instruments *vs.* no) and a 3-level (no disinfection task performed weekly; weekly use of disinfectants to clean surfaces only; weekly use of disinfectants to clean medical instruments, regardless of the use of disinfectants to clean surfaces) variable. Exposure to specific disinfectants according to JTEM was studied using 3-level variables (low, medium, or high exposure level), with separate models for each disinfectant. In each model, occupational exposure was handled as a time-varying variable and was evaluated at the questionnaire cycle before time of diagnosis. All Cox models were stratified by age and calendar year. Analyses were adjusted for race (white *vs.* non-white), ethnicity (Hispanic *vs.* non-Hispanic), smoking habits (non-smoker, ex-smoker or current smoker), and body mass index (BMI, <20, 20–24.9, 25–29.9, ≥30 kg/m^2). We tested effect modification by age group (≤50 years *vs.* >50 years), smoking status (never smokers *vs.* ever smokers), BMI (<25 *vs.* ≥25 kg/m^2), and menopausal status (pre- vs post-menopausal). Analyses were run using SAS V.9 (SAS Institute, Cary, NC, USA). A two-sided $P<0.05$ was considered statistically significant.

Sensitivity analyses to evaluate presence of a healthy worker effect

The presence of a healthy worker effect could bias the association between occupational exposure and incident asthma toward the null.[28] In our study, a healthy worker effect can occur if an intermittent poor health status present before asthma diagnosis, such as another respiratory condition or a general poor health status, is associated both with subsequent exposure and subsequent asthma development.[29,30] To evaluate the presence of this form of healthy worker effect, we conducted several analyses. First, as employment status (leaving work) is commonly used as a surrogate of poor health status to evaluate a potential healthy

worker survivor effect,[29,31] we examined whether leaving nursing (before baseline or during follow-up) was associated with subsequent asthma development. Second, we excluded from analyses all women (a) with symptoms of asthma (which may occur several years prior to diagnosis) before baseline, evaluated retrospectively based on the age at first symptoms reported in the supplemental asthma questionnaire; or (b) with COPD before baseline, evaluated prospectively in biennial questionnaires. Third, to account for a potential decrease in exposure level over time because of degrading health status prior to asthma diagnosis, we conducted a sensitivity analysis using the highest exposure level at any of the questionnaire cycles from 2009 to time of diagnosis instead of exposure level at the most recent questionnaire cycle.

RESULTS

Among the 116,429 participants in the NHSII, 98,811 returned at least one biennial questionnaire during the follow-up period (2011–2015), of which 76,331 were still in a nursing job. Among them, 185 women with missing data for occupational exposure and 14,607 women who ever reported asthma diagnosis before or at baseline were excluded. This yielded a population of 61,539 women eligible for analysis. At baseline, participants were on average 55 years old (range 44–68 years); 96% were white, 6% were current smokers and 28% were ex-smokers. Regarding cleaning/disinfection tasks, 23% of the nurses reported weekly use of disinfectants to clean surfaces only, and 19% reported weekly use of disinfectants to clean medical instruments. Slight but statistically significant differences were seen in socio-demographic characteristics according to disinfection tasks (Table 1); in particular, nurses reporting weekly use of disinfectants were younger and more often ex- or current-smokers. Some variations were observed in use of disinfectants during the follow-up period. For example, among nurses who reported weekly use of any disinfectant (to clean surfaces and/or instruments) in 2009, 30% reported no use of disinfectant in 2013; among nurses who reported no use of disinfectant at baseline, 21% reported weekly use of any disinfectant in 2013.

During 277,744 person-years of follow-up, from 2009 to 2015, 370 nurses reported incident physician-diagnosed asthma. In multivariable models, no association was observed between nursing job types, weekly use of disinfectants, or weekly use of sprays, and asthma incidence (Table 2). Use of any disinfectants was not associated with incident asthma with allergy (n=288 cases; adjusted Hazard Ratio [aHR]: 1.19, 95% confidence interval: 0.94–1.51) or without allergy (n=75 cases; aHR: 0.92, 0.58–1.47). Associations between use of any disinfectants and asthma incidence did not differ by age group (P_{inter}=0.48), smoking status (P_{inter}=0.75), BMI (P_{inter}=0.33), or menopausal status (P_{inter}=0.50). Similarly, using the JTEM estimates, no significant association was observed between exposure to specific disinfectants and incident asthma, with aHRs ranging from 0.97 to 1.14 (Table 3).

In analyses investigating presence of a healthy worker effect, we found that leaving nursing before baseline or during follow-up was not associated with subsequent asthma development (analysis conducted in 77,833 women, aHR: 1.09, 0.90–1.32). In addition, all results were similar in sensitivity analyses excluding all women with symptoms of asthma (occurring prior to diagnosis) or COPD before baseline, or examining the highest exposure level at any

of the questionnaire cycles from 2009 to time of diagnosis instead of exposure level at the most recent questionnaire cycle (aHRs ranging from 1.00 to 1.22, all P>0.17).

