The Risk of Prostate Cancer in Pilots: A Meta-Analysis

David Raslau; Douglas T. Summerfield; Abd M. Abu Dabrh; Lawrence W. Steinkraus; Moham[illegible]d H. Murad

BACKGROUND: Aviation exposes pilots to various occupationally related hazards, including ionizing radiation and chemical combustion. The possible increased risk of prostate cancer among pilots in comparison [illegible] general population is a subject of debate. This systematic review and meta-analysis aimed to determine [illegible] quali[illegible] supporting evidence and magnitude of this association.

METHODS: All studies pertaining to prostate cancer in pilots were retrieved from multiple databases and from a manual search. Any study that assessed the incidence of prostate cancer relative [illegible] the incidence in the general population was included regardless of language or size. A random effect model was used to pool relative risks (RR) across studies. Heterogeneity was assessed using the Q statistic and I^2.

RESULTS: Eight studies with a low risk of bias were include[illegible] the meta-a[illegible]ts had an increased risk of developing prostate cancer compared to the general popul[illegible].0; 95% confidence interval (CI), 1.5–2.7]. The analysis was associated with substantial heterogeneity (I^2 = 7[illegible]). Seve[illegible]groups had significantly increased risk, such as African American pilots (RR 10.00; 95% CI, 5.04–19.86) and [illegible]lit[illegible] pilots (RR 3.30; 95% CI, 2.03–5.39).

CONCLUSION: Pilots are at least twice as likely to d[illegible]rostate [illegible]cer compared to the general population. The implications of these findings are important con[illegible]ering t[illegible] high pre[illegible]ence of prostate cancer and the large number of pilots in the workforce.

KEYWORDS: aviation, pilots, prostate c[illegible]er [illegible].

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Various aspect[illegible]viation [illegible]ave been examined in regards to pilot health, [illegible] analyz[illegible] the specific risk factors of [illegible]rs th[illegible]ay l[illegible] to the development of heart dise[illegible] or u[illegible]rstand[illegible]e utility of electrocardiograms, [illegible] X-ray[illegible]nd MRIs for screening purposes in this population[illegible][7,30] [illegible]orts [illegible] also been made to try to understand if pilot[illegible] at an increased risk for the development of cancers. It has be[illegible]roposed that aviators are exposed to potential carcinogens such as ionizing radiation during flight[22] and jet fuel combustion products.[19] Nonionizing electromagnetic fields[10] and disruption of the circadian rhythm[28] are also potential contributing factors. It is important to understand whether pilots are at an increased risk for certain diseases based on occupational exposures so their health status can be properly evaluated, maintained, and when necessary, treated. Prostate cancer is one of the malignancies that has been investigated in the literature.

Prostate cancer is the second most common type of male cancer worldwide. The most recent data from 2012 estimated that there were 1.1 million cases and over 307,000 deaths worldwide.[32] In the United States, the risk of developing prostate cancer is estimated to be one in six.[26] This cancer is particularly relevant to the field of aviation since about 95% of pilots in the United States are male.[7] Moreover, prostate cancer is also strongly associated with age.[14,21] As populations continue to age and the public use of aviation-based transport continues to rise, the average age of pilots will continue to increase. Over the last 20 yr in the United States, the average age of pilots has increased from 40.5 to 44.7 according to the Federal Aviation Administration.[8,9] If this trend continues, the incidence of prostate cancer will continue to increase. It is

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imperative to understand if a pilot's occupational exposures further increase the risk of prostate cancer.

The increased risk of prostate cancer among aviation pilots is a subject of debate because there is ambiguity in the literature. Some studies suggest that they are indeed at an increased risk while other studies seem to suggest that they are not.[1,11] Determining the incidence of prostate cancer in pilots compared to the general population is important to advance our understanding of the potential risks as well as to help inform policies and screening protocols specific to aviators. Therefore, the aim of this study was to perform a systematic review and meta-analysis to determine whether pilots are at an increased risk of developing prostate cancer compared to the general population.

METHODS

This study was conducted according to guidance from the Cochrane Handbook of Systematic Reviews and is reported according to preferred reporting items for systematic reviews and meta-analyses recommendations (PRISMA).[15,20]

Literature Search

A comprehensive literature search of several databases was performed from each database's inception to November 2013 in any language. The databases included Ovid Medline in-process and other nonindexed citations, Ovid Medline, and PubMed. An experienced librarian from Mayo Clinic designed and conducted the search strategy with input from study investigators. This search was duplicated by an experienced librarian at the Civil Aviation Medical Institute at the Federal Aviation Administration to ensure the completeness of the search protocol. Both librarians used controlled vocabulary supplemented with keywords to search for studies that assessed the incidence of prostate cancer in pilots. We also manually searched PubMed, Ovid Medline, and the Defense Technical Information Center, and crossed-referenced pertinent articles to ensure the completeness of the search protocol.

