Prostate Cancer in Pilots

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BACKGROUND: Aviation exposes pilots to various occupationally related hazards, including ionizing radiation and chemical combustion. The possibility of increased prostate cancer incidence and mortality among pilots is a subject of debate. This systematic review and meta-analysis aims to summarize the supporting evidence and determine the magnitude of association.

METHODS: All studies reporting prostate cancer incidence and mortality in pilots compared to the general population were included regardless of language or size. The comprehensive search included multiple databases and manual search. A random effect model was used to pool relative risks (RR) across studies.

RESULTS: The final search yielded nine studies with good methodological quality. Four studies reported the incidence of prostate cancer while six reported on mortality. Pilots had a small but statistically significant increase in the risk of developing prostate cancer [RR 1.20; 95% confidence interval (CI), 1.08-1.33], but not in prostate cancer mortality (RR 1.20; 95% CI, 0.91-1.60).

CONCLUSION: Pilots appear to have a very small increase in prostate cancer incidence, but not in mortality. The clinical significance of this finding is uncertain.

KEYWORDS: aviation, pilots, prostate cancer, incidence, mortality.

Raslau D, Abu Dabrh AM, Summerfield DT, Wang Z, Steinkraus LW, Murad MH. *Prostate cancer in pilots*. Aerosp Med Hum Perform. 2016; 87(6):565–570.

Various aspects of aviation have been examined in regards to pilot health, such as analyzing specific risk factors for aviators that may lead to the development of heart disease or understanding the utility and efficacy of various screening and diagnostic tests in this population.[4,29,32] It has been proposed that aviators are exposed to potential carcinogens such as ionizing radiation during flight, jet fuel combustion products, and disruption of the circadian rhythm.[19,23,30] It is important to understand if pilots are at increased risk for certain diseases or death based on occupational exposures so their health status can be properly evaluated and, when necessary, treated. Several studies looked into the risk of developing and dying from various types of cancers in pilots, and prostate cancer is one of these cancers that have been investigated in the literature.[3,10]

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.[34] In the United States, the risk of developing prostate cancer is estimated to be one in six.[28] This cancer is particularly relevant to the field of aviation since about 95% of pilots in the United States are male.[6] Moreover, prostate cancer is also strongly associated with age.[13,21] 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] It is imperative to understand if a pilot's occupational exposures further increase the risk of prostate cancer.

The risk of prostate cancer among pilots has been reported. Some studies found increased risk in incidence while other studies did not.[2,10] Likewise, the literature assessing mortality is conflicted.[18,22] Determining the incidence and mortality of prostate cancer in pilots compared to the general population is important to advance our understanding of the potential risks in this population. Therefore, the aim of this study was to perform a systematic review and meta-analysis to determine if pilots (civilian and military) have an increased incidence or mortality from prostate cancer compared to the general population.

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This manuscript was received for review in August 2015. It was accepted for publication in February 2016.

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DOI: 10.3357/AMHP.4453.2016

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).[14,20] The GRADE methodology was used to assess the quality of evidence.[11]

Data Sources and Study Strategy

A comprehensive literature search of several databases was performed from databases' inception to August 2015 in any language. The databases included Ovid Medline in-process and other non-indexed 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 from the Civil Aerospace 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.

Selection Criteria

All studies were considered regardless of publication language or study design. Studies were eligible if they compared the incidence or mortality 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 or as a hazard ratio in one study. The mortality from prostate cancer was reported as either a standardized mortality ratio, mortality rate ratio in one study, or as a mortality odds ratio in another study.

The methodological quality of the included studies was assessed by using the Newcastle-Ottawa scale.[33] 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.

Statistical Analysis

Incidence of prostate cancer was defined as a first-time or new-onset diagnosis of prostate cancer during the study period as determined by public registries. These incidence rates were then standardized to the general population. Prostate cancer mortality was defined as death caused by this cancer during the study period as determined by public registries. The mortality rates were then compared to the respective population.

The estimated incidence and mortality rates as well as the related standard error were extracted from the included studies. The random effect model as described by DerSimonian and Laird was used to pool results, thereby accounting for variance between studies.[5] Heterogeneity across the included studies was estimated using the Cochrane Q test (value under 0.10 implies significant heterogeneity) and the I^2 statistic, in which I^2 values of ≤25%, 50%, and ≥75% represent low, moderate, and high inconsistency, respectively.[15,16] We planned to explore heterogeneity by conducting subgroup analyses based on race, estimated radiation exposure, and profession (military vs. civilian). We used Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX) for analysis.

