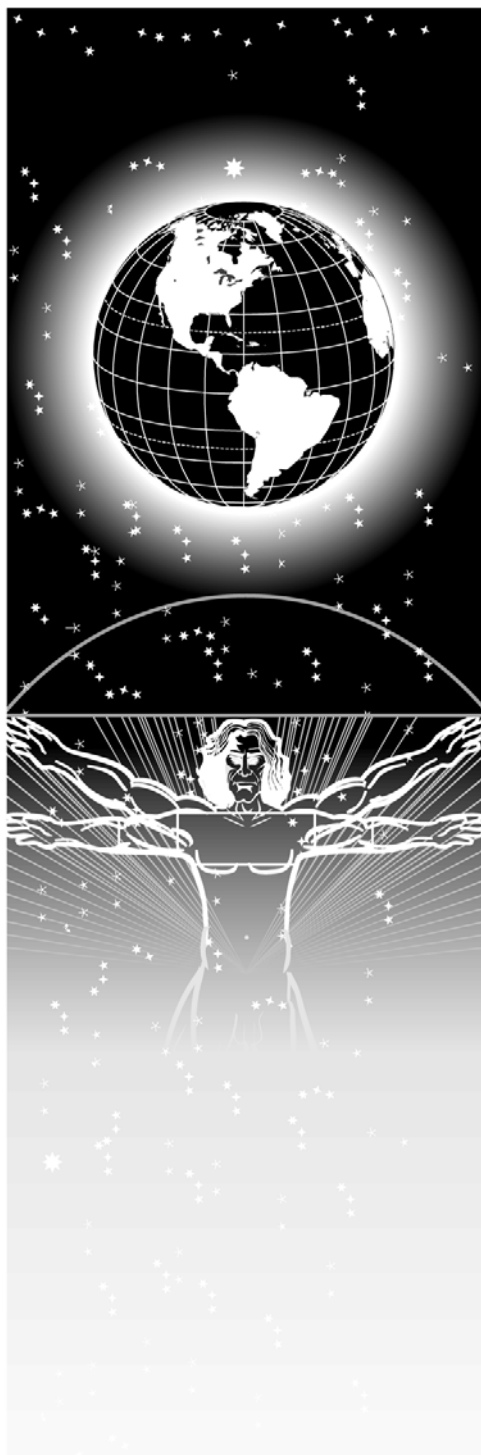




UNITED STATES AIR FORCE AFIOH

Occupational Jet Fuel Exposure and Invasive Cancer Occurrence in the United States Air Force, 1989 - 2003

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OCCUPATIONAL JET FUEL EXPOSURE AND INVASIVE CANCER OCCURRENCE IN THE UNITED STATES AIR FORCE, 1989-2003

INTRODUCTION

Jet propulsion fuel type eight (JP-8) is the primary aviation and high performance vehicle and equipment fuel used by the United States Air Force (USAF), and comprises the largest chemical exposure for these personnel [1-5]. Consequently, occupational exposure to this substance is of major concern, especially among individuals in fuel-related professions. Aircraft fuel system workers are at particular risk considering this occupation entails entry into aircraft fuel tanks and provides the potential for oral, dermal and inhalational exposures [1, 3, 6]. However, an even larger number of individuals in propulsion, aircrew egress systems and vehicle equipment maintenance professions come into contact intermittently with jet fuel and may also be at risk for adverse events.

Several studies have identified acute health effects of jet fuel exposure and include skin irritation, nausea, balance problems, headaches, loss of concentration and lingering fuel taste and odor; biological markers, namely blood and urine, were also identified as valid indicators of jet fuel exposure [1-3, 5, 7-11]. There is some evidence that the long-term effects of jet fuel exposure include increased psychiatric symptoms, impaired sensory responses and postural imbalance [4, 12]. However, the overall paucity of work pertaining to the chronic effects of jet fuel exposure is somewhat surprising considering that aromatic hydrocarbons, compounds containing at least one benzene ring, can comprise 10-20% by volume of kerosene based fuels, and have been associated with carcinogenesis [13, 14]. Most notably, benzene has already been classified as a potent human carcinogen, while naphthalene is considered a possible human carcinogen because of the significantly increased nasal cancer incidence observed in rat models following inhalation exposure [7, 13, 15]. Interestingly, there has yet to be an adequate epidemiologic assessment of the carcinogenic potential of jet fuel in humans.

