2010

Investigating the Risk of Cancer in 1990–1991 US Gulf War Veterans With the Use of State Cancer Registry Data

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Investigating the Risk of Cancer in 1990–1991 US Gulf War Veterans With the Use of State Cancer Registry Data

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PURPOSE: The purpose of this study was to determine whether proportional cancer incidence is greater among Gulf War veterans compared with non-Gulf War veterans.
METHODS: Files obtained from the Defense Manpower Data Center included data for 621,902 veterans who were deployed to the Persian Gulf during the 1990 to 1991 Gulf War (August 2, 1990, to March 1, 1991) and 746,248 non-Gulf War veteran controls. Identification of veterans who received a cancer diagnosis between 1991 and 2006 was accomplished through record linkage of the Defense Manpower Data Center dataset with files from 28 state cancer registries and the Department of Veterans Affairs Central Cancer Registry. By the use of logistic regression, proportional incidence ratios adjusted for demographic and military characteristics were calculated by comparing the proportion of a specific cancer among all cancers in the Gulf War veterans to the proportion of that specific cancer among all cancers in the non-Gulf War veterans.
RESULTS: Only lung cancer showed a statistically significant relative excess among Gulf War veterans compared with non-Gulf War veterans (adjusted proportional incidence ratios, 1.15; 95% confidence interval, 1.03−1.29). When adjusted for race, age, and sex, the overall proportion of cancers among Gulf War and non-Gulf War veterans was similar (odds ratio, 0.99; 95% CI, 0.96−1.02).
CONCLUSIONS: With the exception of lung cancer, there is little evidence of excess risk of cancer associated with Gulf War deployment. A follow-up study is warranted to confirm this finding and to evaluate the role of greater smoking rates among deployed personnel.
Ann Epidemiol 2010;20:265–272.

KEY WORDS: Gulf War, Neoplasms, Veterans.

INTRODUCTION

The 1996 Presidential Advisory Committee on Gulf War Veterans' Illnesses reported that a number of Gulf military personnel from Operation Desert Storm may have been exposed to potential human carcinogens such as chemical warfare agents, aflatoxin, and certain petroleum products, including smoke from oil well fires (1). Therefore, the Presidential Advisory Committee recommended developing long-term studies for investigating increased rates of lung, liver, and other cancers among Gulf War veterans.

A few studies have attempted to compare cancer incidence for Gulf War veterans and non-Gulf War comparison groups. One of the first used the Department of Defense (DOD) hospitalization database and reported increased risks of hospitalization for testicular cancer shortly after return from the Gulf War (2). A subsequent study of the DOD hospitalization data found that the increased risks did not persist during a 4-year follow-up period (3). A pilot study of matching records of approximately 1.4 million US Gulf War era veterans with two state cancer registries was conducted to compare cancer patterns among Gulf War and non-Gulf War veterans. The study suggested that the proportional incidence of testicular cancer was significantly increased among Gulf War veterans (4). A cohort study of 1990 to 1991 UK Gulf War veterans found no excess risk of any site-specific cancers or overall cancer (5). Also, a survey of 30,000 Gulf War era veterans in 2005 showed no significant difference in the incidence of cancer between Gulf War veterans and non-Gulf War veterans (6).

Cancer mortality studies can be a useful proxy for incidence for cancers with low survival rates. A mortality follow-up study of the entire cohort of US Gulf War veterans for 1990 to 1997 did not indicate any excess mortality as the result of cancer among Gulf War veterans

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This work was supported by Merit Review funding awarded by the Office of Research and Development, Department of Veterans Affairs.
Received July 24, 2009; accepted November 19, 2009.

1047-2797/10/$–see front matter
doi:10.1016/j.annepidem.2009.11.012

AEP Vol. 20, No. 4
April 2010: 265–272

Selected Abbreviations and Acronyms

DOD = Department of Defense
DMDC = Defense Manpower Data Center
SEER = Surveillance, Epidemiology, and End Results
PIR = proportional incidence ratio
95% CI = 95% confidence interval
SIR = standardized incidence ratio
VACCR = Veterans Affairs Central Cancer Registry
VA = Veterans Affairs

compared with non-Gulf War veterans (7). A post war (1991–1999) mortality study of UK Gulf War veterans also reported no significant difference in the risk of cancer mortality between those who were deployed and nondeployed (8). However, more recent studies of the US Gulf War veterans who have had potential exposure to nerve agents reported an increased risk of brain cancer mortality among those veterans who were exposed to the plume from the 1991 Khamisiyah munitions destruction (9, 10). This plume occurred when US troops destroyed a large storage complex at Khamisiyah that contained stacks of rockets loaded with nerve agents (11).