DISCUSSION

In this analysis of a cohort of 61,538 late-career nurses followed-up over 6 years, no association was observed between occupational exposure to disinfectants and asthma incidence. These findings contrast with previous reports from many cross-sectional and a few longitudinal studies of an increased risk of asthma associated with exposure to cleaning products and disinfectants, generally in younger cohorts.

Several cross-sectional studies have established an association between exposure to cleaning products and disinfectants and current asthma or asthma symptoms/exacerbations.[6,9–11,23,32] However, in such studies, it is difficult to determine whether the observed associations are driven by occupational asthma (new-onset asthma caused by occupational exposure) or work-exacerbated asthma (pre-existing asthma worsened by occupational exposure). Cases of occupational asthma caused by different types of cleaning or disinfecting agents have been reported in the literature.[33,34] Epidemiologic evidence for an association of exposure to cleaning products and disinfectants with new-onset asthma is currently based on a few prospective European studies. First, an increased risk of asthma development has been reported among cleaners[35] and nurses.[12] Then, studies reported that occupational exposure to cleaning products evaluated by self-report[36] or job-exposure matrices[12–14] were prospectively associated with increased risk of asthma development. Two longitudinal studies have also reported an association between use of cleaning products at home – in particular use of sprays – and asthma development.[37,38] The current results differ from these earlier findings.

In our study, asthma was well-characterized, based on a questionnaire definition previously validated in this population of healthcare professionals. Indeed, in the validation study, 95% of the nurses' reports of doctor-diagnosed asthma were confirmed.[25] Occupational exposure was evaluated before the report of asthma diagnosis, so differential recall bias is unlikely. We used both self-report and a JTEM to evaluate exposure. These assessment methods may generate non-differential misclassification, and bias the associations with asthma toward the null. However, the use of a JTEM, that assigns exposure level based not only on nursing job types but also on disinfection tasks, is likely to reduce exposure misclassification (as compared to a job-exposure matrix). Moreover, using the same methods for occupational exposure assessment, we recently found in NHSII that exposure to cleaning products and disinfectants was significantly associated with COPD incidence,[39] and with poor asthma control among participants with asthma.[23]

In NHSII, we have previously reported that women with a history of asthma were less often employed in nursing jobs likely to involve high disinfectant exposure (e.g., nursing in operating room, emergency room or inpatient units) at the start of the cohort (1989) and were more likely to move to jobs involving a lower level of exposure during follow-up,[26] consistently with earlier findings in a related cohort of nurses.[40] These results suggested health-related selection out of exposed jobs ("healthy worker effect") *after* asthma diagnosis.

[26] In the current analysis, we excluded all women with a diagnosis of asthma before baseline (2009). Nonetheless, a healthy worker effect can also occur if an intermittent poor health status present *before* asthma diagnosis is associated both with subsequent exposure and subsequent asthma development, therefore acting as a confounder.[30,41] Although sensitivity analyses did not suggest the presence of this case of healthy worker effect, we could only evaluate a limited number of intermittent health conditions that could act as such a confounder - i.e., report of asthma symptoms (evaluated retrospectively) or COPD before diagnosis, and employment status as a surrogate of poor health status. Moreover, a healthy worker effect can also result from a selection bias, occurring because of a differential probability of workers with different underlying risks of disease to stay in exposed jobs.[42] Such selection is likely to occur in our study based on a population of late-career nurses. Indeed, occupational asthma typically occurs after a latency period which can last from a few weeks to a few years,[2] with an average of ~8–10 years.[43] In addition, susceptibility (disease risk) to occupational exposure is known to vary between individuals;[44] for instance, gene-environment interactions have been reported in adult-onset asthma related to occupational exposure to chemicals/irritants.[45] In our study, by selecting women free of asthma after several decades in nursing, it is likely that we have excluded the most susceptible individuals. All previous longitudinal studies reporting an association between occupational exposure to disinfectants and incident asthma were conducted in younger cohorts, probably less affected by such selection. In NHSII, no detailed data on occupational exposure to disinfectants and cleaning products was available before 2009, limiting our ability to study nurses at an earlier career stage and to precisely characterize exposure duration.

Finally, occupational exposure to cleaning products and disinfectants may be associated with specific asthma phenotypes. Our findings did not suggest an association between exposure to cleaning products/disinfectants and late-onset asthma, as no difference in the association by age or menopausal status was observed. Previous studies have suggested a predominant role of irritant agents in cleaning products/disinfectants, and an association with non-allergic asthma.[46,47] In the current study, we did not observe an association with incident asthma either with or without allergy. However, allergy was defined by questionnaire only, based on the report of hay fever, seasonal allergies or allergic rhinitis, and the number of asthma cases without allergy was limited. Moreover, this single characteristic (allergic *vs.* non allergic) only accounts for a small part of asthma heterogeneity and is likely not sufficient to define relevant asthma phenotypes. Further studies using a better definition of allergic status, and with information on a broader range of clinical characteristics and relevant biomarkers, such as oxidative stress-related markers,[48,49] are needed to evaluate more accurately the association between occupational exposure and incidence of specific asthma phenotypes.