The USAF provides an ideal population for conducting data records analysis because of the detailed information that is routinely collected about active duty personnel. Additionally, the implementation of a tumor registry in late 1980's allowed for linkage of cancer data with other existing databases. Consequently, the purpose of this exploratory study was to provide a foundation and direction for future work in this field by utilizing USAF personnel records and tumor registry data to measure the association between occupational jet fuel exposure and invasive cancer occurrence.

METHODS

A nested case-control study design was utilized in which the source cohort was defined as USAF active duty personnel with at least one year of active duty service in the 16-year period between 1 January 1988 and 31 December 2003.

Case subjects were obtained from the Automated Central Tumor Registry (ACTUR) [16]. The ACTUR was established on 5 May 1986 by the Assistant Secretary of Defense for Health Affairs to serve as the Department of Defense's main cancer data collection, clinical tracking and reporting system. It is operated by the Armed Forces Institute of Pathology in Washington, D.C.

and covers active duty personnel, as well as eligible beneficiaries of the Military Health System (e.g., Reserve and National Guard personnel during temporary duty activations, family members of active duty personnel, military retirees and foreign military personnel on temporary assignment to U.S. military units). Two service regulations require the report of USAF cancer patients to the ACTUR [17, 18]. Coding, data entry, and registry database management are performed by trained tumor registrars. Like the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, ACTUR includes all invasive cancer types except cutaneous basal cell and squamous cell cancers.

To allow the military services an adequate amount of time to develop, organize, fund and implement ACTUR-related business processes within their medical treatment facilities, case subject selection was restricted to cancer diagnoses made in the 15-year period between 1 January 1989 and 31 December 2003. Cancer types were determined from the case subjects' International Classification of Diseases for Oncology (ICDO)-1, ICDO-2 or ICDO-3 topology and morphology codes.

Control subjects were obtained from archival military personnel databases kept at the Data Retrieval Branch, Air Force Personnel Center (AFPC), Randolph AFB, TX. These records contain various demographic, occupational and military service-related data for current and former USAF personnel. For each case subject, four control subjects, matched on year of birth, gender and self-reported race, were randomly selected from those who met the definition for the source cohort (i.e., USAF personnel with at least one year of activity duty between 1 January 1988 and 31 December 2003). Additionally, control subjects were required to be on active duty at the time the respective case subject was diagnosed with invasive cancer.

Each subject's Social Security Number (SSN) was used to link data from multiple sources. Cancer, demographic and military occupational data were obtained from ACTUR and the AFPC personnel databases and archived at the end of each month. Every attempt was made to use data recorded in the month prior to the date of invasive cancer diagnosis. However, in several years of the study period, monthly data archives were only infrequently available. In these instances, the closest monthly data archive was used. For all subjects, the archive used was from the same calendar year as the invasive cancer diagnosis. Subjects were excluded if demographic or military occupational data were missing.

In a previous risk assessment of JP-8 in the USAF, Kendall et al (2001) created an occupational matrix based on job descriptions, bioenvironmental engineer assessments and individual questionnaires. Using similar classification schemes and methodologies, multiple studies have shown significant differences in various biological indicators of jet fuel exposure, namely urine and blood components, between the exposed and referent categories [1, 19]. Therefore, the occupational categorizations identified by Kendall et al were utilized to classify the jet fuel exposure of subjects in the present study.

All occupational data were gathered from the AFPC using the subjects' SSN's. Specifically, information was collected regarding each subject's Air Force Specialty Code (AFSC) – an alpha-numeric designation representing a specific military occupation. The official job duties associated with each AFSC are detailed in two Air Force Manuals [20, 21]. Due to

education and training requirements, it is generally uncommon for individuals to have multiple unrelated AFSC's during their military career. However, in order to fully account for any occupational jet fuel exposure that may have occurred during the course of a career, jet fuel exposure was based on all AFSC's listed for each individual. Each individual was classified according to the occupation with the highest level of jet fuel exposure.

As detailed in Table 1, subjects in the Aircraft Fuel Systems category were categorized as having had high exposure. This occupation involves frequent entry into fuel tanks and direct contact with aircraft fuel-containing structures. Several occupations dealing with fuel storage and distribution systems involved intermittent and/or indirect contact with jet fuel and were therefore classified as moderate exposure. Subjects in the remaining occupations, whose duties would not normally involve jet fuel contact, were grouped into the reference level of exposure (e.g. administrative, medical, legal occupations).