Limitations of these previous studies included focus on mortality rather than incidence, reliance on hospitalization data, relatively short follow-up periods, or small numbers of observed cancers. This study was designed to partially overcome these limitations by identifying incident cancers obtained through matching of veterans' data to data obtained from cancer registries representing a large portion of the US population for up to 15 years of follow-up.

The primary purpose of this study was to determine whether the overall cancer pattern differed between Gulf War and non-Gulf War veterans and to determine whether proportional cancer incidence of specific cancers was greater among Gulf War veterans in comparison with non-Gulf War veterans. The secondary purpose was to determine whether those cancers that showed significantly different proportions between the Gulf War and non-Gulf War veterans differed from the expected incidence in the general population. Finally, for those cancers that showed relative excess in the Gulf War veterans, the time of diagnosis patterns were compared between Gulf War and non-Gulf War veterans.

METHODS

Study Population

The study population included 621,902 veterans who were deployed to the Persian Gulf during the 1990-1991 Gulf War (August 2, 1990, to March 1, 1991) and 746,248 non-Gulf War controls. The former group represents the entire population deployed during the time frame, whereas the latter consists of a stratified random sample of veterans from all military personnel who served during the conflict but were not deployed to the Gulf region. The data source for these veterans consisted of files obtained from the Defense Manpower Data Center (DMDC). Both groups included personnel on active duty, in the reserves, and in the National Guard. The details for the selection of the two study groups and their military and demographic characteristics are detailed elsewhere (7, 12). Institutional review board approval was obtained from The George Washington University, the Department of Veterans Affairs, and individual state registries where required.

Cancer Matching Methodology

Identification of military personnel who received a diagnosis of cancer between January 1, 1991, and December 31, 2006, was accomplished by record linkage of the DMDC database with files at 28 state central cancer registries and the Veterans Affairs Central Cancer Registry (VACCR). Table 1 lists participating registries. The registries used a variety of probabilistic record linkage software that weighs the likelihood of subject identity on the basis of identical or near identical information in the records. Uncertain matches were hand reviewed. Key matching variables were name, date of birth, Social Security number, sex, date of death (if available), and race. Missing data on a single key variable did not exclude the possibility of a match as other variables could be used in the matching software algorithm. All veterans in the cohort had data for Social Security number.

The criteria for selection of collaborating state registries were population size of the state and number of years since 1991 that the registry has been population based. On the basis of 2000 Census data, the state registries that were included captured 84% of the United States population. Cancer type was determined using the International Classification of Diseases for Oncology, 3rd Edition (13) and in one state (Kentucky), the Surveillance, Epidemiology, and End Results (SEER) site recode (14). For analysis purposes, cancers were grouped into 30 categories.

Statistical Analysis

To determine whether the proportion of Gulf War and non-Gulf War veterans with a cancer diagnosis differed, a logistic regression controlling for age, race, and sex was performed. For this purpose, data from the VACCR were excluded as the result of differences in the eligibility for VA care between Gulf War and non-Gulf War veterans (Web Appendix). Next, to determine whether there were differences in overall cancer pattern between Gulf War and non-Gulf War veterans, the Mantel Haenszel procedure,

TABLE 1. Characteristics of data received from state cancer registries used in comparison of US Gulf War and non-Gulf War veterans, 1991–2006

