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Spirometric Abnormalities and Lung Function Decline in Current and Former Microwave Popcorn and Current Flavoring Manufacturing Workers

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Abstract

Objective: The aim of this study was to compare spirometry results in microwave popcorn and flavoring manufacturing workers.

Methods: We used NIOSH data on current and former microwave popcorn workers (MPWs) and surveillance data on flavoring manufacturing workers (FMWs).

Results: Former MPW had higher prevalence of mixed and high severity abnormalities, some had excessive lung function drops. Current MPW had lowest occurrence of excessive lung function drops. FMW with excessive drops and spirometric abnormalities at last test had developed a restrictive pattern. Spirometric abnormalities and excessive drops were associated with work-related factors.

Conclusion: There was evidence of a healthy worker survivor effect in MPW. Importantly, removal from exposure did not always stabilize lung function decline indicating a need for continued monitoring. The development of a restrictive pattern should raise the level of suspicion for possible work-related disease in flavoring-exposed workers.

Keywords

diacetyl; flavoring-exposed workers; healthy worker survivor effect; lung function

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Occupational exposure to butter flavorings containing diacetyl has been documented to be a risk for obliterative bronchiolitis and fixed airway obstruction.[1–4] Earlier work by the National Institute for Occupational Safety and Health (NIOSH) on flavoring-exposed workers concentrated on spirometric indications of obstructive abnormalities.[1,3,5,6] More recently, an analysis by NIOSH of data from 1407 microwave popcorn (MP) or flavoring manufacturing (FM) workers at nine facilities in eight states included a restrictive spirometry pattern in a case definition of possible flavoring-related lung disease.[7]

Studies have defined a restrictive spirometry pattern differently, but the hallmark is a preserved forced expiratory volume in 1second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) with a reduced FVC. A restrictive spirometry pattern has been found in some patients with biopsy-documented obliterative bronchiolitis, including soldiers returning from Iraq and Afghanistan.[8,9] Although a restrictive spirometry pattern can indicate interstitial lung disease, it has a low positive predictive value.[10] In the presence of a low FEV1/FVC ratio consistent with airways obstruction, a low FVC often indicates air-trapping.[10] However, a restrictive spirometry pattern may also be an indicator of air-trapping and small airways disease.[11,12]

Previous publications describing the burden of respiratory abnormalities at the sentinel MP plant focused on current workers.[1,3,13] However, the health status of current workers may not fully capture the burden of work-related disease due to the healthy worker survivor effect where workers with illness tend to leave the work-force.[14,15] Cases of obliterative bronchiolitis and severe airways disease from the sentinel MP plant studied by NIOSH were former workers at the time of diagnosis,[2] which is consistent with a healthy survivor effect due to work-related illness in the MP workers.

This study sought to evaluate for evidence of healthy worker survivor effect in current and former workers at the sentinel MP plant. In addition, it sought to compare the frequency and patterns of abnormal spirometry and spirometric lung function drops in MP and FM workers. Finally, associations between work-related factors and abnormal spirometry, including excessive drops in lung function, were investigated.

METHODS

We analyzed periodic spirometry data collected during eight health surveys from 2000 to 2003 by NIOSH on current and former workers from a MP plant in Missouri as part of a health hazard evaluation investigation,[16] and collected from 2004 to 2009 by 20 companies on California FM current workers as part of a medical surveillance program.[6,17] We signed a data use agreement with the California Department of Public Health whereby we obtained de-identified surveillance data for use in this analysis.

We compared the burden of all types of spirometric abnormalities at each worker's most recent test and excessive drops in lung function among the FM workers and three groups of MP workers with different employment status during the original study: workers employed at the plant during their entire participation in the study ["Microwave Popcorn Current" (MPC)]; workers who were currently employed at the start of their participation and continued in health surveys after leaving the plant [“Microwave Popcorn Current-to-Former [MPCF]); and workers who had left employment at the plant before the start of the surveys in 2000 and whose entire participation was as former workers [“Microwave Popcorn Former” (MPF)]. All current employees at the MP plant had been invited to participate in the 2000 to 2003 surveys. Recruitment of former workers at the MP plant for the original survey in November 2000 had involved three approaches: newspaper advertisements, referral by coworkers, and telephone invitations to former workers identified by plant management and two temporary agencies that supplied the plant with employees. Employee rosters may have not included contract workers or employees with short tenure. Outreach efforts were supplemented by phone directory searches for disconnected or incorrect phone numbers, and at least three additional call attempts if a person was not reached. However, records of refusals or unsuccessful contacts were not maintained. Recruitment of former workers for the seven subsequent surveys involved announcement mailings to previous participants and referrals from former coworkers for new participants.

