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Breast cancer incidence among female flight attendants: exposure–response analyses [1]

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[1] *Supplementary material*

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SUPPLEMENTARY METHODS

Creation of analysis variables for covariates

Date of birth, parity, age at first birth, and family history of breast cancer in a first degree relative (biological parent or sibling) were assessed as described by Schubauer-Berigan et al. (1). In this analysis, restricted cubic spline terms were used for year of birth. Other covariates were assessed as described below. Covariates were primarily based on interview data. Interview data were supplemented with data on race, education, height, and body mass index in the company records.

Covariates included in the final models

Age at menarche was assessed based on the interview data and related comments without assumptions.

Height was assessed as described below for body mass index.

Alcohol status was based on the following assumptions when data were missing: 1) ever drinkers were assumed to be current drinkers (n=5), 2) ever drinkers were assumed to have started drinking at age 21, the median age drinkers with data began drinking (n=41), 3) former drinkers were assumed to have stopped drinking at the midpoint of the age first drank and the age at interview or date of death, whichever was earlier (n=7), and 4) former drinkers were assumed to have drank from age 21 to an age equal to the midpoint of 21 years at the age at the interview or date of death, whichever was earlier (n=7).

Menopause was based on whether the subject had a menstrual period in the last 12 months according to the interview. The age at menopause, when missing, was assumed to be the age at hysterectomy for 12 subjects who reported menopause from surgery, 6 subjects who didn't report a reason for menopause, and 2 subjects for whom a proxy reported natural menopause but a young age at hysterectomy. If the reason for menopause was unknown, the reason was assumed to be natural if the age of menopause was greater than the lowest quartile of the cohort and the reason was assumed to be for other reasons if the age of menopause was greater than the lowest quartile of the cohort.

Hormone replacement therapy was based on interview data and related comments on whether the subject had ever taken estrogen or progestins in combination with estrogens (or female hormones, if the respondent was a proxy) for two months or more for a reason related to menopause, the age started and ended, and duration of use. Respondents were instructed not to include birth control pills; however, based on the interview data collected on birth control pills, it appeared that some respondents did include use of birth control pills when responding to questions about hormone replacement therapy. Thus, reported hormone replacement therapy was assumed to reflect birth control pill use (or hormone replacement therapy for a reason other than menopause) in the following situations: 1) the age at which the subject last took hormone replacement was similar to the age at which the subject last took birth control pills and ≤ 40 years, and there was no indication of early menopause from other data in the interview, 2) both the ages at which the subject began and stopped taking hormone replacement therapy and birth control pills were similar, the age at which the subject began taking these was < 40 years, and there was no indication of early menopause, and 3) both the ages at which the subject began and stopped taking hormone replacement therapy and birth control pills were similar, the age at which the subject began taking these was ≥ 40 years, and the date of the last menstrual period was long after the age at which they stopped taking these. The age at which the subject started taking hormone replacement therapy was assumed to be the minimum of the age at which birth controls were last taken and the age at menopause in the following situations: 1) the ages at which the subject began taking hormone replacement therapy and birth control pills were similar and the age at which they last took hormone replacement therapy was years later than the age at which they last took birth control pills, and 2) the ages of hormone replacement therapy and birth control pill use overlapped and birth control pill use ended when the subject was in the mid 50s. When both the ages at which the subject began and stopped taking hormone replacement therapy and birth control pills were similar and the age at which the subject began taking these was < 40 years, the age at which the subject began taking hormone replacement therapy was assumed to be the age at menopause or the age at which combined hormone replacement therapy was started, if different. In addition, the following assumptions were made: 1) if hormone replacement therapy use preceded birth control pill use and the subject was still menstruating, the subject was assumed to have never taken hormone replacement therapy, 2) if the dates for estrogen replacement therapy were provided but not the dates for combined hormone replacement therapy, the dates of combined therapy were assumed to be fully contained in the dates of estrogen replacement therapy.