TABLE 1. Air Force Specialty Codes and Corresponding Fuel Exposure Level

Fuel Exposure Level	AFSC	Equivalent AFSCs in Previous Coding System	Job Title/Category
High	2A6X4	454X3	Aircraft Fuel Systems
Moderate	2A6X1	454X0	Aerospace Propulsion
	2A6X3	454X2	Aircrew Egress Systems
	2E4XX	309X0	Space Systems
	2FOXX	631X0	Fuels
	2T3XX	472X0, 472X1	Transportation and Vehicle Maintenance
Low	All others	All others	Operations
			Non-Fuel Maintenance and Logistics Occupations
			Support
			Medical and Dental
			Legal and Chaplain
			Finance and Contracting
			Special Investigations
			Special Duty Assignments

All statistical analyses were performed using Stata 8 statistical software. Conditional logistic regressions were used to calculate odds ratios for fuel exposure with cancer occurrence as the primary outcome of interest. Based on the chronic adverse effects associated with exposure and metabolism of aromatic hydrocarbons (e.g., benzene), and the location of exposure to jet fuel, the following cancer types were assessed as individual outcomes: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), bladder, breast, dermatofibrosarcoma, Hodgkin's Disease, liver, lung, multiple myeloma, nasal, non-Hodgkin lymphoma and renal [13-15, 22]. In order to assess possible effect modification, gender stratified analyses were also performed on all models.

The study protocol was reviewed and approved by the Institutional Review Board at the 311 Human Systems Wing, Brooks City-Base, Texas.

RESULTS AND DISCUSSION

Based on the data in ACTUR, 3,194 unique incident cancer cases occurred between 1 January 1989 and 31 December 2003. Of these individuals, only 2,898 met the criteria for at least one year of active duty prior to cancer diagnosis. After excluding individuals who did not

have complete medical or occupational data, there 2,754 cases included the final study sample. This resulted in an 86.2% inclusion rate. Each case was matched with four controls on year of birth, gender and race, resulting in a total study population of 13,770 individuals (Table 2).

TABLE 2. Study Sample Demographics

Characteristic	Controls (N=11,016) N (%) ^{a,b}	Cases (N=2,754) N (%) ^{a,b}	1995 USAF Population (N=396,102) N (%)
Median Age	37 ^c		29
Gender			
Female	3730 (27.1)		63540 (16.0)
Male	10040 (72.9)		332558 (84.0)
Race			
Caucasian	11654 (84.6)		318161 (80.3)
Black	1575 (11.4)		58425 (14.7)
Asian/Pacific Islander	60 (0.4)		210 (0.05)
American Indian/Alaska Native	15 (0.1)		52 (0.01)
Other	365 (2.7)		19157 (4.8)
Unknown	101 (0.7)		97 (0.02)

^a Cases and controls matched on year of birth, gender and self-reported race; Controls also had to be on active duty status at the time respective case was diagnosed with invasive cancer

^b Columns may not sum to 100% due to missing values and rounding

^c Median age at diagnosis

As illustrated in Table 3, 428 subjects were categorized as moderately exposed and 45 as highly exposed. There was no association observed between occupational jet fuel exposure and invasive cancer occurrence. The odds ratios for cancer occurrence in the moderate and high exposure groups were 0.84 (95% CI 0.65-1.09) and 0.73 (95% CI 0.32-1.64), respectively, when compared to the low exposure group.

TABLE 3. Occupational Jet Fuel Exposure and Invasive Cancer Occurrence

Level of Occupational Jet Fuel Exposure	Number of Cases	Number of Controls	Total Number	Odds Ratio	95% CI	p-value
High	7	38	45	0.73	0.32-1.64	0.44
Moderate	75	353	428	0.84	0.65-1.09	0.19
Low	2672	10625	13297	1.00	--	--

As indicated in Table 4, there were no significant associations observed in subsequent analyses stratified by gender.

TABLE 4. Occupational Jet Fuel Exposure and Invasive Cancer Occurrence, by Gender

MALES (N=10040)						
Level of Occupational Jet Fuel Exposure	Number of Cases	Number of Controls	Total Number	Odds Ratio	95% CI	p-value
High	6	34	40	0.70	0.29-1.67	0.42
Moderate	65	305	370	0.85	0.64-1.11	0.23
Low	1937	7693	9630	1.00	--	--
FEMALES (N=3730)						
Level of Occupational Jet Fuel Exposure	Number of Cases	Number of Controls	Total Number	Odds Ratio	95% CI	p-value
High	1	4	5	1.00	0.11-8.95	1.00
Moderate	10	48	58	0.83	0.42-1.65	0.60
Low	735	2932	3667	1.00	--	--

Additionally, no significant associations were observed between the occurrence of specific types of cancer and occupational jet fuel exposure (Table 5). Although the null findings in this study indicate a lack of association, the implications of these results are important, especially with respect to the direction of future work.