Registry group number[a]	State	Starting year	Ending year	Total years	% of US population[b]
1					
	Arizona	1991	2006	15	1.80
	Georgia	1991	2006	15	2.86
	Michigan	1991	2006	15	3.53
	Tennessee	1991	2006	15	2.05
	Texas	1991	2006	15	7.15
	California	1991	2005	14	11.77
	Colorado	1991	2005	14	1.53
	Connecticut	1991	2005	14	1.23
	North Carolina	1991	2005	14	2.88
	Virginia	1991	2005	14	2.50
2					
	Indiana	1991	2004	13	2.16
	Iowa	1991	2004	13	1.05
	Massachusetts	1991	2004	13	2.33
	Wisconsin	1991	2004	13	1.92
	Illinois	1991	2003	12	4.40
	New York	1991	2003	12	6.86
	Pennsylvania	1991	2003	12	4.49
	Florida	1991	2002	11	5.90
	Washington	1992	2003	11	2.08
3					
	Alabama	1996	2006	10	1.59
	Kentucky	1994	2004	10	1.46
	Oregon	1995	2005	10	1.24
	Oklahoma	1996	2005	9	1.22
	South Carolina	1996	2005	9	1.43
	Ohio	1996	2003	7	4.06
4					
	New Jersey	1991	1999	8	3.04
	Maryland	1991	1998	7	1.88
	All states combined				84.41
	VACCR[c]	1991	2006	15	

VACCR = Veterans Affairs Central Cancer Registry.
[a]Registry group number is a variable created to categorize registries into similar groups on the basis of starting year, ending year, and the total number of years of data covered in this study.
[b]State population as a percent of US (excluding Puerto Rico) civilian population ages 18 and older from US Census Bureau, Census 2000.
[c]Data from the VACCR were included in group 1.

which controlled for age, race, and sex, was used to provide a global test of these differences.

To determine whether there were differences in specific cancers, crude proportional incidence ratios (PIRs) and 95% confidence intervals (95% CIs) were then calculated. The proportional incidence was calculated by comparing the proportion of each specific cancer type among all cancers in the Gulf War group with the proportion of that specific cancer type among all cancers in the non-Gulf War group. A subgroup analysis compared ground (Army and Marines) Gulf War veterans with non-Gulf War veterans. This analysis was of interest because it is believed that the in-theater exposures of the ground troops differed from those of the nonground (Air Force and Navy) troops with regard to proximity, duration, and intensity of potential exposures such as smoke from oil well fires and Khamisiyah munitions.

To control for potential confounding, adjusted PIRs were computed through logistic regression analyses predicting each specific cancer (against all other cancers) from Gulf status while controlling for sex, diagnosis age, diagnosis age squared, diagnosis year, race, branch of service, unit type, and registry group. Diagnosis age squared was included as a term in the model to improve the model fit. Because registries varied on the years covered including starting and ending year, a variable was created to categorize the registries into similar groups based on years of coverage and starting and stopping year. Assignment of registry groups is detailed in Table 1.

For those cancers that showed statistically significant adjusted PIRs, the study groups were compared with the general population by use of the SEER database. Age, race, and sex adjusted standardized incidence ratios (SIRs; also known as observed versus expected ratios) were calculated by dividing, within 5-year age categories for white male subjects, the observed number of cases of a specific cancer by the expected number. The expected number was based on the relative proportion of that specific cancer extracted from the SEER incidence database for the years 1992 to 2006 (15). Exact 95% CIs around the SIRs were calculated as an extension of the Poisson method (16).

The adjusted proportions of each cancer that showed statistically significant adjusted PIRs were calculated and plotted by year of diagnosis to examine time of diagnosis patterns. These proportions were adjusted for race, age at diagnosis, age squared, and sex through logistic regression equations predicting each cancer type with mean values for covariates substituted into the equations. Analyses were conducted using SAS version 8.2 (17).

RESULTS

Descriptive Results

Table 2 shows the demographic characteristics of veterans with cancer matches compared with all veterans stratified by Gulf War versus non-Gulf War status. Racial distributions were similar between the Gulf War and non-Gulf War cancer matches whereas Gulf War veterans were slightly more likely to be male than non-Gulf War veterans. Gulf War veterans were younger than non-Gulf War veterans. Similarly, among the cancer matches the Gulf War veterans were more likely to be younger in 1991 and

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TABLE 2. Demographic and military characteristics of US Gulf War and non-Gulf War veterans with matched cancer diagnoses compared with all veterans, 1991–2006

