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Cancer Incidence among Female Flight Attendants: A Meta-Analysis of Published Data

ALESSANDRA BUJA, M.D., Ph.D.,[1] GIUSEPPE MASTRANGELO, M.D.,[1] EGLE PERISSINOTTO,[1] FRANCESCO GRIGOLETTO,[1] ANNA CHIARA FRIGO,[1] GIUSEPPE RAUSA, M.D.,[1] VALERIA MARIN, M.D.,[1] CRISTINA CANOVA,[1] and FRANCESCA DOMINICI[2]

ABSTRACT

Background: **Flight attendants are exposed to cosmic ionizing radiation and other potential cancer risk factors, but only recently have epidemiological studies been performed to assess the risk of cancer among these workers. The aim of the present work was to evaluate the incidence of various types of cancer among female cabin attendants by combining cancer incidence estimates reported in published studies.**

Methods: **All follow-up studies reporting standardized incidence ratio (SIR) for cancer among female flight attendants were obtained from online databases and analyzed. A meta-analysis was performed by applying Bayesian hierarchical models, which take into account studies that reported SIR = 0 and natural heterogeneity of study-specific SIRs.**

Results: **A total of seven published studies reporting SIR for several cancer types were extracted. Meta-analysis showed a significant excess of melanoma (meta-SIR 2.15, 95% posterior interval [PI] 1.56-2.88) and breast carcinoma (meta-SIR 1.40; PI 1.19-1.65) and a slight but not significant excess of cancer incidence across types (meta-SIR 1.11, PI 0.98-1.25).**

Conclusions: **Although further studies are necessary to clarify the exact role of occupational exposure, all airlines should, as some companies do, estimate radiation dose, organize the schedules of crew members in order to reduce further exposure in highly exposed flight attendants, inform crew members about health risks, and give special protection to pregnant women.**

INTRODUCTION

Flight attendants' occupational exposure to cosmic rays corresponds to an annual radiation dose ranging from 0.2 to 5 millisievert.[1] Among cosmic radiation components, neutrons are high linear energy transfer particles that may induce DNA damage and no radioadaptative response.[2,3] Chromosomal aberration was reported to be higher in members of a flight crew than in a control group.[4] However, the disruption of circadian rhythm that occurs due to flight attendants' work shifts might reduce melatonin production,[5] leading to a decreased oncostatic effect of this hormone.[6]

Several epidemiological studies on cancer in female flight attendants have been completed,[7–13] with some conflicting results. The sample size in

[1]Department of Environmental Medicine and Public Health, University of Padua, 35128 Padua, Italy.
[2]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

most original studies was too small to produce robust results, and some authors tried to overcome the problem by performing meta-analysis of cancer in women.

A pooling study on cancer mortality, published in 2003,[14] was carried out in a large cohort of European female flight attendants. The authors reported a reduction in all-site cancer mortality (meta-standardized mortality ratio, meta-SMR 0.78, CI 0.66, 0.95) and a slight but nonsignificant excess in mortality from breast cancer (meta-SMR 1.11, CI 0.82, 1.48). In contrast, no meta-analysis was undertaken on cancer incidence in a similarly large cohort of female flight attendants. In fact, combining only two studies, one published in 1995 (on 1577 females employed in all Finnish airlines[13]) and one published in 1998 (on 287 retired females[12]), meta-standardized incidence ratios (meta-SIR) of 2.31 (CI 1.24, 4.30) and 1.89 (CI 1.40, 2.56) for melanoma and breast cancer, respectively, were reported by Ballard et al.[15] In 2001, Lynge aggregated observed and expected incident cancer cases of five studies, without carrying out a formal meta-analysis,[16] and found higher than expected cancer cases for melanoma (31 vs. 15.54), breast cancer (105 vs. 74.76), other skin cancers (6 vs. 2.28), leukemia (4 vs. 3.72), and all-site cancers (243 vs. 209.43).

In this paper, we perform an updated and comprehensive meta-analysis of all cancer incidence studies (including two earlier studies and those published in 1998–2005) carried out in European and U.S. cohorts of female flight attendants in order to provide more stable cancer risk estimates.