For this current analysis, we classified all spirometry tests from the MP and FM workers using the same grading scheme based on the acceptability and repeatability criteria recommended by the American Thoracic Society.[18,19] Each test received a separate quality grade for FEV1 and FVC. Any trial deemed not usable by the testing technician was not considered when grading the quality of the test session. We included spirometry tests in our analyses if the session contained at least two trials with acceptable starts and adequate inspiration for FEV1 and FVC, and additionally, acceptable end of test for FVC, and the highest two values for FEV1 and for FVC were within 250mL. We compared spirometry results with reference values based on a worker’s age, sex, height, and race.[20] Each worker’s largest FVC and FEV1 were selected for analysis. Workers were classified as having borderline airway obstruction if they had an FEV1/FVC ratio below the lower limit of normal (LLN) (5th percentile) with a FEV1 at or above the LLN. If the FEV1 was also below the LLN, the classification was obstruction. A restrictive pattern was classified as a FEV1/FVC ratio at or above the LLN with an FVC below the LLN. Workers with an FEV1/FVC ratio, FEV1, and FVC below the LLN were classified as having mixed obstructive and restrictive pattern abnormalities. When a spirometry test was determined to have an obstructive, restrictive, or mixed pattern, the severity was graded using the percent of predicted FEV1 (ppFEV1) as follows: mild if ppFEV1 was 70 or higher; moderate if ppFEV1 was from 60 to 69; moderately severe if ppFEV1 was from 50 to 59; severe if ppFEV1 was from 35 to 49; and very severe if ppFEV1 was less than 35.[21]

Statistical Methods

The data analysis was part of a study reviewed and approved by the NIOSH Institutional Review Board. Statistical analyses were carried out using JMP 13, SAS 9.4 statistical software (SAS Institute Inc., Cary, NC), and the NIOSH Spirometry Longitudinal Data Analysis (SPIROLA) software (http://www.cdc.gov/niosh/topics/spirometry/spirola-software.html). Using the last included test for each worker, we calculated the prevalences of spirometric abnormalities. We categorized severity as high if severity was moderately severe, severe, or very severe. We compared the prevalences of spirometric abnormalities and the severity of abnormalities among current and former MP workers and current FM workers using prevalence ratio regression (PROC GENMOD with a binomial distribution and a log link) adjusted for smoking (ever, never) and body mass index (BMI). We used the ilink and diff option in the lsmeans statement to obtain statistical tests on the prevalences of the spirometric abnormalities. We compared the prevalence of obesity (likelihood ratio test) and mean BMI (t-test) in workers with and without a restrictive spirometry pattern.

We ran analysis of variance models (ANOVA) on ppFEV1, ppFVC, and FEV1/FVC at last test in relation to the different worker groups and in relation to indicators of flavoring exposure with adjustment for smoking and BMI. We applied the Tukey–Kramer multiple means comparison method to the prevalence ratio and the ANOVA models. We assessed associations between any spirometric abnormality and indicators of flavoring exposure using multivariable logistic regression adjusted for smoking, and BMI. For the MP models, we used categories of cumulative diacetyl exposure (low, medium, and high) with cut-points at the 25th and 75th percentile of cumulative exposures calculated separately for models on last spirometry test results (all workers) and for the models on excessive drops in lung function (workers with two or more spirometry tests). Methods for the calculation of cumulative diacetyl exposures have been given in detail elsewhere.[22] As we did not have exposure measurements for the FM group, we used work in compounding/mixing as reported from questionnaires completed during the follow-up period. We assigned workers as having any work history in compounding if they listed “compounder” or “mixer” as their current job title in any survey. In addition, we used ever having a mixing job as reported in questionnaires for the MP workers to compare with the FM models. This was done under the assumption that compounding and mixing jobs had a potential for exposure to flavoring chemicals. Published results on the study MP facility indicated the highest diacetyl exposures in the mixing room[3,16] and a study of 16 flavor manufacturing companies described the potential for diacetyl exposure during compounding/mixing activities.[23]

We used SPIROLA software to assess excessive drops in FEV1 and in FVC using the relative longitudinal limit of decline (LLDr). As described in the SPIROLA manual,[24] excessive decline in FEV1 and FVC over time with less than eight years of total follow-up is evaluated using the LLDr limit. LLDr limit values for both FEV1 and FVC are calculated using the first test values as baseline, follow-up time, the rate of decline due to ageing (referential slope), and an estimate of the standard error of the referential slope of decline. This standard error formula includes an estimate of the within-person standard deviation. Different within-person standard deviations will correspond to different LLDr decline limits. A 4% within-person standard deviation and a 6% within-person standard deviation will correspond to a 10% and a 15% LLDr threshold, respectively. We calculated the LLDr using two different settings in SPIROLA: (1) a 30mL/year referential decline to account for aging and a10%decline limit in the first year, with the limit increasing by an additional 30mL for each year of follow-up; and (2) a 30mL/year referential decline and a 15% decline limit in the first year, with the limit increasing by an additional 30mL for each year of follow-up. The American College of Occupational and Environmental Medicine recommends using a 10% to 15% decline from baseline after accounting for aging when the test quality is adequate, and a disease endpoint is known.[25] Furthermore, the American Thoracic Society statement on spirometry in the occupational setting acknowledges that declines of less than 15% over shorter time periods may be clinically important for diseases that develop rapidly.[26]

We characterized the presence of an excessive drop at the 10% LLDr threshold and again at the 15% threshold by considering if any test value during the follow-up period was below the respective LLDr limit. We categorized workers as having excessive drops in FEV1 only, FVC only, and both FEV1 and FVC. We compared the prevalence of smoking and obesity (likelihood ratio test) and mean BMI (t-test) in workers with and without excessive drops in lung function. We assessed associations between excessive drop (yes/no), based on a 10% LLDr, and indicators of flavoring exposure using multivariable logistic regression adjusted for smoking, BMI, and person-months of follow-up.