Family history of breast cancer in a second degree relative was defined as breast cancer in a biological grandmother or aunt.

Covariates that were evaluated but not included in the final models

Race/ethnicity was based on interview data supplemented with data in the company records. When ethnicity was unknown (n=13), the subject was considered non-Hispanic because most (93%) of subjects with data on ethnicity were non-Hispanic.

Education was based on the number of years or type of school completed and related comments as reported in the interview. When education from the interview was missing, refused, or don't know, personnel records were searched to locate education.

Religion was based on self- or proxy-reported religion and categorized into Jewish and other than Jewish because women of Ashkenazi Jewish descent are more likely to have *BRCA1* and *BRCA2* gene mutations and thus, Jewish women may have an increased breast cancer risk. Responses of Jewish or other responses that indicated Jewish religion were considered Jewish. All other responses were considered a religion other than Jewish. Subjects for whom self- or proxy-reported religion was missing were considered "other than Jewish".

Birthplace was based on country of birth, according to the interview, and categorized into westernized versus non-westernized countries since some non-westernized countries have low background rates of breast cancer. The United States (and its territories), Canada, Greenland, Australia and countries in western Europe (or general responses of Europe) were considered "westernized". All other self- and proxy-reported countries were considered "non-westernized".

Body mass index at age 20 was calculated from weight at age 20 and height, as reported in the interview. Body mass index at the time of the interview or, if deceased, during the last ten years of life was calculated in an analogous manner. When weight at age 20 or height from the interview was missing, personnel records were searched to locate self-reported or measured height and weight. If the body mass index at age 20 or at the time of interview (or during last ten years of life) was deemed highly improbable, the questionnaire and personnel records were reviewed to identify and correct transcription errors. Proxy-reported weight at age 20 and height were compared to information in the personnel records; values that were discrepant were changed based on the subject's data in the personnel records. Change in body mass index was calculated as the difference between the body mass index at the time of the interview (or during the last ten years of life) and the body mass index at age 20.

Average number of alcoholic drinks consumed per week and cumulative number of alcoholic drinks consumed were assessed as described above for alcohol status. Subjects with an unknown alcohol status were excluded from models including these candidate covariates. When data on the number of drinks consumed per week were missing, ever drinkers were assumed to have drunk four alcoholic drinks per week, the median for ever drinkers with data.

Cigarette smoking status and pack-years of smoking were based on responses to questions about smoking and related comments. The following assumptions were made when data were missing: 1) ever smokers were assumed to be current smokers (n=3) and to have smoked 10 cigarettes per day (n=56), the median among smokers with data, 2) ever smokers who reported smoking 0 years (n=30) were assumed to have smoked for 0.5 years, 3) ever smokers were assumed to have begun smoking at 18 years of age (n=14), the median age smokers began smoking among those with data, 4) former smokers were assumed to have stopped smoking at age 33 years (n=6), the median age former smokers with data stopped smoking, 5) former smokers were assumed to have smoked from age 18 years to age 33 years (n=8).

Breastfeeding and breastfeeding duration was assessed based on self- or proxy-reported breastfeeding and duration for each live birth. For 174 pregnancies for which the respondent reported the subject breastfed for two weeks or more but did not report the duration of breastfeeding, breastfeeding duration was assumed to be two weeks. For 89 pregnancies for which breastfeeding status was not reported, the subject was assumed not to have breastfed.

Age at menopause and age at natural menopause were determined from the interview data without imputation for missing data beyond that described above for menopausal status.

Benign breast disease was assessed from the interview data as having a breast biopsy or aspiration that led to a diagnosis of a breast condition other than cancer before or in the same year as being diagnosed with breast cancer. Seven women were assumed to have had benign breast disease, regardless of their breast cancer history, even though the age (or year) at the time of the first biopsy or aspiration leading to a non-cancer diagnosis was unknown. If a benign breast disease such as polycystic breast disease was reported in comments related to the breast biopsy questions, the subject was considered to have benign breast disease even if they did not report a breast biopsy or aspiration that led to a non-cancer diagnosis.

