Cancer Causes Control (2008) 19:107–114
DOI 10.1007/s10552-007-9076-7

ORIGINAL PAPER

Nested case–control study of occupational physical activity and prostate cancer among workers using a job exposure matrix

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Received: 6 November 2006 / Accepted: 4 October 2007 / Published online: 7 December 2007

Abstract
Objective We conducted a nested case–control study of 362 cases diagnosed between 1 January 1988 and 31 December 1999, and 1,805 matched controls to examine the association between occupational physical activity and prostate-cancer incidence among workers at a nuclear and rocket engine-testing facility in Southern California.
Methods We obtained cancer incidence data from the California Cancer Registry and seven other state cancer registries. Data from company records were used to construct a job exposure matrix (JEM) for occupational physical activity during employment. Conditional logistic regression was used to estimate associations.
Results With adjustment for occupational confounders, including socioeconomic status and trichloroethylene (TCE) exposure, high activity levels at work were inversely associated with prostate-cancer incidence among aerospace workers (odds ratio [OR] = 0.55; 95% CI = 0.32–0.95), but not among radiation workers (OR = 0.95; 95% CI = 0.43–2.1).
Conclusions Our results suggest that adult men who are more continually active at work may have a decreased risk of prostate cancer.

Keywords Occupational physical activity · Prostate cancer · Job exposure matrix · Nested case–control study

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Introduction

There is substantial evidence that regular physical activity is inversely associated with the incidence of certain cancers [1]. While physical activity seems to be generally protective against colon and breast cancers [2], a consistent inverse association with prostate cancer has not been observed across studies [3, 4]. Possible reasons for these inconsistencies are difficulties in measuring physical activity retrospectively by self-report in case control studies and the use of mortality instead of incidence data in occupational cohort studies.

While population-based studies of prostate-cancer incidence often involve subjects with a wide range of physical-activity levels, they may be prone to exposure misclassification due to recall problems when relying on self-reported lifetime activity [5]. Occupational studies on the other hand can rely on company records identifying job titles and tasks such that job-related activity levels can be derived from records via expert assessment, independent of subject recall. Furthermore, in occupational studies, physical activity is more homogeneous within job categories than in population-based studies. Nonetheless, occupational studies often rely on mortality data, and thus, are missing a large proportion of non-fatal cancers such as those of the prostate [6].

We investigated the influence of occupational physical activity measured by a job exposure matrix (JEM) on prostate-cancer incidence in a case–control group nested within a cohort of aerospace and nuclear employees of Rocketdyne (now a division of the Boeing Company). In addition, we collected information on lifestyle factors, including leisure-time physical-activity (LTPA), from a subset of workers still alive at end of our follow-up period.

Materials and methods

Cases and controls were selected from two cohorts of radiation and aerospace workers that had been previously assembled to estimate the effects of radiation and chemical exposures on cancer mortality among Rocketdyne workers who were employed between 1950 and 1993 [7, 8]. Members of both cohorts worked at the same facility (Santa Susana Field Laboratory), where research, development, and testing of nuclear power systems and rocket and jet engines were conducted for national defense and space programs. The aerospace cohort consisted of 6,107 workers who were primarily engaged in rocket-engine development and testing activities. This cohort was restricted to men who started their employment prior to 1980, worked at least two years at Rocketdyne, and never engaged in radiation work [9]. The radiation cohort included 4,607 employees enrolled in the company's Health Physics Radiation Monitoring Program, who were monitored for external and/or internal radiation exposure during employment. For the present study of prostate cancer, we excluded from the latter cohort 276 females. Furthermore, we excluded 1,410 workers who died before 1988 according to data from company retirement beneficiary records, the U.S. Social Security administration and California Mortality records, and the U.S. National Death Index (NDI).

Case ascertainment and control selection

We identified 392 cases of prostate cancer diagnosed between 1 January 1988 and 31 December 1999: 337 from California; eight from Nevada; twelve from Arizona; six from Texas; fifteen from Washington; eleven from Florida; two from Arkansas; and one from Oregon. Necessary approvals from Human Subjects committees in all states were obtained to access these data. Cancer registry coverage was incomplete during the follow-up period in four states: Texas (coverage period: 1996–1999), Washington (1992–1999), Arkansas (1996–1999), and Oregon (1996–1999). We were also unable to obtain cancer incidence data from other U.S. states where 11% of our workers had died during follow-up, according to NDI records.