Characteristic (%)	All veterans in sample used for matching		All matches from cancer registries	
	Gulf War veterans (n = 621,902)	Non-Gulf War veterans (n = 746,248)	Gulf War veterans (n = 8,211)	Non-Gulf War veterans (n = 12,864)
Race[a]				
White	67.4	69.4	69.0	71.8
Black	23.0	21.4	23.0	21.4
Hispanic	5.0	4.9	4.0	3.6
Other	4.3	3.8	3.0	2.6
Sex[a]				
Male	92.7	86.3	88.0	82.5
Female	7.0	13.3	12.0	17.2
Service branch				
Air Force	11.5	11.3	13.0	13.0
Army	51.8	55.7	59.0	59.7
Marine	14.8	15.3	10.0	10.3
Navy	21.9	17.7	19.0	17.0
Unit type				
Active	83.3	70.2	72.0	61.1
Guard	6.6	10.5	13.0	14.2
Reserve	10.1	19.3	16.0	24.7
Median age in 1991	26	28	36	39
Age in 1991, years				
<20	6.7	9.5	3.0	2.7
20–24	34.3	25.2	15.0	8.7
25–29	25.3	22.7	14.0	10.7
30–34	15.4	16.0	14.0	12.1
35–39	10.0	12.0	18.0	16.3
40–44	5.6	8.7	18.0	20.1
45–49	2.0	4.0	11.0	15.3
50–54	0.6	1.4	5.0	8.6
55–59	0.2	0.6	3.0	4.4
60+	0.0	0.1	0.0	1.2
Median age at diagnosis			45	48
Age at diagnosis, years				
<20			0.0	0.2
20-24			2.0	1.3
25-29			7.0	4.9
30-34			13.0	9.5
35-39			13.0	10.0
40-44			14.0	12.2
45-49			16.0	16.2
50-54			15.0	19.0
55-59			11.0	14.5
60+			7.0	12.2

[a]Information on this measure was missing for some veterans.

at age of diagnosis compared to non-Gulf War veterans. Those veterans who were cancer matches were much more likely to be older in 1991 than the overall sample of veterans.

Overall Cancer Patterns

The linkage process identified 21,075 matches of the total number of approximately 1.4 million veterans, with 1.3% Gulf War group having a cancer match (8,211 cancers/621,902 Gulf War veterans) and 1.7% of the non-Gulf War group having a cancer match (12,864 cancers/746,248 non-Gulf War veterans). These proportions are underestimates of the actual 15-year incidence because not all states and years within states had registry data for this study. Of the cancers, 1277 of the Gulf War matches and 1519 of the non-Gulf war matches were identified from the VACCR. After controlling for age, race, and sex, there was no significant association between Gulf status and the proportion of veterans with a cancer (odds ratio, 0.99; 95% CI, 0.96–1.02) identified from a state registry (Supplemental Data). Although there was no difference in the proportion of veterans with a cancer identified, there was a significant difference in overall cancer patterns between Gulf War and non-Gulf War veterans by the Mantel Haenszel test of general association after controlling for the same covariates as noted ($p < .001$). Similarly, there was a significant difference in cancer patterns between the ground group and non-Gulf War group ($p < .001$).

Specific Cancer Types

Table 3 shows the number of cancer matches in specific primary site groupings for Gulf War and non-Gulf War as well as the PIRs and 95% CIs comparing Gulf War with non-Gulf War and ground with non-Gulf War after adjusting for covariates. Lung cancer was found proportionally more often in the Gulf War veterans compared with the non-Gulf War veterans (PIR, 1.15; 95% CI, 1.03–1.29) and ground troops compared with non-Gulf War veterans (PIR, 1.21; 95% CI, 1.07–1.38). No other cancer groupings showed significantly increased PIRs. However, testicular cancer showed a significantly decreased PIR of 0.85 (95% CI, 0.75–0.98) when comparing Gulf War veterans with non-Gulf War veterans as did Kaposi sarcoma (PIR, 0.54; 95% CI, 0.37–0.79).

For those cancers that showed statistically significant PIRs, SIRs comparing the Gulf and non-Gulf to the SEER population are displayed in Table 4. Neither Gulf War nor non-Gulf War veterans showed significantly increased risks of lung or testicular cancer over the general population whereas both Gulf War and non-Gulf War veterans showed significantly decreased risks of Kaposi sarcoma when compared with the general population.