Other factors considered in the sensitivity analyses

Women were considered to have had "high dose" radiation (>100 mGy absorbed dose to the breast) from diagnostic examinations or radiation treatment if one or more of the following procedures were reported to have occurred prior to a breast cancer diagnosis in the interview: a fluoroscopic examination of the chest to monitor lung collapse treatment for tuberculosis or a radiation treatment to the chest or spine for any of the following conditions: scoliosis, enlarged thymus, acne, scar tissue, Hodgkin disease, amyloidosis, non-Hodgkin lymphoma, lung cancer, bone cancer, spine cancer or tumor, malignant melanoma, oral/neck cancer or tumor, colon cancer, and unknown cancer or tumor.

Some women may have been pre-menopausal but have not had a menstrual period in the last twelve months because they had a hysterectomy without a complete bilateral oophorectomy before their menstrual periods stopped. Thus, a time dependent variable (with values of yes, no, and unknown) was created to identify women who had a hysterectomy without a complete bilateral oophorectomy before menopause or age 50, the mean and median age of natural menopause in the cohort, whichever was earlier. Three subjects had a bilateral oophorectomy but data on whether both ovaries were completely removed was missing. These subjects were assumed to have had a complete bilateral oophorectomy because most (96%) bilateral oophorectomies, where the data were available, were complete.

SUPPLEMENTARY RESULTS

Assessment of potential effect modification by covariates in the final models other than parity

In exposure-response analyses, there was no evidence of effect modification by age at menarche, height, use of hormone replacement therapy, or family history of breast cancer in power or linear ERR models (the best fitting model before assessing effect modification and the final model form, respectively). Effect estimates were larger among women with younger ages at first birth, but the age at first birth interaction terms were not statistically significant ($p \geq 0.19$ and ≥ 0.41 in the linear ERR and power models, respectively). Findings for alcohol consumption status and menopausal status were not robust, but depended on the model form. In the linear ERR model, the exposure-response relations for absorbed dose and time zones crossed were modified by alcohol consumption status (p-value for the interaction term was 0.05 and 0.07, respectively) and the magnitude of the effect estimates was largest (and negative) among former drinkers. In contrast, in the power model, there was no evidence of effect modification by alcohol consumption status (p-value for the interaction terms ≥ 0.72) and the magnitude of the effect estimates was greatest among never drinkers. In the power model, the effect estimates for time spent working in the SSI varied somewhat by menopausal status (p-value for interaction term, 0.18), and the effect estimate was greatest and statistically significant for pre-menopausal women. In contrast, in the linear ERR model, there was no evidence of effect modification by menopausal status (p-value for interaction term was 0.44) and the effect estimate was greatest for women who were post-menopausal due to natural menopause.

REFERENCES

1. Schubauer-Berigan MK, Anderson JL, Hein MJ, Little MP, Sigurdson AJ, Pinkerton LE. Breast cancer incidence in a cohort of U.S. flight attendants. Am J Ind Med 2015;58:252–266.

Supplementary Table S1. Characteristics of eligible non-participants and participants[a]

	Non-Participants[b] (N=3368)		Participants (N=6093)	
	n	%	n	%
Race/ethnicity:				
White, non-Hispanic	2923	87	5568	91
Other	445	13	525	9
Vital status (as of 12/31/2007)[c]:				
Alive	3063	91	5871	96
Deceased	305	9	222	4
Year of birth:				
Before 1944	817	24	1465	24
1944-1947	745	22	1685	28
1948-1953	793	24	1446	24
1954 or later	1012	30	1497	25
Age at first employment[d], years:				
< 20	91	3	159	3
20-24	2594	77	4939	81
25-29	527	16	806	13
30-34	92	3	115	2
35+	63	2	74	1
Duration of employment[d], years:				
<1	83	2	117	2
1-<5	1607	48	2663	44
5-<10	648	19	1259	21
10-<15	405	12	870	14
15-<20	335	10	654	11
20+	290	9	530	9

[a] Of the 9617 women in the mortality cohort, 156 were ineligible (105, last known address outside the United States; 49, initially unknown citizenship and not a U.S. citizen according to a screening question; 2, diagnosed with breast cancer before entry into the cohort).