To make an employment-record review for the ascertainment of physical activity of workers feasible, we employed risk-set sampling and randomly selected five controls for each case among eligible workers at risk of prostate cancer from the two Rocketdyne cohorts (9,028 subjects). Controls were matched to cases on age at diagnosis (±2 years), age at the start of employment at the company (±2 years), and cohort (radiation or aerospace). Thus, initially, 1,896 controls were matched to 392 prostate cancers diagnosed and identified during follow-up.

After obtaining additional information during our record review, we subsequently excluded (1) 105 workers (17 cases and 88 controls) employed after 1980 or who worked for less than two years at Rocketdyne to ensure that workers from both cohorts were similar in terms of minimum years of employment; (2) two presumed male controls found to be female; and (3) fourteen cases and one control found to have received a secondary diagnosis of prostate cancer within three years of another primary cancer. The final study population consists of 362 cases and 1,805 controls. The study protocol was approved by the relevant Institutional Review Board.

Exposure assessment

Company records provided us with job titles and codes, dates of employment and job description manuals containing specific information about physical effort, and typical materials, tools, and equipment used for each job. Our industrial hygienist (NK) observed and conducted interviews with workers, health and safety personnel, and administrators at the facility. Utilizing company records and manuals, she rated the intensity of physical effort for each job on a five-category ordinal scale (1–5) without knowledge of case status. Ratings were reviewed by two investigators (BR and AK) who are familiar with the facility operations and records, and who conducted worker interviews independently. Discrepancies were discussed and resolved by consensus. These ratings were used to construct a JEM for occupational physical activity.

The job title for the job held longest at the facility was linked to our JEM and an occupational physical-activity score was assigned to each worker. For 80% of the subjects, the longest held job was the only job a worker held at the company. We did not have information on jobs outside of Rocketdyne employment; however, workers in this population were employed for an average of 19 years. Thus, employment at this facility covers a significant portion of their total work history. Furthermore, interviews of retired workers suggested that they commonly held previous and subsequent positions in the same industry, e.g., rocket-engine development and testing. We assigned

the lowest physical-activity score to 44 workers for whom we were unable to find any job title information. Note that excluding these workers did not alter our results. We ranked occupational physical activity into ‹low' (intensity score of one; mainly sitting), ‹moderate' (intensity score of two; sitting and standing), and ‹high' (intensity score of three or higher; walking with light to heavy manual work) activity categories. Table 1 lists common company job titles associated with each occupational activity level.

Pay-status information for the longest job held was used to categorize workers into three categories of socioeconomic status (SES): (1) professional/salaried workers, who were administrators and engineers (e.g., research, test, design, and industrial); (2) non-professional/salaried workers, who were senior-level technicians, mechanics, and inspectors in various areas (e.g., propulsion and testing, instrumentation, electrical, assembly, and laboratory); and (3) hourly workers, who were entry level or junior mechanics and technicians, welders, machinists, and maintenance workers.

Table 1 Examples of job titles for each occupational physical-activity level

Occupational physical-activity level	Common job titles
Low	Manager/supervisor
	Analyst—methods, service, wage and salary, data processing, public relations, production, maintenance
	Inspector
	Administrator—VP, buyer, clerk, secretary, special writer
	Graphic artist/technical photographer/illustrator
	Senior engineer—logistics, design, computer, quality control, manufacturing
	Engineer—research and test (radiation cohort)
Moderate	Senior mechanic/technician—assembly, instrumentation, laboratory
	Inspector—reactor assembly
	Engineer—research and test (aerospace cohort)
High	Junior mechanic/technician—propulsion testing, maintenance, automotive
	Patrol man/fire man
	Electrician
	Janitor
	Truck driver/lift truck operator
	Tool and die maker
	Industrial painter
	Crater and packer
	Welder
	Metal fitter
	Mason and bricklayer

Our industrial hygienist also created a chemical JEM that estimated intensity of exposure to several known and suspected carcinogens used at the facility, including hydrazine, trichloroethylene (TCE), benzene, polycyclic aromatic hydrocarbons (PAHs), and mineral oil. The procedures have been described in detail elsewhere [10, 11]. Briefly, exposure scores incorporated duration and intensity for each of these chemicals and were applied to the two longest jobs held at the company. Exposures were assessed for three time periods: the 1950–1960s, the 1970s, and the 1980–1990s. Since exposures to chemicals differed for aerospace and radiation workers, job titles common to both cohorts were assessed separately.