Figure 1 shows the adjusted relative proportion of all cancers that were lung cancers by group at each year of diagnosis. Although the trend in the figure suggests that the overall incidence of lung cancer is flat or decreasing over time, this is an artifact of controlling for age at diagnosis.

TABLE 3. Proportional incidence ratios for cancer diagnoses among matched US Gulf War veterans compared with matched US non-Gulf War veterans, 1991–2006

				Gulf War vs. non-Gulf War		Ground[a] vs. non-Gulf War	
Primary site	No. Gulf	No. non-Gulf	Total no.	PIR[b]	95% CI	PIR[b]	95% CI
Oral cavity and pharynx	289	439	728	0.97	0.83–1.13	0.98	0.81–1.17
Esophagus	69	133	202	0.85	0.63–1.15	0.82	0.57–1.18
Stomach	133	169	302	1.17	0.93–1.48	1.21	0.93–1.57
Liver	50	97	147	0.73	0.52–1.04	0.67[c]	0.45–0.99
Gallbladder and pancreas	110	180	290	1.07	0.84–1.36	1.10	0.82–1.47
Other digestive system	841	1250	2091	1.07	0.97–1.18	1.03	0.92–1.15
Lung	620	966	1586	1.15[c]	1.03–1.29	1.21[c]	1.07–1.38
Other respiratory system	104	159	263	1.01	0.78–1.30	1.07	0.79–1.45
Bones and joints and soft tissue	172	208	380	1.04	0.85–1.29	0.95	0.73–1.23
Melanomas	749	1100	1849	0.98	0.89–1.09	0.99	0.87–1.12
Other skin	35	49	84	0.82	0.53–1.28	0.77	0.46–1.29
Breast (males)	12	24	36	0.78	0.39–1.58	0.61	0.24–1.57
Breast (females)	396	918	1314	1.01	0.86–1.20	1.00	0.82–1.21
Female genital system	238	520	758	0.94	0.77–1.15	0.90	0.71–1.13
Prostate	1397	2514	3911	1.01	0.93–1.10	1.00	0.91–1.11
Testis	496	590	1086	0.85[c]	0.75–0.98	0.85[c]	0.72–1.00
Other male genital system	35	32	67	1.55	0.95–2.53	1.73	0.97–3.09
Bladder	255	379	634	1.16	0.98–1.36	1.13	0.93–1.37
Other urinary system	264	459	723	0.87	0.74–1.01	0.89	0.74–1.07
Eye and orbit	20	30	50	1.06	0.60–1.90	1.46	0.70–3.02
Brain	278	410	688	0.86	0.73–1.01	0.86	0.71–1.04
Other nervous system	78	106	184	1.03	0.76–1.38	1.08	0.76–1.54
Endocrine system	301	433	734	0.95	0.82–1.11	0.93	0.77–1.12
Hodgkin lymphoma	239	245	484	1.10	0.91–1.33	1.12	0.89–1.40
Non-Hodgkin lymphoma and chronic lymphocytic leukemia	478	671	1149	1.00	0.88–1.13	0.93	0.79–1.09
Multiple myeloma	83	125	208	1.03	0.78–1.37	1.03	0.75–1.43
Other leukemias	204	293	497	0.93	0.78–1.12	0.94	0.76–1.17
Mesothelioma	10	20	30	0.95	0.44–2.05	0.98	0.33–2.90
Kaposi sarcoma	46	85	131	0.54[c]	0.37–0.79	0.65	0.40–1.06
Ill-defined and unknown	209	260	469	1.17	0.97–1.42	1.21	0.96–1.52
Total cancers	8211	12,864	21,075				

95% CI = 95% confidence interval; PIR = proportional incidence ratio.
[a]Ground veterans were limited to Army and Marine branches.
[b]PIR derived from a logistic regression model controlling for sex, diagnosis age, diagnosis age squared, diagnosis year, race, branch of service, unit type, and registry group number.
[c]$p < .05$.