RESULTS

Study Population MP

Over the years of the health hazard evaluation surveys at the MP plant, the participation for current workers ranged from 71% to 91% and the workforce ranged from 135 to 165 workers.[13,16] It was calculated from company records that of workers employed at the MP plant from 1992 to 2000, 425 no longer worked there as of May 2000.[27] Although approximate, the participation among workers not employed at the plant at the start of the study is estimated at 160/425 (38%). Of the 535 MP workers participating in spirometry testing, 527 (98.5%) had at least one test included in the analyses; all had smoking, BMI, and work-history information. If a worker went on extended sick or medical leave and did not return to work during the study, they were considered a former worker for that portion of the study. Of the 527 participants, 333 were current workers (MPC) during the full course of the study, 160 were former workers during the entire study period (MPF), and 32 were current workers at the start of the study and became former workers during the study (MPCF); we were unable to calculate a participation rate for the MPCF workers. Two workers changed status from former to current during the study and were not included in the analyses, leaving a total of 525. Of these 525 participants, there were 266 MP workers with two or more tests included in the analyses and 151were MPC workers, 83 were MPF workers, and 32 were MPCF workers.

Study Population FM

Participation in medical surveillance by potentially exposed workers was required by the state regulatory agency. Participation was not independently confirmed, but this policy likely resulted in a high participation rate. Of the 724 FM workers tested, 572 (79.0%) had at least one spirometry test included in the analyses, of whom 547 had the demographic data needed for lung function interpretation. Of the 547 workers, there were 484 with smoking information, 507 with BMI information, and 446 with smoking and BMI information. Tenure information was available for 480 FM workers. Included in the longitudinal analyses were 251 workers with two or more tests; one of whom did not have the demographic information needed for spirometry interpretation. Smoking information was available for 215 workers, 223 for BMI, and smoking and BMI together were available for 187 workers. Information on working as a compounder/mixer was available for 217 of the 251 workers.

Characteristics of Total Study Population

The MP workers were predominately white, with approximately equal numbers of males and females, except for fewer males in the MPF group (Table 1) and ranged in age from 18 to 69. Tenure for MP workers had a wide range from days to 19 years. The FM workers were predominantly Hispanic males, 17 to 68 years old. Their tenure ranged from days to 28 years. There were 61 (12.3%) compounders/mixers in the FM group and 25 (4.8%) in the MP workers.

Characteristics of Workers With Two or More Spirometry Tests

The demographics and the patterns of lung function results for the subset of the study participants who had two or more spirometry tests were similar to the total study population (see Table, Supplemental Digital Content 1, http://links.lww.com/JOM/A728). The FM (17.8) and MPC (18.9) workers had shorter mean follow-up times in months than the MPF (22.2) workers or the MPCF (23.8) workers. The FM workers also had a lower mean number of spirometry tests (3.1) than the MP groups (4.1 to 4.6). The mean cumulative diacetyl exposure was lowest numerically in the MPC workers, but this was not significantly different than the MPF workers. There were 32 (14.7%) compounders/mixers in the FM group and 20 (7.5%) in the MP workers.

Spirometry at Last Test

Unadjusted comparisons between the four worker groups' spirometry results are given in Table 1. Comparisons adjusted for smoking and BMI (Fig. 1) showed that there was statistically less obstruction in the FM workers than the MPF workers, and marginally (P=0.086) less obstruction between the FM and the MPCF workers. A mixed pattern and high severity abnormalities were more prevalent in the MPF and MPCF workers than in either the MPC or the FM workers. The prevalences of borderline obstruction and a restrictive spirometry pattern were not statistically significantly different between MP and FM workers. Compared with all other workers, those workers with a restrictive spirometric pattern had a statistically higher ($P<0.05$) prevalence of obesity (54.4% vs 30.1%) and a higher mean BMI (31.2 vs 28.1). Although 16.7% of obese workers had a restrictive pattern, 6.8% of nonobese workers had a restrictive pattern.

Comparisons of ppFEV1, adjusted for smoking and BMI indicated lower mean values in the MPF (86.8%) and MPCF (83.5%) groups, while the FM group (95.6%) had a similar mean ppFEV1 to the MPC group (95.7%). Adjusted mean ppFVC for MPC (99.3%) was higher than FM (97.0%), MPF (91.6%) and MPCF (91.7%). Mean FEV1/FVC was additionally adjusted for age and was highest in the FM group (80.8%), the MPC group had the next highest at 79.0%, while the MPF (77.0%) and MPCF (74.3%) groups were lower, and not statistically different from each other.