Mail and phone survey

We obtained current address and telephone information for 734 workers who were still alive in 1999 (according to the NDI data) by matching social security numbers to on-line information services (http://www.Discreetresearch.com and http://www.Cleanlist.com). Surveys were mailed to workers with pre-addressed and stamped return envelopes. Reminder letters were sent at four and eight weeks and after 12 weeks, and we tried to contact nonresponders by phone. Subjects who provided their phone number on the mailed questionnaire (69%) were called back to clarify responses. We were able to obtain data for 338 subjects (46%; including six wives as proxy respondents). We were unable to obtain information from the remaining workers because of death (13%), refusal (17%), missing contact information (12%), and nonresponse (11%). All participants gave signed or verbal informed consent.

We asked subjects to report how many hours a week they spent in housework and recreational activities during different age intervals (18–25, 25–44, 45–64, and >65 years) for three different intensity levels: light, moderate, and heavy activity. Specific examples for each intensity levels were included in the survey. For example, heavy housework was "carrying heavy objects or children upstairs, heavy digging, pushing a push mower, loading and unloading a truck, heavy manual labor" and heavy recreation was "jogging, backpacking, bicycling uphill, aerobics, exercise-machine workouts, tennis (singles), competitive sports like basketball and soccer." For data analyses, we calculated LTPA scores for each of the four age intervals by multiplying the number of hours per week of each activity (housework and recreational) by a metabolic equivalent score (MET score; for Housework: Light—3.0, Moderate—4.7, Heavy—6.0, and Recreational Activity: Light—3.0, Moderate—4.7, Heavy—7.0), and then summing across intensity levels and activity type. We created four indicator variables for heavy LTPA for each age interval using the 75th percentile MET score cutpoint. We also collected

information on weight history and height to calculate body mass index (BMI), race, smoking history, education, diabetes, family history of prostate cancer in first degree relatives, and participation in regular prostate-cancer screening.

Statistical methods

We conducted risk-set analyses using conditional logistic regression models (PHREG procedure in SAS Version 9.1) to estimate associations (odds ratios (OR) and 95% confidence intervals (CI)) between level of physical activity at work and prostate cancer [12, 13]. In this type of analysis, each case is compared with subjects still at risk of prostate cancer at the time of the case's diagnosis (the case's risk-set). The matching variables (age at diagnosis, age at the start of employment, and cohort) were treated as covariates in all models. Occupational physical-activity level was treated as two indicator variables with the low-activity group as the reference category.

We first estimated physical-activity effects controlling only for the matching variables, then extended the model to adjust for SES and TCE exposure, which was the only chemical found to be associated with prostate cancer in this worker population [14]. We also estimated associations for each cohort (aerospace or radiation) and lagged TCE exposure by 10 and 20 years. Finally, we examined associations by cancer type, i.e., advanced stage (defined as cancer that was at least spread to regional lymph nodes (non-localized), high grade (defined as Grade III (poorly differentiated) or Grade IV (or undifferentiated), and fatal prostate cancer in all workers and by cohort. In all models, we tested for monotonic associations across the three levels of physical activity.

We intended to use the information derived from our survey of workers to assess potential confounding due to non-work related risk factors for prostate cancer. However, the survey population differed considerably from the cohort population in terms of their occupational histories and exposures suggesting selection bias. Participants were more likely to hold professional/salaried positions (60 vs. 52%), experienced lower occupational physical-activity levels, and were slightly more likely to have been exposed to high levels of chemical exposures.

Thus, we conducted some limited analyses of these survey data. That is, we broke up the risk sets and employed unconditional logistic regression, while controlling for matching variables. We also examined the distributions of risk factors across occupational physical-activity levels to assess their potential for confounding. Finally, we used Axelson's Formula [15], to assess the degree of possible confounding of factors that were associated with both prostate cancer and occupational physical activity in the entire study population.

Results

Prostate-cancer cases were slightly less likely to hold more physically active jobs and non-professional/salaried positions (Table 2). Cases were more likely than controls to be highly exposed to the chemicals we evaluated, i.e., hydrazine, TCE, benzene, PAHs, and mineral oil. Mean duration of employment was similar for cases and controls.

