Reviewer’s report

Title: Incidence of cancer among licenced commercial pilots flying North Atlantic routes

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Reviewer: timothy Jorgensen

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This is a very weak paper and it provides no new insight into the carcinogenicity of cosmic radiation. The associations that it reports are most likely attributable to statistical randomness, confounding, or biases. Furthermore, its conclusions contradict much of what we know about radiation carcinogenesis.

Major weaknesses:

Lack of power. The median cumulative ionizing radiation dose for the pilots in this study was 22.55 mSv, with a maximum dose of 83.2 mSv (Table 1). Years of cohort studies with large groups of medical patients and atomic bomb survivors tells us that the relative risks for such doses should be about 1.001 and 1.004, respectively (i.e. ERR= 0.00005/mSv). This is way too small an increase in risk to be seen in a cohort this small (n=551) or for that matter in a cohort of any size. At these dose levels, radiation risks are purely theoretical because they are too small to be measured.

In fact, we can see that the pilot doses are barely above background doses at ground level. If we take the total person-years (8,514) and divide them by the number of exposed pilots (286), we can see that the average number of years of exposure per pilot were 30 years. Given that background doses at sea level are typically 3 mSv per year, subjects who never flew would have received 90 mSv over this 30-year period. So even the pilots with the highest doses are but two-fold above background radiation doses. So it seems incredulous that significant increases in any cancers could be seen at these extremely low ionizing radiation doses.

Potential Confounding. So how do we explain the statistically significant increases skin cancers that were found among the pilots? The most likely explanation is that they were caused by increased exposure to ultraviolet (UV) radiation. UV exposure is the most important risk factor for skin cancers. The UV doses of the pilots would have been collinear with their ionizing radiation exposure. So their UV exposure is likely a confounder in the study. (A confounder is a variable that is associated with both the exposure and the disease, and results in a false apparent association between the two.) If UV doses had been measured, the potential for UV confounding could have been assessed. But UV doses were not determined. So we cannot be sure that confounding is the explanation, and we cannot discount them (notwithstanding the face versus trunk incidence comparison).
Potential Biases. But UV doses don't explain the prostate cancer association that was found. How can that be explained? Prostate cancer is the most prevalent cancer among men. Virtually all men eventually get prostate cancer if they live long enough, since age is the most important risk factor. But there are other risk factors for prostate cancer (e.g., obesity and being sedentary). But the prevalences of obesity and a sedentary lifestyle also increase with age. So it is very important that all of these known risk factors be adjusted for when assessing radiation's prostate cancer risk. In this study, only age was adjusted for.

Further complicating the analysis is that the cumulative radiation dose is also primarily driven by age (i.e., the more years if flying you experience, the older you'll be, and the higher your cumulative dose will be). Thus, all the age-related risk factors must be carefully adjusted for, otherwise residual age-related confounding could result in false association.

In addition, prostate cancer is highly susceptible to surveillance bias, particularly if it is detected by PSA testing. The Icelandair pilots' annual physicals are probably not exactly the same as other pilots. If there is any difference between the two groups in how they are screened for prostate cancer, the study will be prone to surveillance bias. There is no discussion or assessment of the potential for surveillance bias in this study.

Other problems:

SIR analysis. It is not clear what group the SIR is being standardized too. SIR is usually used to account for differences in incidence rates between populations that can be explained by differences in demographics such as age, gender and race. These pilots are a very homogeneous group. They are men within a very narrow age range, who are presumably all Caucasians. It is not clear what the SIR is supposed to achieve, and whether the standard population is relevant.

Cox Regression analysis. Cox regression would seem like the most appropriate tool for analyzing these data, but we are told that "the data did not meet the criteria for Cox analysis." We are not told, however, in what way the data did not fit the criteria. This is a red flag.

Unexposed. The non-Icelandair pilots were defined as the "unexposed group." Why would non-Icelandair pilots not have radiation exposure?

Age 40 cut-off. Cumulative dose was calculated up to age 40 because "exposure after this age did not induce BCC among atomic bomb survivors." How is that relevant to this study?

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