In summary, in a population of late-career nurses, we observed no significant association between exposure to disinfectants and asthma incidence. Nonetheless, the role of disinfectant exposures in asthma development warrants further study among healthcare workers at earlier career stage to limit the healthy worker effect, and to investigate the association between occupational exposure and specific asthma phenotypes.

Acknowledgements:

The Nurses' Health Study II is coordinated at the Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA. We would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions.

Funding:

Centers for Disease Control and Prevention R01 OH-010359; National Institutes of Health UM1 CA-176726. The research leading to these results has received funding from the People Program (Marie Curie Actions) of the European Union's Seventh Framework Program (FP7/2007–2013) under REA grant agreement n. PCOFUND-GA-2013–609102, through the PRESTIGE program coordinated by Campus France.

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Table 1

Age-standardized baseline characteristics of the study population according to disinfectant use in US female nurses, n=61,539

	Weekly use of disinfectants to clean surfaces and/or instruments			
	None (n=35,665)	**Surface only (n=14,149)**	**Instruments (n=11,725)**	**P**
Age, mean (SD) *	55.0 (4.6)	54.6 (4.6)	54.1 (4.6)	<0.001
Race				
White, %	96	96	95	<0.001
Black, %	2	2	2	
Other, %	2	2	3	
Hispanic				
Hispanic, %	2	2	2	0.32
Non-Hispanic, %	98	98	98	
Smoking habits				
Never smoker, %	66	66	64	<0.001
Ex-smoker, %	29	27	28	
Current smoker, %	6	7	8	
BMI at baseline (kg/m2)				
<20, %	5	5	5	0.08
20 to 24.9, %	37	37	36	
25 to 29.9, %	31	31	32	
>=30, %	28	28	27	

Abbreviations: BMI, body mass index; SD, standard deviation.

Values of categorical variables may not sum to 100% due to rounding.

* Value is not age adjusted

Table 2.

Prospective association between self-reported cleaning/disinfection tasks and asthma incidence in US female nurses

	Person-years	No. of cases	Age-adjusted HR		Multivariable-adjusted HR	
			HR	95% CI	HR	95% CI
Job type						
Education or administration	47,195	63	1	-	1	-
Outpatient, other nurses	152,605	225	1.14	0.86–1.51	1.19	0.90–1.57
ER or inpatient unit	60,293	68	0.87	0.61–1.22	0.90	0.63–1.26
Operating room	17,651	14	0.63	0.35–1.13	0.67	0.37–1.19
Weekly use of disinfectant						
None (ref.)	154,936	200	1	-	1	-
Any disinfectant	122,809	170	1.11	0.91–1.37	1.12	0.91–1.38
Surface only	71,189	97	1.11	0.87–1.42	1.12	0.87–1.43
Instruments	51,620	73	1.12	0.85–1.46	1.13	0.86–1.48
Weekly use of sprays[†]						
No (ref.)	150,788	147	1	-	1	-
Yes	32,334	35	1.11	0.76–1.60	1.10	0.76–1.59

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, emergency room.

Multivariable models were adjusted for age, race, ethnicity, smoking status and body mass index.

Use of disinfectants was evaluated at the questionnaire cycle before time of diagnosis.

[†]Use of sprays for patient care, instrument cleaning or disinfection, surface cleaning or disinfection, air-refreshing, or other. Follow-up period: 2009–2015 for job type and use of disinfectants; 2011–2015 for use of sprays.

Observations with missing values for smoking status (0.1%) were excluded from analyses (multivariable-adjusted models). Observations with missing value for body mass index (3.6%) were included in the model as a “missing” category.

Table 3.

Prospective associations between exposure to specific disinfectants/cleaning products evaluated by the JTEM and asthma incidence in US female nurses

	Person-years	No. of cases	Multivariable-adjusted HR	
			HR	95% CI
Formaldehyde	25,031	32	0.97	0.67–1.40
Glutaraldehyde	79,152	108	1.11	0.88–1.41
Hypochlorite bleach	76,751	109	1.07	0.84–1.36
Hydrogen peroxide	88,054	117	1.06	0.84–1.34
Alcohol	95,331	142	1.14	0.91–1.42
Quats	96,780	124	1.00	0.79–1.26
Enzymatic cleaners	40,994	52	0.97	0.72–1.30

Abbreviations: HR, hazard ratio; CI, confidence interval; JTEM – Job-Task-Exposure Matrix.

Multivariable models were adjusted for age, race, ethnicity, smoking status and body mass index.

Exposure to disinfectants/cleaning products was evaluated at the questionnaire cycle before time of diagnosis. Associations presented compare high exposure level vs. low exposure level, for each product. No association was observed when comparing medium vs. low exposure level. Observations with missing values for smoking status (0.1%) were excluded from analyses (multivariable-adjusted models). Observations with missing value for body mass index (3.6%) were included in the model as a “missing” category.