Among all workers, we found little association between physical activity and prostate cancer, adjusting only for the matching variables (OR for high versus low = 0.91; 0.70, 1.2; Table 3). When also adjusting for SES and TCE exposure, however, high physical-activity level was associated with a decreased risk of prostate cancer (OR for high versus low = 0.63; CI: 0.40, 1.0). Note this decrease in risk was mainly due to adjustment for TCE exposure.

Separate analyses conducted for radiation and aerospace workers showed that the physical-activity cancer association differed for the two groups of workers (Table 3). We saw little association in radiation workers (OR for high versus low = 0.95; CI: 0.43, 2.1), but a moderately inverse

Table 2 Number (%) of cases and controls, by category of selected occupational variables

Occupational variable	Cases	Controls
Total number of subjects	362	1,805
Occupational physical activity		
Low	148 (41)	756 (42)
Moderate	128 (35)	565 (31)
High	86 (24)	484 (27)
Cohort		
Radiation	127 (35)	626 (35)
Aerospace	235 (65)	1179 (65)
Pay status		
Professional/salaried	193 (54)	914 (51)
Non-professional/salaried	104 (29)	597 (34)
Hourly	59 (17)	264 (15)
High chemical exposure[a]		
Hydrazine	38 (10)	127 (7)
TCE	45 (12)	124 (7)
Benzene	18 (5)	49 (3)
PAHs	48 (13)	145 (8)
Mineral oil	20 (6)	82 (5)
Mean employment duration (years)	19	18

[a] Highest quartile based on duration and intensity of exposure to each chemical

Table 3 Adjusted odds ratios (OR) and 95% CI (confidence intervals) for the association between occupational physical-activity level and prostate cancer, for all workers and by cohort

Physical activity level	No. of cases (%)	No. of controls (%)	OR[a]	95% CI[a]	OR[b]	95% CI[b]
All workers						
Low	148 (41)	756 (42)	1.0		1.0	
Moderate	128 (35)	565 (31)	0.91	0.70, 1.2	0.96	0.70, 1.3
High	86 (24)	484 (27)	1.1	0.90, 1.4	0.63	0.40, 1.0
			p trend = 0.63		p trend = 0.06	
Radiation cohort						
Low	50 (39)	307 (49)	1.0		1.0	
Moderate	48 (38)	185 (30)	1.5	1.0, 2.2	1.3	0.77, 2.3
High	29 (23)	134 (21)	1.3	0.82, 2.1	0.95	0.43, 2.1
			p trend = 0.15		p trend = 0.97	
Aerospace cohort						
Low	98 (42)	449 (38)	1.0		1.0	
Moderate	80 (34)	380 (32)	0.97	0.72, 1.3	0.84	0.57, 1.2
High	57 (24)	350 (30)	0.76	0.55, 1.1	0.55	0.32, 0.95
			p trend = 0.11		p trend = 0.04	

Results of conditional logistic regression analyses

[a] Adjusted for the matching variables (age at start date of employment, cohort, and age at diagnosis)

[b] Adjusted for matching variables, pay status, and TCE exposure (low, moderate, high)

dose–response association in aerospace workers: OR for high versus low = 0.55 (CI: 0.32, 0.95); and OR for moderate versus low = 0.84 (CI: 0.57, 1.2) (p for trend = 0.04).

We did not observe much difference in estimates for occupational physical activity by type of prostate cancer, such as advanced stage, high grade, and fatal cancer. However, these analyses were limited by sample size and our data was too uninformative to draw any firm conclusions.

Survey population analysis results

For the 338 workers who participated in the survey, controlling only for matching variables, the following risk factors were positively associated with prostate cancer: African-American race, obesity (BMI $\geq$ 30), regular participation in prostate-cancer screening, and having a family history of prostate cancer; being diabetic was inversely associated with prostate cancer (Table 4). Obesity and diabetes were not associated with occupational physical activity; however, workers with high occupational physical-activity levels were less likely to have reported a family history of prostate cancer or have been screened regularly for prostate cancer, and were more likely to be African-American.