RESULTS

The initial search resulted in 53 total citations referencing incidence and mortality. **Fig. 1** shows the breakdown for incidence and mortality separately. After abstract and full text reviews, four studies met the inclusion criteria for incidence and six for mortality. We excluded the studies by del Junco and Yamane, which included non-pilot Air Force personnel. The incidence studies assessed over 90,000 pilots and the mortality studies evaluated almost 20,000. The year of publication ranged from 1996 to 2012 and earliest data included in the studies were from 1946. Four studies assessed populations in North America, while the remaining six looked at populations in Europe.

Table I shows the characteristics of the included incidence and mortality, respectively. The risk of bias of the included studies was low as shown in **Table II**. Pilots had a higher incidence of prostate cancer [RR = 1.20 (95% CI, 1.08–1.33); **Fig. 2**], but

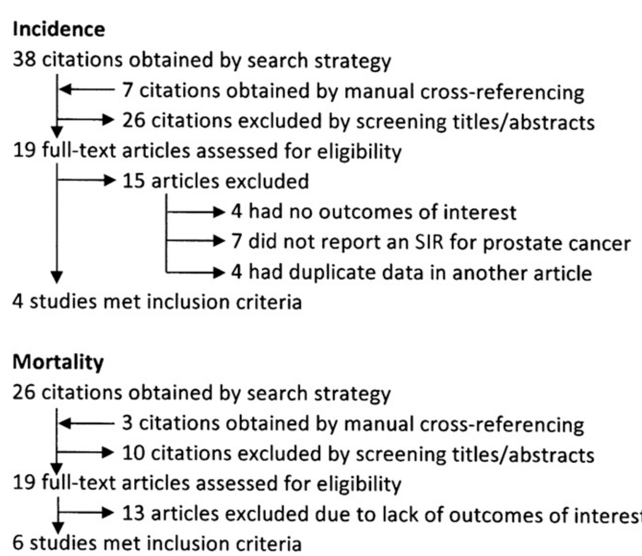

Fig. 1. Flowchart showing the literature search yield and selected studies.

Table I. Study Characteristics.

STUDY	PILOT POPULATION	STUDY LENGTH	SIZE	SERVICE	TYPE OF PILOTS	AGE RANGE	RISK FACTORS
				INCIDENCE STUDIES			
Band et al. 1996[2]	Canada	1950–1992	2680	Civilian	Professional	Not Specified	Radiation exposure
Pukkala et al., 2002[24]	Denmark, Finland, Iceland, Norway, and Sweden	1946–1997	10,032	Civilian	Professional	Not Specified	Flight hours, radiation exposure
Rogers et al., 2011[26]	United States	1987–2008	61,844	Military	Professional	35-80	Flight hours, military status
dos Santos Silva et al., 2012[6]	United Kingdom	1989–2008	15,867	Civilian	Professional	Not Specified	Not Specified
				MORTALITY STUDIES			
Ballard et al., 2002[1]	Italy	1965–1996	3022	Civilian	Professional	20.4–61.2	Radiation exposure
Band et al., 1996[2]	Canada	1950–1992	2680	Civilian	Professional	Not Specified	Radiation exposure
Hammer et al., 2012[12]	Germany	1960–1997	6006	Civilian	Professional	Not Specified	Radiation exposure
Irvine and Davies, 1999[18]	Great Britain	1950–1992	6209	Civilian	Professional	Not Specified	Long-haul vs. short-haul
Nicholas et al., 1998[22]	United States	1984–1991	1513	Civilian	Professional	Not Specified	Not Specified
Reynisdóttir et al., 2011[25]	Iceland	1960–2009	454	Civilian	Professional	Not Specified	Radiation exposure, race

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

mortality was not significantly elevated [RR = 1.20 (95% CI, 0.91–1.60); **Fig. 3**]. The estimate for prostate cancer incidence was associated with moderate heterogeneity ($I^2 = 72.3\%$, $P = 0.01$). The estimate for prostate cancer mortality was associated with low heterogeneity ($I^2 = 0.0\%$, $P = 0.89$).