The time trend shows a sharp relative excess of lung cancers among the deployed veterans in 1993 and small relative excess in 1995 and 1996. No deployment group related differences are apparent from 1997 through 2003. For 2004 through 2006, the pattern shows a widening relative excess in the Gulf War group. Online Supplemental Figure 1 illustrates the 95% CIs corresponding to the adjusted proportions in Figure 1.

TABLE 4. SIRs[a] and 95% CIs for US Gulf War and US non-Gulf War Veterans, 1992–2005

	Gulf War veterans		Non-Gulf War veterans	
Primary site	SIR	95% CI	SIR	95% CI
Lung	1.09	0.98–1.20	0.93	0.86–1.00
Testicular	0.95	0.86–1.05	1.10	1.0–1.20
Kaposi sarcoma	0.08	0.05–0.12	0.18	0.13–0.24

95% CI = 95% confidence interval; SIR, standardized incidence ratio.
[a]Age-adjusted and includes only white male subjects; expected numbers calculated from SEER incidence data 1992–2005.

DISCUSSION

The finding that the proportion of cancers identified from state registries was not statistically different between Gulf War and non-Gulf War veterans, after controlling for age, race and sex, is consistent with the UK incidence study with similar methodology that showed no additional overall risk of cancer among Gulf War veterans (5). Lung cancer was the only specific cancer that showed a significant relative excess in the Gulf War group on the basis of PIR analyses. Neither group showed a statistically significant excess of lung cancer as compared with the general population data from SEER.

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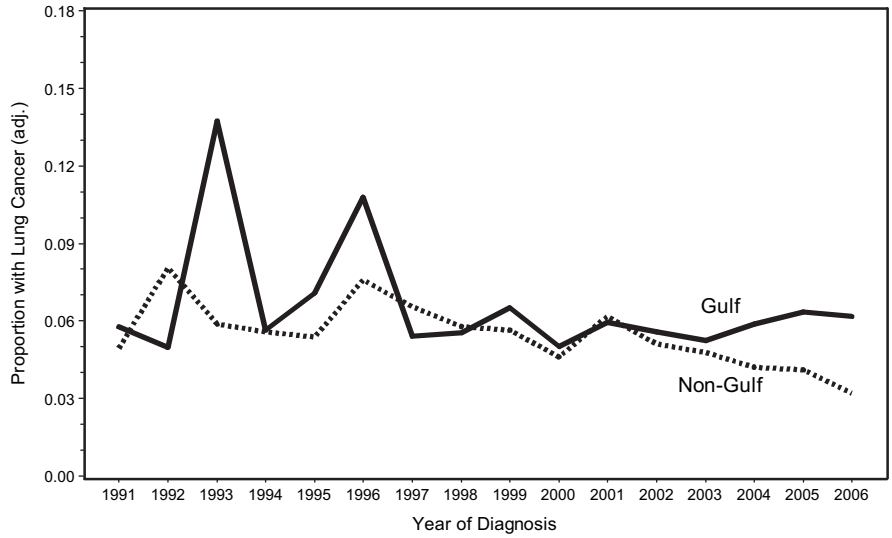

FIGURE 1. Adjusted relative lung cancer proportions for US Gulf War and US non-Gulf War veterans, 1991 to 2006. Proportions were adjusted for race, age at diagnosis, age at diagnosis squared, and sex and estimated at the mean for each covariate.

Data on smoking were not available for the cancer matches, so the lung cancer analysis was not adjusted for smoking patterns. However, Kang et al. (12) showed a significantly greater proportion of smokers among Gulf War veterans as compared with non-Gulf War veterans (34.7% vs. 29.9%) among 15,000 Gulf War and 15,000 non-Gulf War veterans who were randomly sampled from the study cohorts. Although confounding by cigarette smoking may explain the difference in lung cancer between the Gulf War and non-Gulf War group, the relative excess of lung cancer among the Gulf War group, particularly the widening relative excess for 2004 to 2006, suggests that a follow-up study should be conducted to confirm this finding and to evaluate the role of smoking. The length of follow-up in this study was a maximum of 15 years, a relatively short latency period for lung cancer. Various studies of air pollution and lung cancer suggest latency periods of 20 to 30 years (18, 19).