Study Selection

All studies were considered regardless of publication language or study design. Studies were eligible if they compared the incidence of prostate cancer in pilots to the general population. Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility, and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were harmonized by consensus and, if not possible by consensus, through arbitration by a third reviewer.

Data Extraction

Information on the studies' characteristics and demographics was recorded, such as authors, publication year, country, number of years in the evaluation, type of pilot population studied, and outcome. The incidence of prostate cancer was reported as either a standardized incidence ratio (SIR) or as an incidence rate ratio (IRR) in all studies.

Assessment of Methodological Quality (Risk of Bias)

The methodological quality of the included studies was assessed by using the Newcastle-Ottawa scale.[31] This scale consists of three domains (cohort selection, comparability, and outcome) and evaluates each study's overall risk of bias. Two reviewers independently assessed the quality of each study.

Outcome Definition

The primary outcome, incidence of prostate cancer, was defined as new onset prostate cancer during the study period as determined by public registries. The incidence rates were then standardized to the respective populations to determine the SIR or IRR.

Statistical Analysis and Subgroup Analysis

The SIR or IRR was retrieved from each study as well as the 90% or 95% confidence interval (CI) from each study. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance (ranging from 0 to 100%). I^2 values of $\leq$ 25%, 50%, and $\geq$ 75% represent low, moderate, and high inconsistency, respectively. The random-effects model was used to pool results, thereby accounting for variance between studies.[6] This model was chosen because of the anticipated significant heterogeneity between the studies. Comprehensive Meta-Analysis, version 2 (Englewood, NJ) was used for statistical analysis. All *P*-values are two tailed and the threshold for significance was set at $P < 0.05$.

The a priori hypothesis is to conduct subgroup analysis based on race (white or African American), the type of pilot (military or civilian), and estimated exposure to radiation (low, medium, or high). Although the SIR and IRR are both relative effects measures (risk ratios) and may approximate each other, their estimation methods differ. Therefore, using subgroup analysis, we explored whether the pooled effect size differed between studies reporting IRR and SIR. The relative estimates from subgroups were compared using the ANOVA test to determine if a statistically significant difference was present among the estimates derived from each subgroup.

RESULTS

The initial search resulted in 44 publications and, after abstract and full text reviews, 8 studies met the inclusion criteria (**Fig. 1**). More than 128,000 pilots were evaluated. The year of publication ranged from 1996 to 2011, and earliest data included in the studies were from 1946. Three studies took place in North America, while the remaining five took place in Europe.

Table I shows details of the baseline characteristics of the included studies. Risk of bias of the included studies was found to be low according to the Newcastle-Ottawa quality

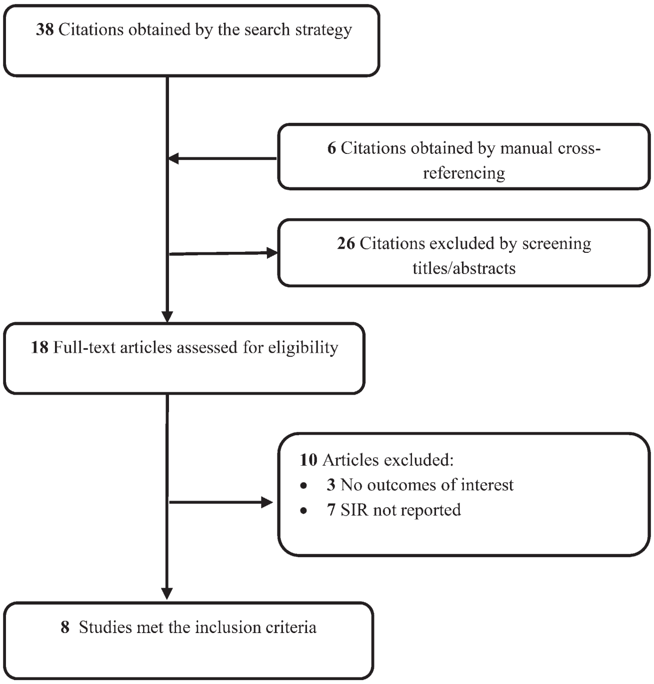


Fig. 1. Flowchart showing the literature search yield and selected studies.

assessment scale. Pilots were twice as likely to develop prostate cancer compared to the general population (RR 2.0; 95% CI, 1.5–2.7). The analysis was associated with high heterogeneity (I^2 = 79%) that was explained by subgroup analysis (**Fig. 2**).