Excessive Lung Function Drops

Workers from both the MP and FM groups showed excessive drops in FEV1 alone, FEV1 and FVC together, and FVC alone during their follow-up period. As would be expected, excessive drops were more prevalent for a 10% than a 15% LLDr threshold (Table 2 and Table Supplemental Digital Content 2, http://links.lww.com/JOM/A729). Using the 10%

LLDr threshold, for all MP workers regardless of employment status, there were 20.7% with a drop in FEV1, FVC, or both (termed “any” drop), and a similar percentage of FM workers (21.5%) had any drop. Using the 15% LLDr threshold, 9.0% of all MP workers and 8.4% of FM workers had any drops. MPC workers had the lowest occurrence of any excessive drop of at the 10% and 15% LLDr threshold. Notably, both groups of MP workers who had left employment at the facility (MPF and MPCF) had excessive drops in lung function at the 10% and 15% LLDr thresholds. FM workers had a statistically higher prevalence of excessive drops in FVC only compared with MP workers at the 10% LLDr threshold (8.4% vs 4.1%, $P<0.05$).

The prevalence of having ever smoked, the prevalence of obesity, and the mean BMI were not statistically different between workers with or without excessive drops in lung function at the 10% LLDr threshold. In MP workers, 38% of those with excessive decline were obese, their mean BMI was 29.0, and 56% had ever smoked; while 35% of MP workers without excessive drops in lung function were obese, their mean BMI was 28.6, and 55% had ever smoked. In FM workers, 37% of those with excessive decline were obese, their mean BMI was 28.6, and 48% had ever smoked; while 31% of MP workers without excessive drops in lung function were obese, their mean BMI was 28.1, and 35% had ever smoked.

FM workers with excessive drops had higher percentages of individuals with normal spirometry at first testing and at last testing than did MP workers (Table 2). For the 10% LLDr threshold, there were eight MP workers with normal spirometry at first test but abnormal spirometry at last test. These eight workers had a variety of spirometric abnormalities (three borderline obstruction, two obstruction, two restrictive pattern, one mixed pattern). In contrast, there were 10 FM workers normal at first test who were abnormal at last test and all 10 had developed a restrictive pattern. At first testing, these 10 FM workers had a mean BMI of 27.5. Three of the 10 workers had a BMI of 30 or more, with a maximum of 34.4. At last testing two of the 10 workers had missing BMI information, but at first testing, their BMIs had been 22.6 and 27.2. Of the eight workers with data, the mean BMI was 29.4. Five workers had a BMI of 30 or more, with a maximum of 35.0.

Lung Function in Relation to Work-Related Factors

Last Spirometry—Higher diacetyl exposures and working in a mixing job were associated with higher odds of abnormal spirometry after adjustment for smoking and BMI in the MP workers (Table 3). Compared with FM workers in other jobs, FM compounders/mixers had an odds ratio of 1.7 (P=0.11) for having abnormal spirometry and an odds ratio of 1.9 (P=0.12) for having a restrictive spirometry pattern. Models on ppFEV1, ppFVC, and FEV1/FVC indicated that the MP workers in the high category of cumulative diacetyl exposure had lower values as compared to those with the low-level exposure. Furthermore, the MP compounders/mixers had lower ppFEV1 and FEV1/FVC than other MP workers, while in the FM workers, compounders/mixers had a lower FEV1/FVC, with the magnitude of the difference being smaller in the FM workers than in the MP workers.

Lung Function Drops Using a 10% LLDr Threshold—Using a 10% LLDr threshold, drops in FEV1, FVC, or both were significantly related to cumulative diacetyl exposure (Table 3). Working as a compounder/mixer was associated with a drop in lung function with an odds ratio of 2.7 (P=0.06) in the MP workers and an odds ratio of 2.8 (P<0.05) in the FM workers. Using a 10% LLDr threshold for a drop in FVC only as the outcome variable gave a similar, but not statistically significant odds ratio of 2.7 for compounder/mixer in the FM workers. Small numbers of excessive drop in FVC only precluded the use of this analysis in the MP workers.

DISCUSSION

Using data that included both current and former MP workers and those MP workers who left employment during the study period, we found evidence for a healthy worker survivor effect at the sentinel MP plant. Current workers had higher mean ppFEV1 and FEV1/FVC ratio, fewer mixed spirometry abnormalities, fewer severe abnormalities, and a lower percentage of excessive drops in lung function than either the workers who had left employment before the study began or those who had first participated as current workers and left employment during the course of the study. Previous work on the current workers has documented that workers starting work at the MP plant after major exposure controls had been put in place had fewer respiratory abnormalities than those who had worked there during the period of higher exposures.[13] The former workers experienced exposures at the plant before controls were in place, but so did many of the current workers included in our analyses. The range of exposures would have varied for both groups depending on where they worked in the plant. The healthy worker survivor effect is consistent with the idea that workers who get ill from an occupational exposure will leave the workforce and thus leave less affected workers as current workers, this could be due to both changes in exposure and other susceptibility factors. Excessive drops in lung function could not be explained by obesity or smoking and were associated with work-related factors. Taken together, these findings indicate that the burden of respiratory abnormalities in this cohort is greater than previously described by cross-sectional analyses limited to current workers.[1,2]

There have been two previous publications on the FM workers that took part in the surveillance program in California, one cross-sectional analysis on a smaller cohort,[6] and a longitudinal analysis of decline in FEV1 based on data from the same cohort as the present study.[17] In the current analyses, we included data from this cohort to compare the burden of all types of spirometric abnormalities and excessive drops in lung function between the MP and FM workers. The observed similarities in respiratory health profiles between current MP and FM workers indicate that it is possible that current FM workers who participated in surveillance were healthier than former FM workers and those FM workers who left employment during the surveillance period. Our results support recommendations that medical surveillance of flavoring-exposed workers include spirometric evaluation at the end of employment,[22] and suggest that protocols for periodic monitoring after employment should be explored. This need is further supported by our finding that excessive drops in lung function were found in both current and former MP workers. Thus, an important finding was that removal from work-related exposure did not always lead to immediate stabilization of lung function.