The results in this study do not support the pilot study findings of an increased proportion of testicular cancer among Gulf War veterans (4). This study showed a significantly lower relative proportion of testicular cancer among the Gulf War veterans when compared with the non-Gulf War veterans (PIR, 0.85; 95% CI, 0.75–0.98). However, the results of this study are similar to those of Knoke et al. (3), which showed that there was no overall difference in the risk of testicular cancer between Gulf War and non-Gulf War veterans. The pilot study (4) contained data from only the District of Columbia and New Jersey and examined a much shorter time period than the current study. Knoke et al. (3) suggest that an immediate post-war increase in testicular cancer among Gulf War veterans may be attributable to an increased DOD health care utilization among returning military personnel resulting from deferment of care during deployment.

The overall findings in this study are consistent with findings from the earlier Kang and Bullman (7) mortality study performed in the same cohort of veterans. The authors noted no significant excesses of overall cancer deaths or deaths from specific cancers comparing Gulf War with non-Gulf War veterans (7). The finding in this study of a significantly decreased proportional rate of Kaposi sarcoma among the Gulf War veterans is also supported by the previous mortality study, which showed a significant deficit of deaths attributable to HIV infection in Gulf War veterans (7). US military personnel who screened positive for HIV, a known risk factor of Kaposi sarcoma, were not deployed in the 1991 Gulf War. A more recent mortality study following this cohort through 2004 also notes no significant excess of overall cancer deaths or deaths from cancers at any specific sites and confirms the significant deficit of deaths due to HIV infection in the Gulf War veterans (10).

Although mortality studies (9, 10) note increased risks of brain cancer mortality among those exposed to the 1991 Khamisiyah chemical munitions destruction, our study did not reveal any excess in brain cancer. However, these mortality studies only showed significantly increased risk when specific exposure variables detailing length of exposure time were included in the models. Unlike the mortality studies, this study did not have the specific Khamisiyah exposure information available, and the brain cancer risk associated with Khamisiyah chemical munitions destruction could not be evaluated.

Limitations

There were some limitations with the methodology of this study. Because data from all 50 state cancer registries were not available, this study did not look at true incidence rates but was limited to examining match rates and proportional incidence. Match rates underestimate true incidence, and the main limitation of a PIR study is that a proportional incidence for one cancer can be affected by the relative frequencies of other types of cancers.

Another limitation is that the various registries used a variety of linkage software and methods. This may have resulted in slightly different match rates between the registries. Issues of data quality in both state and DMDC datasets were also a limitation. Although state registry data is generally of high quality, data quality was variable between registries and by year.

There is the possibility of duplication between states and Veterans Affairs (VA) registries, but this possibility is very small. At the time of the study, there would be little to no overlap between state registries and the VACCR because it was the policy of the VACCR to not allow state registries to release data from VA facilities for research purposes (20).

Although the Gulf War and non-Gulf War veterans were similar on the basis of race, the Gulf War veterans were slightly younger, more likely to be male, and more likely to be active duty than the non-Gulf War veterans. We adjusted for race, sex, age, and status as appropriate in the analysis, but there is the potential for residual confounding by unmeasured variables. Those sent to the Gulf War may have been healthier than those who were not sent. The magnitude of this difference has been shown to be relatively small and any differences in health status between Gulf War and non-Gulf War soldiers were not apparent by the end of the Gulf War (2).

There is a possibility of an excess in a rare cancer that was missed as the result of small sample size. In addition, cancers with long latency periods may not show excesses because of the limited time period of study. The length of follow-up in this study was limited to 15 years, which is a relatively short latency period for some cancers. In addition, the age of the veterans in this study was relatively young. The number of certain types of cancers in this cohort may increase with time as the cohort ages and the latency period lengthens; therefore differences in relative excesses of particular types of cancer may be underestimated in this study.

Finally, although we were able to perform linkages with 28 registries representing 84% of the US population, there was concern about how representative the matches in the 28 linked states were of the potential cancer matches in the remaining unlinked states. Any differences in characteristics between linked and unlinked state matches were likely the result of the fact that the states in which linkages were performed represent larger and more urban population centers and are not demographically representative of the entire US population. Overall the limitations discussed here were likely to nondifferentially underestimate the true number of cancers in both the Gulf and non-Gulf groups and result in an underestimate of the true risk.