MATERIALS AND METHODS

Epidemiological cohort studies published in peer-reviewed sources until February 2004 were sought in MEDLINE, Toxline, NIOSHTIC, and NLM Gateway bibliographic databases, using the folllowing terms as key words: aircrew, flight attendants, neoplasms, aviation, cosmic radiation, and epidemiology. Six independent studies[7–11,13] on cancer incidence among female cabin attendants were found. The references included in the selected papers were inspected to identify other studies. Cancer data found by Wartenberg and Stapleton[12] in retired U.S. cabin attendants were drawn from Ballard's meta-analysis.[15]

We extracted and entered into an electronic database the observed and expected cases of cancer. We included in the meta-analysis cancer sites for which at least two studies reported at least one observed case, and at least two expected cases were counted in the total population.

When studies estimated an SIR equal to 0, the results were reported in three different circumstances: (1) the expected number of cases and the upper limit of CI of the estimated SIR were reported, (2) the upper limit of CI of the estimated SIR was reported, and (3) no information in addition to an SIR = 0 was reported (we denoted such cases with a No in Table 2). To include in the meta-analysis the SIR = 0 for circumstances 1 and 2, we used a two-stage Bayesian hierarchical model. In circumstance 1, we know that the observed number of cases is equal to zero, and we have the expected number of cases. In circumstance 2, we also know that the observed number of cases is equal to zero, but now we impute the expected value by taking

$$E = \mu_{\text{sup}}/U$$

where U is the upper limit of the SIR CI, and μ_{sup} is such that the probability that zero cases would occur under a Poisson model:

$$P(Y = 0|\mu) = \exp(-\mu)$$

would be <0.025. Taking into account circumstances 1 and 2, we assumed that the observed number of cancer cases in the study s (Y^s) has a Poisson distribution with mean μ^s, where

$$\log \mu^s = \log E^s + \alpha + \beta^s \text{ (first stage)}$$

and

$$\beta^s \sim N(0, \tau^2)$$

where τ^2 denotes the between-study variability of the $\log(\mu^s/E^s)$ with respect to the overall mean α (second stage). Thus, under this model specification, the meta-SIR is defined as $\exp(\alpha)$. Unfortunately, we were obligated to exclude the SIR = 0 for circumstance 3 because without any information on the expected number of cases or on the CI, we could not make any assessment of the statistical uncertainty of the SIR. This occurred in one study for leukemia, colo-rectal cancer, and bone cancer, in two studies for non-Hodgkin's lymphoma and bladder cancer, in three studies for other skin cancers, and in four studies for cancer of the kidneys.

We estimated the posterior distribution of the meta-SIR by using Bayesian hierarchical models. Bayesian hierarchical models provide a natural approach for combining SIR across studies, accounting for study-specific statistical uncertainty in the estimated SIR (within study variance) and for natural variability (heterogeneity) of the SIR across studies (between-study variance). In addition, Bayesian hierarchical models allow us to include the studies that reported SIR = 0 for circumstances 1 and 2. We fitted the Bayesian hierarchical models by use of Monte Carlo Markov Chain Methods, implemented by the software WinBUGS.[17,18]

Because of the limited power to detect heterogeneity, we estimated the meta-SIR for the cancer types with fewer than four studies by use of a fixed effect model that assumes that $\tau = 0$.[19]

We also performed an influential/sensitivity analysis[20] by calculating a pooled SIR only for a subgroup of studies reporting similar methodology (such as source of cohort, inclusion/exclusion criteria, and follow-up registry used) after excluding cancer data from Wartenberg and Stapleton,[15] who studied a cohort of retired workers, and Lynge,[8] who reported only breast cancer incidence in flight attendants traced through the 1970 census.

Finally, using Stata programs,[21] we investigated whether there was evidence of publication bias by applying three methods: Begg's test,[22] Egger's test,[23] and a meta-regression model with study size as explanatory variable.[24]

RESULTS

Table 1 shows the main characteristics of the studies included in the meta-analysis. The follow-up period averaged 19.3 years. The first five studies used similar methodology regarding the source of cohort (employers' list of companies or national institutions, or union of the occupational category or both), the inclusion/exclusion criteria, and the follow-up registry (local cancer registry), Wartenberg and Stapleton's study[12] includes a small cohort of only retired workers, and Lynge[8] reported only breast cancer incidence in flight attendants traced through the 1970 census. All studies took into account sex, age, and calendar period when comparing observed cases with expected cases in the general population.