Previous analyses of longitudinal spirometry data from these two cohorts focused on the change in FEV1, reflecting concerns about evolving obstructive abnormalities that could indicate development of flavoring-related obliterative bronchiolitis.[13,17] Accumulating evidence that obliterative bronchiolitis, generally, and flavoring-related lung disease, specifically, can also present with restrictive spirometry, [7,8,28,29] led us to examine the change in FVC as well. We found that in contrast to obstruction and mixed patterns, the prevalence of spirometric restriction did not differ significantly across the MP and FM worker groups, with 8% to 11% of workers showing a restrictive pattern on last test. This was similar to the 8% of spirometric restriction reported in a cohort of 982 MP workers.[30] The authors in that study considered the 8% prevalence elevated compared with 5.4% in the U.S. population.[31] We found that after adjustment for smoking and BMI, there was a trend, although not statistically significant, for FM mixers/compounders to have more spirometric restrictive pattern and higher odds of drops in FVC only, which indicates a possible work-related effect. Of note in our study, the former MP workers and the FM workers appeared to be more likely to have an isolated decline in FVC than other MP workers. Using the more sensitive 10% LLDr threshold, we found that 7% to 8% of former MP workers and FM workers had excessive drop in FVC alone, whereas just 3% of other MP workers did. Although fewer participants met the definition of excessive drop in FVC when the more specific 15% LLDr threshold was used, we observed the same pattern of former MP workers and FM workers having about twice the prevalence of excessive drop on FVC than other MP workers.

For the former MP and the FM workers, these isolated declines in FVC likely reflect distinct functional processes. The former MP workers with two or more spirometry tests had a high prevalence of obstructive abnormalities (35%), and most of those with excessive drops of any kind already had abnormal spirometry at baseline. Thus, in this group, an isolated decline in FVC could indicate air trapping in the setting of obstruction. Conversely, the FM workers with two or more spirometry tests had a low prevalence of obstructive abnormalities (4%), and most of those with excessive drops had normal spirometry throughout the study. For the FM workers, therefore, an isolated decline in FVC is more consistent with evolving spirometric restriction, and indeed, all FM workers in our study with excessive drops who were normal at first testing and became abnormal at last testing had developed spirometric restriction. Although some of these 10 workers were obese, a number were not, suggesting that obesity alone was not the cause of the development of a restrictive spirometric pattern in the FM workforce.

Notably, studies of other FM workers have found evidence of restriction. In one study, analysis of corporate surveillance data demonstrated an excess of restrictive spirometry and evidence that changes in lung function were related to exposure among 106 flavoring workers.[29] In another, data collected as part of a health hazard evaluation revealed associations between exposure surrogates and pp FEV1, FVC, and total lung capacity.[32] Compared with MP workers, flavoring workers' potential exposures are far more diverse, including diacetyl, related alpha-diketones, and a host of other flavoring chemicals, most of which have unknown respiratory toxicity.[32] These differences in exposure could account for the spirometric differences between MP and FM that we observed. More recently, a study on MP workers found significant parallel declines in ppFEV1 and ppFVC in relation to employment duration in a group whose tenure had been in a period of lower diacetyl exposures. The modelsin the study had been adjusted for BMI and smoking. The authors speculated that the lower chronic exposures to diacetyl may have led to low-grade bronchiolitis marked by the spirometric restrictive pattern.[30] A 2016 overview on the recent findings related to the restrictive spirometry pattern pointed out that it is not a simple marker of obesity, and that it has been shown to occur in under weight subjects. Although BMI is often higher is subjects with the restrictive spirometry pattern, studies have reported that the majority of obese subjects have normal lung function.[33] Given that spirometric restriction is a riskfactorforpoorhealthoutcomesgenerally,[33–35] long-term follow-up of the FM workers would help to better understand the consequences of excessive declines in FVC in this group.

It has been shown that a restrictive spirometric pattern can be indicative of airways disease.[11,36] Reduced FVC and a spirometric restrictive pattern were common findings in World Trade Center (WTC)-exposed subjects.[37] Further studies have indicated that the spirometric restrictive pattern in WTC-exposed people was often associated with indications of air trapping and airways disease.[12,38,39] Given that flavoring exposure has been linked to fixed airways disease,[22] it is possible that the spirometric restrictive pattern seen in our flavoring-exposed subjects is related to airways abnormalities, but this has not yet been directly investigated.