Strengths

There are several strengths to this study. It was the first study associating cancer incidence outcomes with the entire population of Gulf War veterans and included a large and representative sample of non-Gulf War veterans. The outcome assessment was based on cancer registry data as opposed to mortality, hospitalization, or self-reported cancer data. The inclusion of the VACCR ensured that we had relatively complete ascertainment of cancers that were diagnosed at VA facilities. For more common cancers, the sample sizes were large enough to provide adequate statistical power to detect relatively small differences between groups.

CONCLUSIONS

This analysis demonstrated that there was no overall increased proportional risk of cancer in Gulf War as compared with non-Gulf War veterans. Lung cancer was the only specific cancer that showed a significant relative excess in the Gulf War veteran group. This relative excess could be explained by differences in smoking patterns, which were not measured in this study. It could also be a real difference related to exposures in the Gulf War theater. The time period in this study was a maximum of 15 years of follow-up, so additional studies should be conducted to determine whether the relative excesses in lung cancer increase or persist as the latency period from a potential Gulf War exposure increases.

The authors thank the staff from the state cancer registries that participated in the study and the staff of the VA Central Cancer Registry for their contributions to this study.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2009.11.012.

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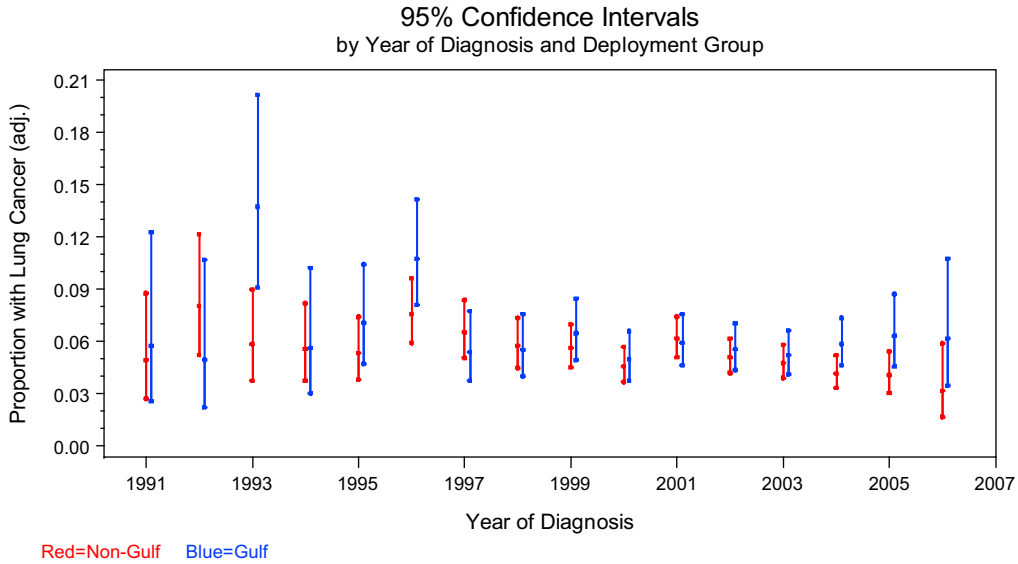
Appendix. Supplemental Data

Cancer diagnosis data that was received from the state cancer registries was deidentified. Therefore, although we desired to analyze the cancer matches relative to the original dataset of all Gulf and non-Gulf veterans we could not simply merge the cancer diagnosis records with the originating dataset. To address this limitation we created a dummy dataset that would allow for the appropriate analyses to be performed. This dataset was created with the same age, gender, racial, and gulf distribution as the original dataset. Only these variables were considered as they were the covariates necessary for the analyses. This dataset included all the cancer diagnosis data from state registries which were matched on the aforementioned covariates. Logistic regression analyses were performed to determine the match rate for any cancer diagnosis and for lung cancer diagnoses.



SUPPLEMENTAL FIGURE 1. Confidence intervals on adjusted relative lung cancer proportions of cancers for US Gulf and US non-Gulf veterans, 1991-2006. Proportions were adjusted for race, age at diagnosis, age at diagnosis squared, and gender, and estimated at the mean or percent for each covariate; the middle dot on each line corresponds to the adjusted proportion presented in Figure 1.