Table 4 Associations (OR and 95% CI) between factors measured in the survey and prostate-cancer incidence

Factor	No. of cases (%)	No. of controls (%)	OR (95% CI)[a]
Total number of subjects	140	198	
African-American race	5 (4)	2 (1)	3.6 (0.7, 19)
Current BMI			
Low (<25)	42 (30)	80 (41)	1
Medium (≥25 and <30)	73 (53)	93 (47)	1.5 (0.9, 2.5)
High (≥30)	23 (17)	23 (12)	2.0 (1.0, 4.2)
Prostate-cancer screening	128 (91)	159 (81)	2.4 (1.2, 4.8)
Family history of prostate cancer	29 (25)	17 (10)	3.5 (1.7, 7.0)
Diabetes	11 (8)	33 (17)	0.4 (0.2, 0.9)
Heavy LTPA[b]			
Young adult	32 (27)	37 (23)	1.4 (0.6, 3.1)
Adult	38 (29)	41 (22)	1.3 (0.6, 2.8)
Middle aged adult	34 (26)	46 (25)	0.8 (0.4, 1.8)
Senior adult	31 (25)	46 (25)	1.0 (0.5, 1.9)

[a] Adjusted for matching variables

[b] All leisure-time physical-activity (LTPA) variables were entered into one model to account for possible mutual confounding

Discussion

In our study of two occupational cohorts, we found an inverse association between level of physical activity at work and prostate-cancer incidence in aerospace, but not in radiation workers. This dissimilarity in the association may be explained by differences in the level of continuous versus intermittent physical activity required by their work. Among aerospace workers in the high-activity group, the most common job titles were mechanics and technicians involved in rocket-engine testing (49%) followed by welders, assemblers, and machinists (15%); while among radiation workers, mechanics, and technicians comprised only 15%, and welders, assemblers, and machinists 19% of all workers who were highly active followed by patrolmen (12%), firemen (10%), and electricians (9%). According to

retired workers, mechanics, and technicians involved in rocket-engine testing sustained high levels of activity more regularly than patrolmen, firemen, and electricians who were likely more highly active on an intermittent, but not daily basis. This may have prevented us from observing an inverse association between activity and prostate cancer in radiation workers, i.e., those classified as highly active generally did not sustain a high enough level of continuous activity at work.

These findings are supported by other studies that suggest that continuous activity, but not intermittent activity, is required to lower the risk of prostate cancer [1, 16, 17]. Among 53,000 Norwegian men, investigators observed a lower risk of prostate cancer among men active recreationally and at work; but no risk reduction among workers classified as heavy manual laborers. Similarly, Hartman et al. [17] found that although men with greater LTPA were less likely to develop prostate cancer, those involved in heavy manual labor were not. They argue that heavy manual labor involves more static work, instead of continuous "dynamic" activity, which may be required to reduce the risk of prostate cancer.

The biologic mechanisms by which physical activity may influence prostate-cancer risk are unknown. Physical activity can alter hormone levels in men; e.g., male athletes and individuals with high levels of sustained physical activity exhibit decreased levels of both total and free testosterone [18]. Normal growth of the prostate gland is dependent on a critical balance of androgen levels, and results from animal and epidemiologic studies suggest that variations in these levels affect prostate-cancer risk. Both testosterone and dihydrotestosterone (DHT) have been shown to induce prostate cancer in experimental rat models [19]. In epidemiologic studies, men with prostate cancer have been shown to have higher levels of endogenous testosterone [4]. African-American men have, on average, a 15% higher testosterone level and a higher risk of prostate cancer than do white men [20]. Therefore, Freidenreich and Thune [3] have argued that increased levels of testosterone may be involved in prostate-cancer risk in humans. At present, one can only speculate that men who are more physically active may have a decreased risk of prostate cancer because they lower their levels of androgens. However, factors related to physical activity, such as dietary intake and body fat content, affect other non-androgenic hormones, e.g., insulin, and sex hormone binding globulin, and insulin-like growth factors. Thus, the interrelations between physical activity, dietary intake, and these endogenous hormones make it difficult to assess any specific pathway independently.

Previously, researchers with access to occupational cohorts often used broad measures of occupational physical activity including: (1) relying on responses to one or two general questions addressing activity levels in the past [21–23]; (2) self-reports of current occupational physical activity only [16, 17]; or (3) occupational titles obtained from work records, census records, hospital records, or death certificates [24, 25].