We used the LLDr method as implemented in SPIROLA software, as it is suitable for follow-up times of 8 years or less[40,41] and takes into account within-person variability as a measure of precision of the spirometry testing. Our mean study follow-up times for the worker groups ranged from 17.8 to 23.8 months and the longest follow-up period was 33.4 months for the MP workers and 56.9 months for the FM workers. Although it is possible to set the LLDr thresholds using the within-person variability calculated by SPIROLA from the data itself [the within-person variability calculated by SPIROLA for our study worker groups ranged from 4% to 6% (data not shown)], we chose to set the relative within-person variability at 4% (corresponding to a 10% threshold) and at 6% (corresponding to a 15% threshold). However, we used the 10% LLDr threshold for our primary analyses on excessive drops over time, as flavoring exposure has been associated with lung disease and it can develop in a short time period[16,22] we used good quality spirometry tests in the study; and we were interested in a sensitive cut point.[25,26] Furthermore, the within-person variability calculated by SPIROLA can also be increased due to effects of exposure and not only represent the quality of the spirometry testing.[24,25] The models using excessive drops based on a 10% LLDr threshold indicated associations with diacetyl exposure or working as a compounder/mixer. This is consistent with these drops in lung function not being primarily due to normal variation in lung function or measurement error, as if they were the dominant reasons for the drops they would not be expected to occur more often in any one exposure group than another.

The strengths of the study include having longitudinal spirometry data on both MP and FM workers, and within the MP workers having data on current workers, former workers, and workers who left employment during the study but remained in the spirometry testing. Furthermore, to have better comparability between spirometry results, we regraded all spirometry tests on the MP and the FM workers using a standardized scheme that applied both acceptability and repeatability criteria. We also used a standardized longitudinal limit of decline approach to estimate excessive drops over time. However, this study has some limitations. There is a possibility for selection bias in the MP former workers, as only 38% participated and being worried about their health and/or having symptoms or poor lung function could have been a reason for participation. The higher spirometric abnormalities in the group of MP workers that left employment during the study and continued follow-up testing is consistent with work-related health concerns being a cause of their leaving and supports the presence of a healthy worker survivor effect in the MP workers. We had no information on former FM workers and on the participation in the surveillance program, thus we could not speak to bias or directly analyze for healthy worker survivor effect in FM workers. Not all FM worker data had information on smoking, BMI, and/or job history as a compounder; thus, statistical models using these variables were run on a smaller number of subjects. We had no information on jobs held by former MP workers after leaving the MP company that may have affected lung function in these subjects. Lastly, the MP and FM workers in the study were followed for different time periods that may affect estimates of prevalence of excessive drops in lung function. This was one of the reasons we chose to look for drops at any time during a subject’s follow-up period. Furthermore, in models where excessive drops were the outcome variable, we included follow-up time in the models to adjust for the different follow-up times when estimating the effect of work-related factors.

CONCLUSION

Health information on former workers can be important to describe the nature, burden, and natural history of lung function abnormalities in flavoring-exposed workers; thus, there is a need to consider the healthy worker survivor effect in such studies to fully characterize work-related disease. Another important finding from our study of former workers was that removal from work-related exposure did not always lead to immediate stabilization of lung function. This suggests that protocols for periodic monitoring after employment should be explored. In flavoring-exposed workers, both obstructive and restrictive spirometric abnormalities should raise suspicion of possible work-related disease. In this regard, an excessive decline in FVC with a preserved FEV1/FVC ratio may indicate signs of possible work-related airways disease and merits further evaluation, although other risk factors such as obesity should be taken into account. Finally, our findings point to the importance of repeated spirometry testing of flavoring-exposed workers over time with attention to excessive drops in lung function that may remain in the normal range as a possible sign of early work-related adverse effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Learning Objectives

- Discuss previous evidence on respiratory disorders in microwave popcorn workers (MPW) and flavoring manufacturing workers (FMW).
- Summarize the new findings on spirometry results in current and former MPW, compared to FMW.
- Discuss the implications for understanding the burden of respiratory disease in these occupational groups, including follow-up after removal from exposure.