TABLE 5. Jet Fuel Exposure and Associated Risk for Specific Types of Cancer

Cancer Type ¹	Cases		Controls		All USAF Occupations		
	Exposed	Unexposed	Exposed	Unexposed	OR	p > z	95% CI
Acute Myeloid Leukemia	1	25	8	96	0.48	0.50	0.06-4.01
Acute Leukemias ²	1	35	11	133	0.35	0.32	0.05-2.79
Acute and Chronic Leukemias ³	1	55	12	212	0.32	0.34	0.04-2.53
All Leukemias	2	69	14	270	0.55	0.45	0.12-2.52
Bladder	1	47	5	187	0.70	0.73	0.10-5.07
Breast	2	215	16	852	0.49	0.35	0.11-2.17
Breast (Females Only)	2	213	15	845	0.53	0.40	0.12-2.33
Hodgkin's Disease	2	133	18	522	0.44	0.27	0.100-1.91
Lung ⁵	1	41	5	163	0.79	0.83	0.09-7.28
Multiple Myeloma	1	16	3	65	1.33	0.80	0.14-12.82
Non-Hodgkin's Lymphoma	4	141	16	564	1.00	1.00	0.33-3.03
Renal Cell	2	47	8	188	0.83	0.79	0.21-3.32

¹ Due to small cell numbers, the following types of cancer could not be analyzed individually: acute lymphocytic leukemia (N=10), chronic lymphocytic leukemia (N=10), chronic myeloid leukemia (N=10), dermatofibrosarcoma (N=23), liver (n=6) and nasal, paranasal and nasopharyngeal (N=8)

² Includes acute lymphocytic leukemia and acute myeloid leukemia

³ Includes acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia

⁴ All leukemias includes ALL, AML, CLL, CML, Leukemia Aleukemic Myeloid, Leukemia Hairy Cell, Leukemia Lymphoid, NOS, Leukemia Lymphoma T-Cell, and Leukemia, NOS

⁵ Includes small cell and non-small cell cancers

There are several possible explanations for these results. First, in light of limited work in this field, it is possible that there truly is no association between occupational jet fuel exposure and invasive cancer occurrence. Selden and Ahlborg (1991) assessed mortality and cancer morbidity in the Swedish Armed Forces, and found there to be no association between military aircraft fuel and mortality and cancer incidence [23]. Similarly, Zhao et al (2005) recently illustrated that among aerospace workers engaged in rocket engine testing, exposure to benzene and other polycyclic aromatic hydrocarbons was not significantly associated with either cancer risk or mortality [24].

Study design may have also played a role in the null association. First, a separate assessment conducted by the Air Force Institute for Operational Health found that the age- and sex-adjusted standardized incidence ratio for cancer was significantly lower in the USAF compared to the general U.S. population (in press). It is likely that the healthy worker effect is involved, but surveillance issues may have also influenced our findings. Although there are multiple surveillance databases and tracking systems in place to monitor USAF personnel, once individuals separate from the military they are not routinely tracked, and loss to follow-up becomes problematic. Specifically, if cancer was not diagnosed while an individual was on active duty, it is likely their diagnosis was not included in ACTUR and would therefore result in an underestimation of the true number of cancers.

Additionally, only individuals with complete demographic and military occupational information were included in analysis. Selection bias may have been introduced if there were significant differences in the completeness of data with respect to jet fuel exposure or cancer occurrence.

It is critical that the strengths and limitations of this study be considered when interpreting these results. The novelty of this study in measuring the association between jet fuel exposure and cancer occurrence in the USAF is its most notable strength. The long-term effects of jet fuel exposure are not well documented and this study provides the basis for addressing this gap in the literature. Additionally, exposure and outcome assessments were based on data collected from official personnel databases and ACTUR, respectively. Both of these systems involved standardized data entry procedures and minimized the risk of recall bias associated with questionnaires. Additionally, as all cancer cases were analyzed, coded and recorded by trained tumor registrars at ACTUR, there is minimal chance of errors or miscoding.

The study limitations are important to assess because they may be useful in guiding the directions of future research. Due to data limitations, no quantification of occupational jet fuel exposure was made outside of the hierarchical assignments based on job titles and associated duties. Using this method, the length of time each individual was exposed to jet fuel was not assessed and could have varied by individual. The likelihood of this however, was determined post hoc to be small considering the substantial training and skill requirements that would be necessary to change occupations. This supposition was supported by the results of a separate study of ADAF fuel system maintenance workers in which the average length of time on the job was more than 47 months [19]. Relying solely on job descriptions also precluded the possibility of assessing individual fuel exposure variations. For example, it has been shown that individuals within the same job category are responsible for different duties, each with significantly different levels of exposure to jet fuel [3, 25]. Consequently, a more objective alternative that could address both of these issues would be to utilize a valid biomarker, such as blood or urine to quantitatively assess and stratify occupational exposure [1, 3, 7, 9, 26]. These might also give valuable insight into the pathway by which jet fuel chemicals are metabolized in the human body including temporal assessment and the long-term effects of exposure.