We believe that we improved the assessment of occupational physical activity in our study compared to many previous studies. We constructed a JEM to assess occupational physical activity during employment using personnel records, job description manuals, industrial hygiene review, and retired worker interviews and, thus, avoided problems of recall and interviewer bias. Although we expect some non-differential misclassification of physical activity because assessments were done at the job rather than individual level, this misclassification is expected to be less severe in an industry-based compared to a population-based JEM [26].

Another strength of our study is that we were able to obtain cancer incidence data for our occupational cohorts for this largely non-fatal type of cancer. However, we were only able to obtain such data for an 11-year period and population-based state cancer registries covered only 89% of our cohort during this period. Thus, we may have missed some cases, i.e., controls may have been diagnosed with prostate cancer outside of the seven states from which we obtained registry data. Based on prostate-cancer mortality rates and assuming that exposure distributions are similar for workers who did and did not move to non-coverage states, we estimated the number of missed prostate cancers to be about 50**.** Using information from NDI, cancer registry data, and updated address information from the survey data and our JEM, we found that workers who left the state did not hold more physically active or inactive jobs than workers who stayed in California. In addition, some controls may have been diagnosed with prostate cancer before 1988. Some cancer registries were active prior to 1988 (Los Angeles County registry: 1972; Nevada: 1986; Arizona: 1981; and Florida: 1981); thus, we were able to use them to identify 35 prostate-cancer cases in our original worker cohorts (aerospace and radiation) diagnosed prior to and still alive in 1988. However, none of these cases were actually selected as controls in our study population. Assuming that these registries covered approximately 40% of our worker population, we may have missed an additional 53 prostate-cancer cases still alive in 1988, but not at risk. From among these, however, we expect to have selected inappropriately no more than three to five men as controls; therefore, we expect the outcome misclassification to be minimal.

As mentioned, we were unable to assess potential confounding due to other lifestyle factors via adjustment of our regression-based estimates because of the apparent selection bias in our survey population. However, we were able

to identify associations between known risk factors and prostate cancer in the survey population (see Table 4), and three of the factors were also associated with occupational physical-activity level. Thus, African-American race, participating in regular prostate-cancer screening and having a family history of prostate cancer may have confounded the estimated effect of occupational physical activity in the total cohorts.

Although we observed an association between current high BMI (≥30) and prostate cancer among workers who participated in our survey, the estimate is unadjusted for potential confounders, so it is difficult to interpret. Also, note that this measure is current BMI and BMI at earlier age periods were not associated with prostate cancer. It is possible that prostate-cancer diagnosis and treatment lead to limited physical activity, and thus, a higher BMI. Many cases were interviewed several years after their prostate-cancer diagnosis. Since BMI and occupational and LTPA were not associated among our survey participants, we did not examine this factor further. Furthermore, since BMI is affected by physical activity and could serve as an intermediate factor, adjustment for BMI when estimating the effect of physical activity in our analyses could lead to bias.

Since Rocketdyne did not systematically collect data on the race of its employees before 1972, we were unable to control for race in our analyses. According to information on death certificates, however, 96% of all deceased workers and 97% of our survey population were white, indicating that only a very small percentage of workers at Rocketdyne were African-American. We were able to identify 54 African-American men in our study population using cancer registry data, company records, and questionnaire data. Excluding these men from analyses did not change the association between occupational physical activity and prostate cancer; therefore, we do not believe that African-American race is an important confounder in this population.

We assessed the degree of potential confounding due to the other two potential confounding factors using Axelson's formula [15], which estimates the influence a particular confounder may have on study estimates based on its strength and prevalence in the population when data on the confounder are missing or only partially available, and found that it is unlikely that the observed reduced risk in highly active jobs were attributable to confounding due to family history of prostate cancer or regular prostate-cancer screening unless one is willing to assume that every worker in highly active jobs had a family history, while none in less active jobs did or else only 20% of all active, but 80% of all inactive workers received regular prostate-cancer screening. Both scenarios seem highly unlikely given the distributions we observed in our survey.

Our results suggest that men who have jobs that require continual high activity levels may have a decreased risk of prostate cancer. Our inability to control for potentially confounding lifestyle factors due to a possible selection bias, however, limits our ability to make causal inference.

Acknowledgments We thank Kavitha Pathmarajah for help with data collection and entry, and the employees of the Rocketdyne/Boeing Company who provided valuable information about work conducted at the facility.

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