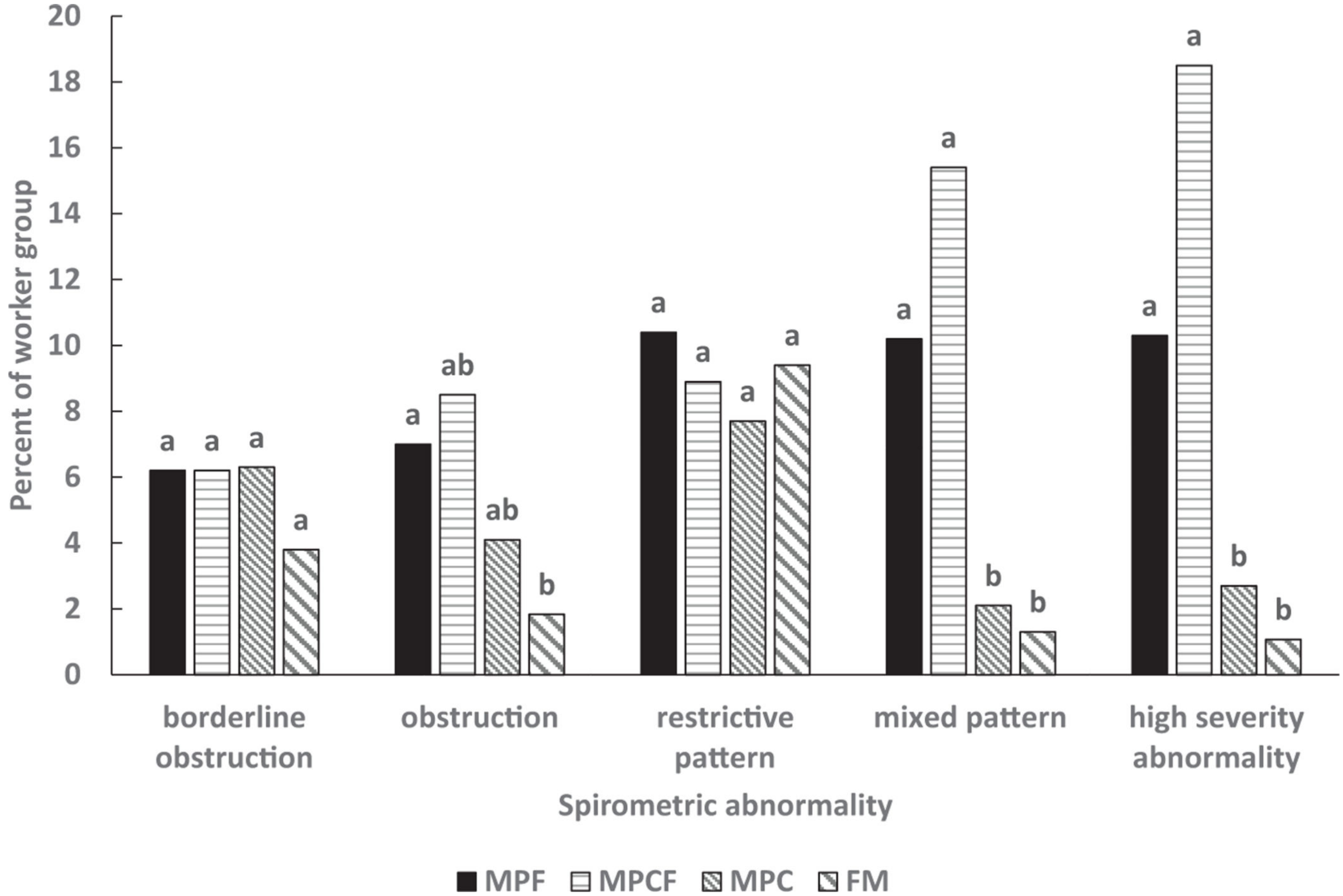

FIGURE 1.

Spirometric abnormalities at last spirometry testing in former and current MP workers and FM workers adjusted for BMI and smoking. FM, flavoring manufacturing workers (current); MPC, current microwave popcorn workers; MPCF, current to former microwave popcorn workers; MPF, former microwave popcorn workers. Within each spirometric abnormality, bars with the same letter are not statistically different at $P \leq 0.05$ (using Tukey–Kramer multiple comparison procedure).

TABLE 1.

Characteristics at Last Spirometry Test of 525 Microwave Popcorn Workers and 547 Flavoring Manufacturing Workers With at least One Spirometry Test

Demographic Characteristic	MPF (*n* = 160)	MPCF (*n* = 32)	MPC (*n* = 333)	FM (*n* = 547)
Age, years: mean (SD)	36.2^{A} (10.9)	41.1^{A} (12.3)	32.4^{B} (12.1)	38.4^{A} (11.9)
Males %	35.0^{B}	46.9^{AB}	54.1^{A}	77.1^{C}
Race/ethnicity %				
White	93.1^{A}	96.9^{A}	74.8^{B}	21.6^{C}
Black	0.0	0.0	0.6	4.4
Hispanic	5.6^{A}	3.1^{AB}	22.8^{B}	58.0^{C}
Asian	0.0	0.0	0.0	13.7
Other	1.3	0.0	1.8	2.4
Smoke ever %	62.5^{B}	50.0^{AB}	61.9^{B}	38.0^{A}
BMI: mean (SD)	29.0^{A} (6.7)	29.6^{A} (7.6)	28.0^{A} (7.1)	28.4^{A} (6.0)
Obese (BMI ≥30) %	38.8^{A}	37.5^{A}	31.2^{A}	31.2^{A}
Tenure years: mean (SD)	1.7^{B} (2.2)	3.8^{AB} (4.5)	2.5^{B} (4.2)	5.9^{A} (6.6)
Compounder/mixer	7 (4.4)	2 (6.3)	16 (4.8)	61 (12.3)
Cumulative diacetyl exposure: mean (SD) ppm.years	4.4^{AB} (6.98)	7.6^{A} (11.68)	3.8^{B} (8.29)	N/A
Borderline obstruction %	6.3^{A}	6.3^{A}	6.3^{A}	3.5^{A}
Obstruction %	8.1^{B}	9.4^{B}	4.8^{B}	1.5^{A}
Restrictive pattern %	11.3^{A}	9.4^{A}	8.4^{A}	11.0^{A}
Mixed pattern %	10.0^{B}	15.6^{B}	2.1^{A}	1.1^{A}
Any spirometric abnormality %	35.6^{B}	40.6^{B}	21.6^{A}	17.0^{A}
High severity abnormality %	10.0^{B}	18.8^{B}	2.7^{A}	0.9^{A}
ppFEV1: mean (SD)	86.7^{B} (21.7)	83.3^{B} (25.0)	95.8^{A} (15.9)	95.6^{A} (13.8)
ppFVC: mean (SD)	91.5^{C} (16.0)	91.4^{BC} (20.1)	99.4^{A} (14.1)	96.5^{B} (12.4)
FEV1/FVC: mean (SD)	76.9^{B} (12.6)	72.9^{B} (13.5)	80.0^{A} (9.0)	80.7^{A} (7.0)