Studies that reported an SIR had an RR of 1.36 (95% CI, 1.18–1.56) compared to the study that reported IRR which had an RR of 3.84 (95% CI, 2.40–6.13). The RR of 2.56 (95% CI, 2.01–3.27) in whites was lower than that in African Americans who had an RR of 10.00 (95% CI, 5.04–19.86). Civilian pilots had an RR of 1.36 (95% CI, 1.01–1.83) while those with military backgrounds had an RR of 3.30 (95% CI, 2.03–5.39). Lastly, the estimated radiation exposure risk was analyzed in terms of low, moderate, and high as defined in the original studies. There was no statistically significant difference among these subgroups. All subgroup analysis is summarized in **Table II**.

DISCUSSION

This systematic review and meta-analysis shows that pilots have twice the risk for the development of prostate cancer as the general population. Among the subgroups analyzed, military pilots and African American pilots had an even higher risk. It was also noted that there was a higher risk in the study that reported IRR compared to the studies that reported a SIR. The reason for this is thought to be that the study which reported IRR was the only study that included men of African ancestry. This subgroup [illegible] the highest risk of all the subgroups that were analyzed, and African ancestry is a known strong risk factor for development of prostate cancer.[18]

Although some of the risk factors for prostate cancer are known, the etiology of this disease process is still poorly

Table I. Study Characteristics.

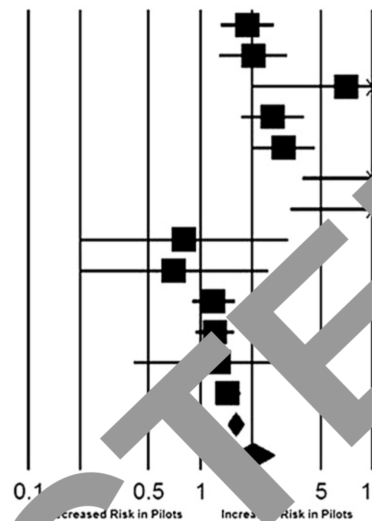
STUDY	PILOT POPULATION	STUDY LENGTH	SIZE	SERVICE	TYPE OF PILOTS	AGE RANGE	RISK FACTORS
Band 1996[1]	Canada	[illegible]–1992	2680	Civilian	Professional and General	Not Specified	Radiation exposure
del Junco 2011[5]	U.S. Air Force	1991–[illegible]	337	Military	Professional	35–64	Race, age
Gundestrup 1999[11]	Denmark	1921–1995	3790	Civilian	Professional and General	Not Specified	Type of aircraft, flight hours, radiation exposure
Haldorsen 200[illegible]	Norway	1946–1994	3815	Civilian	Professional and General	Not Specified	Radiation exposure, smoking status
Hammar 200[illegible]	Sweden	1957–1994	105,025	Military and Civilian	Professional and General	20–80+	Service branch, flight hours, altitude, distance
Pukkala 2002[23]	Denmark, Finland, Iceland, Norway, and Sweden	1946–1997	10,032	Civilian	Professional	Not Specified	Flight hours, radiation exposure, circadian rhythm disturbance, smoking status
Rafnsson 2000[24]	Iceland	1955–1997	458	Civilian	Professional and General	Not Specified	Flight hours, radiation exposure, circadian rhythm disturbance
Yamane 2006[33]	U.S. Air Force	1989–2002	1959	Military	Professional	17–60	Age

Note: For all studies the history of cancer and race (% white) was not specified.

Model	Study name	Risk ratio	Lower limit	Upper limit
	Band et al.	1.9	1.3	2.7
	del Junco et al. a	2.0	1.3	3.2
	del Junco et al. b	7.1	2.0	24.5
	del Junco et al. c	2.6	1.7	4.0
	del Junco et al. d	3.0	2.0	4.6
	del Junco et al. e	12.1	3.9	37.2
	del Junco et al. f	11.2	3.3	37.3
	Gundestrup et al.	0.8	0.2	3.2
	Haldorsen et al. a	0.7	0.2	2.5
	Hammar et al.	1.2	0.9	1.6
	Pukkala et al.	1.2	0.9	1.6
	Rafnsson et al.	1.3	0.4	4.0
	Yamane	1.4	1.2	1.7
Fixed		1.6	1.4	1.8
Random		2.0	1.5	2.7