There were insufficient data to conduct subgroup analyses about possible predicting factors of prostate cancer incidence or mortality in pilots. However, the studies by Silva et al. and Hammer et al. estimated radiation exposure and suggested a potential trend of increasing risk for both incidence and mortality.[6,12] The study by Silva et al. showed a possible trend toward increased incidence of male genitourinary cancers with increasing flight hours. Pilots with entry flight hours <400 had a RR = 0.70 (95% CI 0.45–1.08), those with flight hours 400–5499 had a RR = 0.99 (95% CI 0.73–1.33), and those with flight hours >5500 had a RR = 1.13 (95% CI 0.97–1.32). Similarly, Hammer et al. showed a potential trend toward increased mortality risk. Low-level radiation exposure was associated with a RR = 0.35 (95% CI 0.00–2.37), moderate exposure was associated with a RR = 1.22 (95% CI 0.37–3.06), and high exposure was associated with a RR = 0.85 (95% CI 0.13–3.07). Both of these studies lacked a large enough sample size and further investigation is warranted.

The choice of association measure used (standardized mortality ratio vs. hazard ratio) or the analysis model (random-effects vs. fixed effect) do not significantly change the conclusions of this study. The quality of this evidence (confidence in the estimates) was low due to the observational nature of the included studies. The estimate of prostate cancer incidence is less certain than the estimate of prostate cancer mortality due to heterogeneity.

DISCUSSION

This systematic review and meta-analysis shows that pilots have a small but statistically significant increase in the risk of prostate cancer incidence but not mortality. Trends in data

Table II. Quality Assessment.

	NEWCASTLE OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES								
ASSESSMENT	BALLARD	BAND	HAMMAR	IRVINE/DAVIES	NICHOLAS	PUKKALA	REYNISDÓTTIR	ROGERS	DOS SANTOS SILVA
Selection									
Representativeness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Selection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome not already present	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Comparability									
Controlled for most important factor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controlled for another factor	No	No	No	Yes	No	Yes	Yes	No	No
Outcome									
Assessment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up length	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adequacy of follow-up	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Final Assessment	LROB	LROB	LROB	LROB	LROB	LROB	LROB	LROB	LROB

LROB = low risk of bias; MROB = moderate risk of bias; HROB = high risk of bias.