Table 2 shows the distribution of incident cancer data by author and sites. Four hundred twenty-three cases of cancer occurred in 16,635 female flight attendants using pooled data from all studies. The SIRs reported by Wartenberg and Stapleton[12] were highest in each cancer site. Linnersjö et al.[9] did not report the SIR for cancer site with less than two cases observed. In this event, not specified in the original studies was reported.

Table 3 shows, separately for each cancer site, the number of the studies, posterior mean and 95% posterior region of the heterogeneity parameter (τ), and the posterior mean and 95% posterior interval of the meta-SIR ($\exp(\alpha)$). We found that the meta-SIRs are significantly higher than 1.0 for melanoma and breast cancer. In addition, we found that study-specific SIRs for melanoma are more heterogeneous than study-specific SIRs for breast cancer ($\hat{\tau} = 0.11$ and $\hat{\tau} = 0.07$, respectively).

Note that estimates of the meta-SIR and of the heterogeneity parameter for melanoma, equal to 2.15 and to 0.11, respectively, indicate that 95% of the true log study-specific SIRs are within the interval $\log(2.15) - 1.96 \times 0.11 = 0.55$ and $\log(2.15) + 1.96 \times 0.11 = 0.98$ or, equivalently, that 95% of the true study-specific SIRs are within the interval $1.73 = \exp(0.55)$ and $2.66 = \exp(0.98)$.

Table 1. Main Characteristics of Studies Included in the Meta-Analysis

Author	*Country*	*Publication year*	*No. of workers*	*Person-years*	*Years of follow-up*
Pukkala et al.[13]	Finland	1995	1,577	22,000	1967–1992
Rafnsson et al.[10]	Iceland	2001	1,532	27,148	1955–1997
Haldorsen et al.[7]	Norway	2001	3,105	60,401	1953–1996
Linnersjö et al.[9]	Sweden	2003	2,324	39,135	1961–1996
Reynolds et al.[11]	USA	2002	6,895	n.s.[a]	1988–1995
Wartenberg and Stapleton[12]	USA	1998	287	n.s.	n.s.
Lynge[16]	Denmark	1996	915	n.s.	1970–1987

[a]n.s., not specified in the original studies.

TABLE 2. DISTRIBUTION OF INCIDENT CANCER DATA BY AUTHOR (YEAR OF PUBLICATION) AND TUMOR SITE: INTERNATIONAL CLASSIFICATION OF DISEASES, IX REVISION (ICD-IX)