[b] Non-participants include 33 women for whom a questionnaire was returned but not a signed consent form or withdrew consent to participate in the study.

[c] 12/31/2007 is the date follow-up ended in the mortality study; the latest date of follow-up for women in the current study (which was the earliest of date of death, first breast cancer diagnosis, and questionnaire/interview administration) was in 2005.

[d] Employment as a flight attendant at Pan Am and National, excluding training, according to company records

Supplementary Table S2. Association of demographic, lifestyle, and reproductive factors not included in the final models with breast cancer incidence in the cohort

	HR[a]	95% CI
Year of birth[b]:		
<1937	1	
1937-<1943	1.10	0.74-1.67
1943-<1945	1.19	0.76-1.88
1945-<1948	1.20	0.78-1.87
1948+	1.27	0.82-2.00
Race/ethnicity:		
White, non-Hispanic	1	
Black, non-Hispanic	0.32	0.05-1.00
Asian, non-Hispanic	1.17	0.64-2.00
Other/multi-racial, non-Hispanic	0.74	0.18-1.93
Hispanic	1.11	0.69-1.70
Education:		
High school or less	1	
Some college/professional	1.28	0.77-2.30
College graduate	1.22	0.74-2.19
Post-graduate	1.04	0.61-1.91
Religion:		
All other	1	
Jewish	1.51	0.75-2.69
Birthplace:		
Western	1	
Non-Western	1.02	0.54-1.75
Body mass index at age 20[c]:		
1 kg/m^2	1.02	0.94-1.11
Change in body mass index since age 20[d]:		
1 kg/m^2	0.97	0.94-1.00
Cigarette smoking status:		
Never	1	
Former	0.78	0.58-1.05
Current	0.85	0.66-1.08
Unknown	1.38	0.08-6.35
Pack-years of smoking:		
1 pack-year	1.00	0.99-1.01
Average number of alcoholic drinks per week:		
1 drink	1.00	0.98-1.02
Cumulative number of alcoholic drinks consumed:		
1000 drinks	1.00	0.99-1.02
Breastfeeding status (among parous women):		
Never	1	
Ever	1.14	0.82-1.60
Breastfeeding duration (among parous women):		
Never	1	
<1 year	1.19	0.85-1.71
1 year -<3 years	1.05	0.70-1.58
3+ years	0.90	0.36-1.93
Age at menopause (among menopausal women):		
1 year	1.01	0.99-1.04
Age at natural menopause (among women who were postmenopausal from natural menopause):		
1 year	1.00	0.95-1.04
Benign breast disease:		
No	1	

Yes	1.00	0.76-1.31
Unknown	0.66	0.19-1.72

Abbreviations: HR, hazard ratio; CI, confidence interval

[a] HRs were estimated by adding the potential confounders in the table one at a time to a model that was adjusted for age (time scale) and included all covariates in the final models (and in Table 3). All models exclude subjects missing any covariates without unknown categories in the final models; individual models may also exclude subjects missing the specific covariate.
Alcohol status, parity, age at first birth, menopausal status, hormone replacement therapy use, cigarette smoking status, pack-years of smoking, average number of drinks per week, cumulative number of alcoholic drinks consumed, breastfeeding status, breastfeeding duration, age at menopause, and age at natural menopause were treated as time-dependent variables.

[b] Restricted cubic spline terms were used for year of birth (b1=0.00485; 95% CI -0.029 to 0.042; b2=0.0127; 95% CI -0.019 to 0.043). Results for quintiles of year of birth are shown in the table for ease of presentation.