I^2 =79%

Risk ratio and 95% CI



Meta Analysis

Fig. 2. Forest plot and overall study analysis.

understood. There is little in the literature about what might increase prostate cancer risk in pilots. Some hypotheses suggest exposure to ionizing radiation during flight,[22] jet fuel combustion products,[19] electromagnetic fields,[10] and disruption of circadian rhythm[28] are plausible causes. Consistent with known risk factors, del Junco et al.[5] ascertained a higher risk of prostate cancer among a subgroup of African American pilots. The socioeconomic status of pilots might possibly be another risk factor, but this is not well understood.[25]

This study was not designed to answer the question of causality and is therefore unable to shed light on potential etiologies. Future studies will be needed to try to determine the reason that pilots have an increased risk of developing prostate cancer. In the meantime, it may be prudent to consider whether more aggressive screening practices might be necessary for aviator populations.

It is important to note that studies which assessed the mortality of pilots did not find an increase in mortality due to prostate cancer.[2,3] This may suggest that the increased incidence in pilots is because they are more frequently examined than the general population. However, since screening for prostate cancer during a flight physical is not required, this hypothesis is unlikely to account for the entire increase in incidence seen in this study. Another possible explanation could be that pilots live longer since they are healthier than the general population and prostate cancer is a disease of old age. However, the incidence

Table II. Subgroup [illegible]

COVARIATE	NO. COHORTS	EFFECT SIZE	LOWER LIMIT	UPPER LIMIT	$I^{2\%}$	*P*-VALUE FOR DIFFERENCE
Effect size type						
IRR	6	3.84	2.40	6.13	67.93	0.01
SIR	7	1.36	1.18	1.56	13.78	
Race						
Black	3	10.00	5.04	19.86	0.00	0.01
White	3	2.56	2.01	3.27	0.00	
Pilot type						
Civilian	5	1.36	1.01	1.83	28.94	0.01
Military	7	3.30	2.03	5.39	85.31	
Estimated radiation exposure						
Low	6	0.92	0.64	1.33	0.00	0.28
Medium	3	1.08	0.63	1.86	0.00	
High	6	1.32	1.03	1.69	0.00	

IRR = incidence rate ratio; SIR = standardized incidence ratio.

was standardized by age, which reduces the impact of confounding by age. Lastly, errors in the ascertainment of cause of death in observational studies are common. Future research may better clarify whether prostate cancer mortality in pilots is different from that of the general population.

The results derived from observational studies are subject to confounding. Additionally, there was high heterogeneity between studies. Our a priori analysis explains this heterogeneity. It is most likely due to the diversity of the populations included in the individual studies as well as the variance in when the data were collected. Some studies included data from 1946 while others included data only from 1991. Another limitation is that in one study, there is a potential for overlap of patients among the different cohorts.[23] Since the majority of the studies included only pilots from within their own countries, this limitation is not a concern in other studies.

The strengths of this review include the exhaustive and reproducible search strategy, inclusion of non-English studies, and a large sample size of over 128,000 pilots from 8 studies. Most previous articles that addressed the question of whether pilots are at an increased risk of developing prostate cancer did not focus specifically on prostate cancer but rather on cancers in general. Therefore, they would include at most two or three articles on prostate cancer and conclude that the data were mixed. To our knowledge, this is the largest systematic review that has been performed to date for answering the question of whether pilots are at an increased risk for developing prostate cancer.

Consideration must be given to screening for prostate cancer in pilots. The U.S. Preventive Services Task Force has recently recommended against routine screening for prostate cancer using prostate-specific antigen, the only laboratory test that can be used as a screening tool. Many would assume that this recommendation should also be applied to pilots. This might be reasonable if pilots had an average risk. However, it appears that they are twice as likely to develop this malignancy.

This review highlights the need for more studies on this subject. We need to better understand why aviators are at an increased risk in order to more effectively preserve the health status of pilots. Another incentive for more investigative work is that this study may actually underestimate the increased risk of pilots. Prostate cancer incidence has been rising over the years partially, but not completely, due to increased screening efforts. The study by del Junco et al.[5] seems to suggest that, over time, aviators are developing prostate cancer at an even faster rate than the general population. If this is true, then studies which rely upon data from the mid-1900s might not truly represent the increased risk that is now present in the early 2000s. Given the prevalence of prostate cancer in the general population and the elevated at-risk status of pilots, it is imperative that we gain a more robust understanding of the true risk and the mechanisms underlying that risk. Lastly, shared decision-making tools are needed to communicate the risk of prostate cancer to pilots and aid them in the decision regarding screening.

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