Similarly, it was not possible to distinguish the chemical differences of each individual's jet fuel exposure. Specifically, the timeframe of this study included a large portion of the period during which the USAF converted from jet propulsion fuel type 4 (JP-4) to JP-8, but study design prevented differential assessment of each fuel. This is compounded by the finding that differences in crude oil sources and chemical compositions can contribute to substantial batch-to-batch variation even within the same fuel type [1, 10, 22]. Specifically, military jet fuel specifications are based on performance standards and provide acceptable limits rather than strict chemical formulas. Although the maximum volume of aromatic hydrocarbons is 25% in both JP-4 and JP-8, benzene, a potent human carcinogen is significantly reduced in the latter [13, 14, 22]. Conversely, the approximate percent by weight of naphthalene in JP-4 was 0.50, compared to a range of 0.01-3.0 in JP-8 [7, 22]. These disparities suggest that accurately measuring the association between jet fuel exposure and cancer occurrence may require environmental and biological sampling to assess the actual levels of specific components that are believed to be carcinogenic. It is important to note, however, because a null association was observed, it is unlikely that the effects of benzene in JP-4 masked the influence of other fuel chemicals such as naphthalene, unless they were protective against cancer.

As these data had not been gathered specifically for the purposes of the present study, there were several potential confounders that could not be evaluated because of unavailable

information. Namely, smoking is a risk factor for several types of cancer, provides an abundant source of benzene and confounds the effects of naphthalene [7, 13, 27]. Therefore, it is imperative that this factor be assessed in future studies. Other behavioral characteristics such as diet, physical activity and oral contraceptive use may have been useful factors to consider and may have provided insight into the mechanisms by which jet fuel and its components impose their effects. Based on these limitations, personal interviews may be a useful method for addressing the individual differences and characteristics that influence the exposure and outcome variables.

The small percentage of exposed subjects, as well as the small number of various cancer types, restricted some of the analyses that could be performed and consequently precluded the assessment of these associations. It is also important to note that the epidemiology of cancer occurrence in the USAF may be different from that of the general US population. Specifically, the average age at diagnosis for various types of cancer in the US general population (Table 6) is higher than the median age at diagnosis of 37 reported for USAF personnel [28, 29]. Although Air Force retirees may be a useful group to study in order to address this limitation, their ACTUR data is limited to retirees who were diagnosed while on active duty or who still receive medical care through the Military Health System. Additionally, many types of cancer have long latency periods, and although this study spanned a 15-year period, it is possible that some cancers had not yet developed to the point of detection. Therefore, it may be useful to identify cancer precursors that are more prevalent or manifest themselves in a shorter period of time. This is apt to increase the number of measurable outcomes and provide an endpoint with a greater likelihood of occurring while on active duty and being documented in the medical records databases. As an alternative, military discharge or mortality data could be compared across fuel and non-fuel occupations.

TABLE 6. Average Age at Diagnosis of Select Cancer Types in the General U.S. Population

Cancer Type	Average Age at Cancer Diagnosis in General US Population¹
Acute Myeloid Leukemia	65
Acute Lymphocytic Leukemia	Over 50
Chronic Myeloid Leukemia	66
Chronic Lymphocytic Leukemia	Over 40, most cases over 70
Bladder	Over 55
Breast ²	61
Hodgkin's Disease	25-30 and over 55
Lung ³	Over 65
Multiple Myeloma	Over 40
Non-Hodgkin's Lymphoma	60's
Renal Cell	Over 55

¹ Based on data from American Cancer Society (www.cancer.org)

² Median age at diagnosis

³ Includes both small cell and non-small cell

CONCLUSION

In conclusion, no association was observed between occupational jet fuel exposure and invasive cancer occurrence. Even in light of this study's limitations, the available literature does support our null finding. However, as JP-8 constitutes the largest chemical exposure for USAF personnel, it may still be useful to employ some of the aforementioned methodological improvements to conduct a thorough epidemiologic assessment of this association. This may provide insight into the mechanisms of jet fuel metabolism as well as identify constituents of greatest concern.

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