		Pukkala et al. (1995)[13]				*Rafnsson et al. (2001)*[10]				*Reynolds et al. (2002)*[11]				*Haldorsen et al. (2001)*[7]				*Linnersjö et al. (2003)*[9]				*Wartenberg and Stapleton (1998)*[12]				*Lynge (1996)*[16]			
Cancer sites	*ICD-IX*	*SIR*[a]	*CI*		n	*SIR*	*CI*		n	*SIR*	*CI*		n	*SIR*	*CI*		n	*SIR*	*CI*		n	*SIR*	*CI*		n	*SIR*	*CI*		n
All sites	140–208	**1.2**	0.9	1.7	35	**1.2**	1.0	1.6	64	**1.1**	0.9	1.3	104	**1.1**	0.9	1.3	127	**1.0**	0.8	1.2	76	**1.4**	0.9	2.3	17				n.r.[b]
Stomach	151	**1.0**	0.0	5.8	1	**1.2**	0.0	6.6	1	**1.0**	0.0	5.8	1	**0**	0.0	1.8	0				n.r.	**0**	0.0	61.5	0				n.r.
Colon/rectum	153,154	**1.3**	0.2	4.8	2				n.o.[c]	**0.9**	0.3	2.2	5	**1.3**	0.7	2.1	12	**0.6**	0.1	1.9	3	**2.0**	0.3	14.4	1				n.r.
Lung	162	**1.6**	0.0	9.0	1	**0**	0.0	1.1	0	**0.4**	0.1	1.2	3	**1.3**	0.5	2.9	6	**1.1**	0.2	3.2	3	**0**	0.0	6.0	0				n.r.
Bone	170	**15.1**	1.8	54.4	2	**4.3**	0.1	23.3	1				n.o.	**0**	0.0	13.0	0				n.r.	**0**	0.0	92.2	0	**0**	0	92.2	0
Melanoma	172	**2.1**	0.4	6.2	3	**3.0**	1.2	6.7	7	**2.5**	1.3	4.4	12	**1.7**	1.0	2.7	19	**2.2**	1.1	3.9	11	**3.4**	0.8	13.4	2				n.r.
Other skin[d]	173				n.o.	**1.7**	0.0	9.7	1				n.o.	**2.9**	1.0	6.9	5	**0**	0.0	4.35	0				n.o.				n.r.
Breast	174	**1.9**	1.2	2.2	20	**1.5**	1.0	2.1	26	**1.4**	1.1	1.8	60	**1.1**	0.8	1.5	38	**1.3**	0.9	1.7	33	**2.0**	1.0	4.3	7	**1.6**	0.9	2.7	14
Cervix uteri	180	**0**	0.0	3.7	0	**0.9**	0.2	2.3	4	**0.3**	0.0	1.2	2	**1.2**	0.7	2.0	16	**0.7**	0.2	1.8	4	**5.2**	1.7	16.6	3				n.r.
Body of uterus	182	**0**	0.0	3.0	0	**1.5**	0.3	4.3	3	**1.0**	0.3	2.4	5	**0.5**	0.1	1.6	3	**0.6**	0.1	2.3	2	**121**	17.0	859.0	1				n.r.
Ovary	183	**0.5**	0.0	2.6	1	**0.8**	0.2	2.4	3	**0.9**	0.3	2.1	5	**0.8**	0.3	1.7	6	**0.4**	0.1	1.5	2	**2.1**	0.3	14.6	1				n.r.
Bladder	188				n.o.	**2.0**	0.0	10.8	1	**3.3**	0.3	12.1	2	**1.4**	0.2	5.2	2	**0**	0.0	3.9	0				n.o.				n.r.
Kidney	189				n.o.				n.o.				n.o.	**0.6**	0.0	3.4	1	**1.7**	0.2	6.0	2				n.o.				n.r.
Brain/nervous system	191,192	**0.5**	0.0	2.9	1	**1.4**	0.3	4.0	3	**0.6**	0.0	3.6	1	**0.2**	0.0	1.1	1	**1.1**	0.3	2.7	4	**0**	0	15.4	0				n.r.
Thyroid	193	**0.6**	0.0	3.4	1	**1.6**	0.6	3.4	6	**0.3**	0.0	1.4	1	**0.7**	0.2	2.1	3				n.r.	**4.3**	1.1	17.1	2				n.r.
Non-Hodgkin's lymphoma	200,202				n.o.	**2.1**	0.2	7.5	2	**0.8**	0.1	2.8	2	**1.3**	0.3	3.3	4				n.r.				n.o.				n.r.
Leukemia	204–208	**3.6**	0.4	12.9	2	**1.0**	0.0	5.8	1				n.o.	**0.6**	0.0	3.4	1	**3.1**	0.9	8.0	4		0	13.6	0	**0**	0	6.6	0

[a]SIR, standardized incidence ratio; CI, 95% confidence interval; *n*, number of observed cases.
[b]n.r., none reported.
[c]n.o., none observed.
[d]Basal cell is not included.

Table 3. Aggregated Cancer Data by Site of Tumor: International Classification of Diseases, IX Revision (ICD-IX)