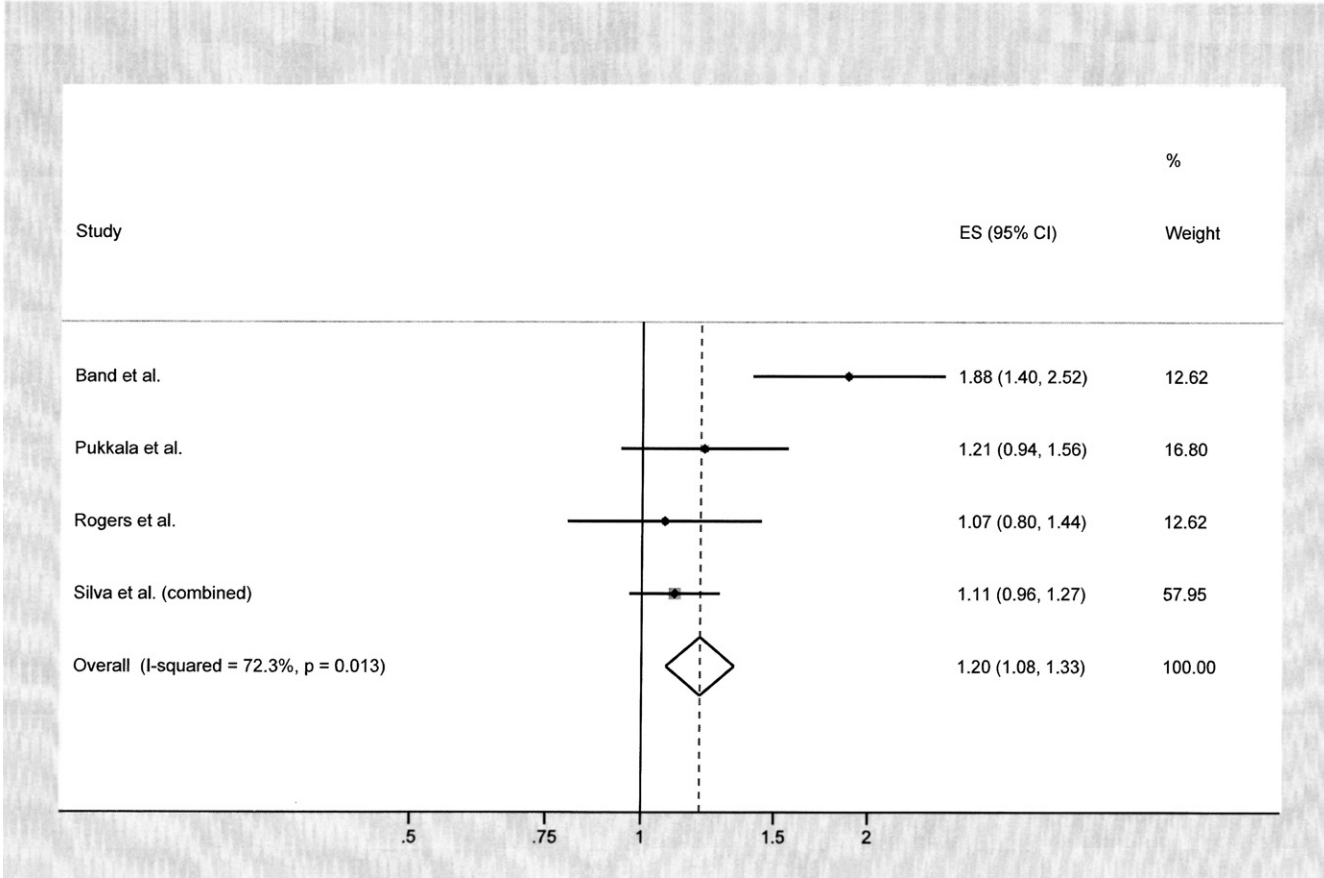

Fig. 2. Forest plot showing meta-analysis results for prostate cancer incidence.

suggest an increasing risk based on estimated radiation exposure, which would be consistent with prior hypotheses.[23] However, due to the limited information gathered in the studies, the other potential risks of combustion products and circadian rhythm disruption cannot be excluded.[19,30]

Despite knowing some of the risk factors for developing prostate cancer, the etiology of this disease remains poorly understood. The aforementioned risk factors may play a role. Race is a known contributor, with African ancestry adding significant risk.[17] Documenting the racial distribution of pilots in future studies will be important to better understand this risk factor's contribution to the overall findings of this paper. The socioeconomic status of pilots might possibly be another risk factor, but this is not well understood.[27] Our data were from countries with universal health care systems or from military personnel who readily have access to health care, so it is unclear how this may have contributed, if at all.

The non-significance of the mortality data is interesting. It may mean that the increased incidence of prostate cancer is limited to low-grade or slowly developing prostate cancer, which does not alter the mortality of the disease. It could highlight that those in a higher socioeconomic status obtain better health outcomes. Or it could suggest that the small increase in incidence is not clinically significant.

Ultimately, this study was not designed to answer these questions and is, therefore, unable to shed additional light on these matters. Future studies are needed to try to determine the reason that pilots have a mildly increased risk of prostate cancer incidence without any change in mortality. We suggest continued assessment of prostate cancer risk in pilots and propose national registries which include information about specific risk factors, including race, age, flight hours, estimated radiation exposure, and family history of prostate cancer, as well as disease outcomes such as age at diagnosis, staging, and treatment.

The results of this study are derived from observational studies which are subject to confounding. There are differences between potential risk factors in different countries as well as differences in medical practices between countries. In addition, some studies included in the analysis had data from as far back as 1946, while others included only more recent data from 1991 onwards. The incidence of prostate cancer may change over time and changes in medical practice can affect prostate cancer mortality.

The strengths of this review include the exhaustive and reproducible search strategy and a large sample size of pilots from the nine included studies. Most previous articles that addressed the question of whether pilots have an increased