Unadjusted comparisons between the four worker groups are given. Tenure, compounder/mixer, smoking, and BMI information was available for 480, 498, 484, and 507 FM workers, respectively. Across columns, values containing the same letters are not statistically different at $P \leq 0.05$ (using Tukey–Kramer multiple comparison procedure).

BMI, body mass index; FM, flavoring manufacturing workers (current); MPC, current microwave popcorn workers; MPCF, current to former microwave popcorn workers; MPF, former microwave popcorn workers; ppFEV1, percent of predicted FEV1; ppFVC, percent of predicted FVC; ppm, parts per million; SD, standard deviation.

TABLE 2.

Excessive Drops in Lung Function Based on an LLDr Threshold of 10%

	Any Number (%)	FEV1 Number (%)	FEV1 and FVC Number (%)	FVC Number (%)	Normal Spirometry at First Test/Any Drop	Normal Spirometry at Last Test/ Normal Spirometry at First Test
All MP (266)	55 (20.7%)	20 (7.5%)	24 (9.0%)	11 (4.1%)	20/55 (36.4%)	12/20 (60.0%)
MPF (83)	21 (25.3%)	8 (9.6%)	7 (8.4%)	6 (7.2%)	5/21 (23.8%)	3/5 (60.0%)
MPCF (32)	10 (31.3%)	1 (3.1%)	8 (25.0%)	1 (3.1%)	6/10 (60.0%)	3/6 (50.0%)
MPC (151)	24 (15.9%)	11 (7.3%)	9 (6.0%)	4 (2.7%)	9/24 (37.5%)	6/9 (66.7%)
FM (251)	54 (21.5%)	8 (3.2%)	25 (10.0%)	21 (8.4%)	49/53 (92.5%)[a]	39/49 (79.6%)

Any, an excessive drop in FEV1 or FVC or FEV1 and FVC.

FM, flavoring manufacturing workers (current); LLDr, relative longitudinal limit of decline; MP, microwave popcorn workers; MPC, current microwave popcorn workers; MPCF, current to former microwave popcorn workers; MPF, former microwave popcorn workers.

[a]One worker with excessive decline had unknown race, thus had no spirometric determination in relation to normal values.

TABLE 3.

Odds Ratios From Logistic Models on Any Type of Spirometric Abnormality, Excessive Drops in Lung Function, and Adjusted Means From ANOVA Models on Lung Function Parameters in MP and FM Workers

	Abnormal Spirometry (Adjusted Odds Ratios)		LLDr 10% Threshold, Drop in FEV1, FVC or Both (Adjusted Odds Ratios)		ppFEV1 (Adjusted Means)		ppFVC (Adjusted Means)		FEV1/FVC (Adjusted Means)	
Variables	**MP**	**FM**	**MP**	**FM**	**MP**	**FM**	**MP**	**FM**	**MP**	**FM**
Cumulative diacetyl exposure		N/A		N/A		N/A		N/A		N/A
High	4.2^{**}		4.2^{**}		83.4^{A}		90.7^{A}		75.8^{A}	
Medium	2.3^{**}		2.7^{*}		94.0^{B}		97.4^{A}		79.6^{B}	
Low	1		1		98.1^{B}		100.6^{B}		80.2^{B}	
Compounder/mixer										
Yes	2.2^{*}	1.7	2.7^{*}	2.8^{**}	80.8^{A}	94.8^{A}	92.7^{A}	97.9^{A}	68.4^{A}	78.5^{A}
No	1	1	1	1	92.8^{B}	95.8^{A}	96.6^{A}	96.8^{A}	79.2^{B}	80.6^{B}

All models adjusted for smoking and BMI, the model for FEV1/FVC was also adjusted for age, models on excessive drops also adjusted for months of follow-up.

FM, flavoring manufacturing workers; LLDr, longitudinal limit of decline; MP, microwave popcorn workers; ppFEV1, percent of predicted FEV1; ppFVC, percent of predicted FVC.

* $P \leq 0.10$. Within a column, means with the same letter are not statistically different at $P \leq 0.05$ (using Tukey–Kramer multiple comparison procedure for the cumulative diacetyl exposure group comparisons).

** $P \leq 0.05$.