Cancer site	*ICD-IX*	n[a]	τ	*PI of* τ	*Meta-SIR*	*PI of meta-SIR*
All sites	140–208	6	0.05	0.01–0.19	1.11	0.99–1.25
Stomach	151	5	0.39	0.01–2.28	0.60	0.09–1.53
Colon/rectum	153, 154	5	0.14	0.01–0.64	1.06	0.64–1.60
Lung	162	6	0.53	0.01–2.61	0.66	0.15–1.27
Melanoma	172	6	0.11	0.01–0.44	2.15	1.56–2.88
Other skin[b]	173	3	n.c.[c]		1.91	0.71–3.73
Breast	174	7	0.07	0.01–0.27	1.40	1.19–1.65
Cervix uteri	180	6	0.49	0.01–1.84	0.89	0.34–1.56
Body of uterus	182	6	0.25	0.01–1.58	0.84	0.39–1.46
Ovary	183	6	0.14	0.01–0.63	0.74	0.41–1.15
Bladder	188	4	0.39	0.01–2.26	1.45	0.33–3.16
Kidney	189	2	n.c.		1.05	0.22–2.53
Brain/nervous system	191, 192	6	0.29	0.01–1.41	0.65	0.24–1.20
Thyroid	193	5	0.37	0.01–1.74	0.92	0.35–1.67
Non-Hodgkin's lymphoma	200, 202	3	n.c.		1.19	0.52–2.15
Leukemia	204–208	6	0.43	0.01–2.15	1.43	0.33–2.86

[a]n, number of studies; τ, posterior mean of the heterogeneity parameter; PI, 95% posterior interval; meta-SIR, posterior mean of the meta-SIR.
[b]Basal cell is not included.
[c]n.c., heterogeneity not calculated because of the small number of studies.

After excluding studies by Wartenberg and Stapleton[12] and by Lynge,[8] meta-SIRs reported in Table 3 were only marginally affected (data not shown).

We investigated publication bias by using SIRs for breast cancer, the only cancer site available for all the seven studies included in the meta-analysis. No publication bias was detected by any of the tests used (Begg's test, $p < 0.37$; Egger's test, $p < 0.48$; meta-regression coefficient for the explanatory variable (study size), $p < 0.69$).

DISCUSSION

In a commentary (that includes all cohorts except those from Linnersjö et al.[9] and Reynolds et al.,[11] Lynge[16] found higher than expected cancer cases for leukemia, melanoma, other skin tumors, and breast and all-site tumors. Likewise, in an earlier analysis using a standard meta-analytical approach with random effects,[25] we evidenced a significant excess for leukemia, melanoma, other skin tumors, and breast and all-site cancer incidence (data not shown). This approach led to an overestimation of the pooled SIRs (because it excludes studies reporting SIR = 0) and too narrow CI (because it assumes that the between-study variance is known, when in fact it is estimated from the data).

The Bayesian hierarchical approach does not exclude studies reporting SIR = 0 and gives wider CIs because it automatically takes into account the extra uncertainty due to the between-study variance. Analysis using Bayesian methods allowed estimation of a significant incidence excess for melanoma (meta-SIR = 2.15, 95% posterior interval [PI] 1.56-2.88) and breast carcinoma (meta-SIR = 1.40; PI 1.19-1.65). A slight but not significant excess (meta-SIR = 1.11, PI 0.98-1.25) was found for all site tumors. Our findings agree with those reported by Ballard et al.[15]

In the multicenter study on mortality,[14] the risk of death from breast cancer was 1.11 (CI = 0.82-0.48) and for melanoma was 0.36 (CI = 0.04-1.37), whereas in the present study, the meta-SIR denotes a 40% excess (PI = 1.19-1.65) and 115% (PI = 1.56-2.88) excess, respectively, for breast cancer and melanoma in female flight attendants, with respect to the general population (Table 3). These differences can be explained by intensive medical surveillance, which increases incidence but reduces mortality. For tumors with a high chance of recovery after early diagnosis, such as melanoma or breast cancer, however cancer incidence is an indicator of increased risk more than of mortality. We, therefore, undertook the present work, which is, to date, the first comprehensive meta-analysis on cancer incidence among U.S. and European female flight attendants.

Occupational cohorts benefit from improved medical surveillance and greater access to diagnostic technologies with respect to the general population. This diagnostic sensitivity bias has increased over time as employers, employees, and physicians have become more aware of work-related diseases. This bias might increase the incidence of cancer. On the other hand, any epidemiological study on cohorts of workers is unavoidably affected by the selection bias known as healthy worker effect (HWE), which presumably derives from a screening process, perhaps a largely self-selection one, that allows relatively healthy people to become or remain workers. The bias arises when workers are compared with the general population, where those who remain unemployed, retired, disabled, or otherwise out of active service are a less healthy group. Bias from HWE is always in the direction of null hypothesis. Therefore, although the net balance is unpredictable, the opposing direction forms of the biases may have cancelled each other out.