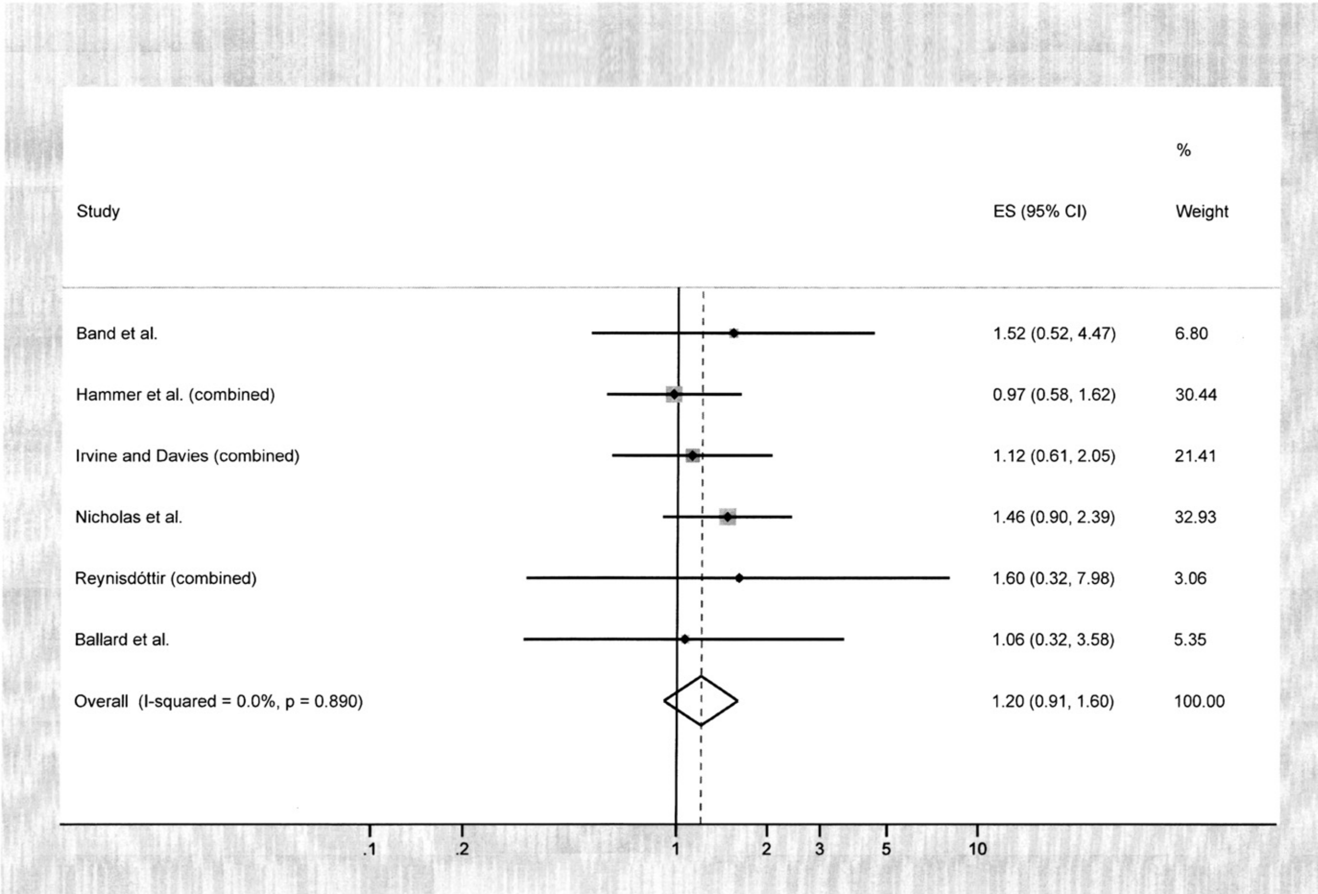

Fig. 3. Forest plot showing meta-analysis results for prostate cancer mortality.

incidence of or mortality from prostate cancer did not focus specifically on prostate cancer, but rather on cancer risk in general. Therefore, they would include a couple articles with prostate cancer data and conclude that the data was mixed.

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.[31] The main reason for this controversial recommendation is the overtreatment of nonlethal cancers. This is a hotly debated topic and we may see some evidence here that, despite a mild increase in incidence, mortality may not have changed in the pilot population. This could be additional supporting evidence that most prostate cancers are not lethal, although we must keep in mind these data are from observational studies and we must seek better quality data.

This review highlights the need for more studies on this subject. We need to better understand why aviators appear to be at an increased risk in order to more effectively preserve their health status. Given the prevalence of prostate cancer in the general population and the apparent at-risk status of pilots, it is important that we gain a more robust understanding of the true risk and the mechanisms that may underlying that risk. Studies assessing incidence and mortality concomitantly may shed better light on whether the increased incidence is clinically significant and if mortality from this disease is truly not a concern to pilots. Lastly, shared decision-making tools are needed to communicate the risk of prostate cancer to pilots and aid them in decisions regarding screening and treatment options.

ACKNOWLEDGMENTS

The authors would like to thank the librarians who aided in the implementation of the search strategies for this study for their technical assistance: Ann Farrell from the Mayo Clinic, and Roni Anderson and Kathy Wade from the Federal Aviation Administration. We would also like to thank Gladdie Hebl from Mayo Clinic Research and Academic Support Services for her technical assistance and editorial support.

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