A bias may also have occurred because of missing data. Linnersjö et al.[9] did not report the SIR for cancer site with less than two cases observed and, therefore, could not be included in the meta-analysis. This could be a publication bias. However, the presence of a publication bias was excluded by the Begg's test, the more sensitive Egger's test, and the meta-regression approach, which was applied because the sensitivity of the former two methods is generally low in meta-analyses based on less than 20 trials.[23]

The association between exposure and melanoma risk might be confounded by intermittent sun exposure, as the frequency of traveling to sunny countries may be greater in flight attendants than in the general population. In a recent case-control study, however, Rafnsson et al.[26] concluded that the increased incidence of malignant melanoma in female cabin attendants cannot be solely explained by excessive sun exposure. Supporting evidence of an association between melanoma and radiation comes from studies carried out in nuclear industry workers,[27] patients undergoing radiotherapy,[28] and U.S. radiology technologists exposed to particularly high radiation doses.[29]

Linnersjö et al.[9] estimated that in female cabin crew, reproductive history could yield a 10% increase in breast cancer incidence, which estimation does not seem to fully explain the cancer excess observed in the same workers. Rafnsson et al.[9] asserted that after taking into account the reproductive history, the risk of breast cancer is unlikely to be explained solely by confounding due to parity. Pukkala et al.[13] found that after the differences in reproductive and other factors related to social class were taken into account, a pronounced excess significant risk of breast cancer remains only 15 years after recruitment. Accordingly, in a recent case-control study, confounding factors (social class, reproductive factors) did not explain the magnitude of excess risk for breast cancer among cabin attendants.[30] Furthermore, an independent effect between radiation exposure and reproductive history on breast cancer risk was reported among survivors of the atomic bomb.[31] However, an occupational origin for breast cancer is supported by the linear dose-response relationship found between radia-tion exposure and breast cancer risk in a pooled analysis of eight cohorts of differently exposed women.[32]

Melanoma and breast cancer excesses might be attributed to radiation exposure largely on the basis of analogy with low-LET radiation-exposed populations. Much less is known about biological effects of low-dose exposure to high-LET than to low-LET. At high altitudes, however, about half of the effective dose would be due to high-LET neutrons rather than low-LET gamma rays.[33] High-LET exposure confers more biological damage than low-LET, mainly because of the higher amount of ionizations that occur in the tissue. The relative biological effectiveness (RBE), the ratio of dose of low-LET gamma-radiation/dose of the high-LET radiation of interest, that caused the same biological effect seems to range from 5 to 20 for neutrons depending on the dose and energy of the neutron exposure. Furthermore, for neutrons the RBE increased with decreasing dose, so RBE would be expected to be close to 20 for the low-dose exposure of the air crew.[34]

A desynchronized production of melatonin by the pineal gland was found in flight attendants, because of disruption of the circadian rhythm.[5] Melatonin was found to have oncosuppressive properties on melanoma cells[35,36] and an oncostatic effect on mammary glands both *in vivo* and *in vitro*.[37,38] Melatonin could also act as a naturally occurring antiestrogen, thereby influencing the proliferative rate of mammary tumor cells.[39,40] Epidemiological evidence confirmed a higher rate of breast cancer with increasing duration of nighttime employment[41,42] and degree of visual impairment in women.[43–45]

CONCLUSIONS

Despite the relatively short follow-up period (19.3 years per study), meta-SIRs for melanoma and breast cancer were significantly increased in flight attendants with respect to the general population. Although further studies are necessary to clarify the exact role of occupational exposure, all airlines should, as some companies do, estimate radiation dose, organize the schedules of crew members in order to reduce further exposure in highly exposed flight attendants, inform them about health risks, and give special protection to pregnant women.

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Address reprint requests:
Alessandra Buja, M.D., Ph.D.
Department of Environmental Medicine and Public Health
University of Padua Via Loredan 18
35128 Padua
Italy

E-mail: alessandra.buja@unipd.it

BUJA

AU1
Meaning of sentence starting with “Cancer” not clear. Please clarify

AU2
Ref 15 is Ballard et al. Please clarify & correct

AU3
Define LET

AU4
Clarify meaning of sentence starting with “Furthermore”.

AU5
Title correct? ref. 5