[c] Body mass index at age 20 by menopausal status was also assessed. Adjusted HRs (95% CI) per 1 kg/m^2 were 1.01 (0.89 to 1.14), 1.10 (0.96 to 1.27), 1.02 (0.87 to 1.18), and 0.53 (0.30 to 0.92) for pre-menopausal, post-menopausal due to natural menopause, post-menopausal for other reasons, and unknown menopausal status, respectively.

[d] Change in body mass index from age 20 to the date of the interview or, if deceased, during the last ten years of life. Change in body mass index by menopausal status was also assessed. Adjusted HRs (95% CI) per 1 kg/m^2 were 0.93 (0.88 to 0.98), 1.01 (0.95 to 1.06), 0.98 (0.92 to 1.04), and 0.99 (0.85 to 1.08) for pre-menopausal, post-menopausal due to natural menopause, post-menopausal for other reasons, and unknown menopausal status, respectively.

Supplementary Table S3. Breast Cancer Hazard Ratios for 10-year lagged cumulative exposure variables from models that include interaction with parity (0/1/2 versus 3+ births)[a,b]

Cumulative exposure metric		AIC	Comparison	Parity: 0, 1, 2		Parity: 3+	
Model[c]				HR	95% CI	HR	95% CI
<u>Absorbed dose (mGy)</u>							
Quintile	Category mean						
<1.6	0.78	5,373.667	Q1 vs. Q1	1		1	
1.6 to <3.5	2.5		Q2 vs. Q1	1.00	0.68-1.49	0.86	0.36-2.04
3.5 to <6.6	4.9		Q3 vs. Q1	1.05	0.72-1.56	1.87	0.77-4.45
6.6 to <14	9.9		Q4 vs. Q1	0.89	0.60-1.34	1.59	0.58-4.11
14+	19		Q5 vs. Q1	0.95	0.63-1.43	3.69	1.02-10.9
Trend p[d]							*0.01*
Log-linear		5,364.809	10-mGy increase	0.98	0.82-1.15	1.99	1.09-3.22
Power		5,364.976	10 vs. 0.78 mGy	1.08	0.89-1.34	2.31	1.05-5.41
Age windows:	accrued 0-<30 years	5,368.993	10-mGy increase	0.76	0.46-1.23	1.81	0.46-5.94
	accrued 30-<40 years		10-mGy increase	1.29	0.90-1.76	1.58	0.40-5.20
	accrued 40+ years		10-mGy increase	0.69	0.38-1.16	3.85	0.59-12.7
Birth windows:	accrued prior to 1st birth	5,368.554	10-mGy increase	0.96	0.78-1.15	1.78	0.60-4.47
	accrued at 1st birth or later		10-mGy increase	1.05	0.71-1.42	2.08	0.98-3.54
<u>Standard sleep interval travel (hours)</u>							
Quintile	Category mean	5,372.858					
<320	150		Q1 vs. Q1	1		1	
320-<780	520		Q2 vs. Q1	1.09	0.74-1.61	1.06	0.46-2.41
780-<1400	1100		Q3 vs. Q1	1.47	1.00-2.19	1.34	0.52-3.28
1400-<2600	2000		Q4 vs. Q1	1.08	0.73-1.60	1.56	0.54-4.05
2600+	3900		Q5 vs. Q1	1.02	0.68-1.54	2.84	0.90-7.74
Trend p[d]							*0.04*
Log-linear		5,367.146	2000 hour increase	0.96	0.82-1.12	1.46	0.89-2.03
Power		5,364.852	2000 vs. 150 hours	1.10	0.91-1.37	2.10	1.03-4.56
Age windows:	accrued 0-<30 years	5,368.891	2000 hour increase	0.82	0.57-1.13	1.05	0.38-2.47
	accrued 30-<40 years		2000 hour increase	1.29	0.95-1.70	1.97	0.57-5.52
	accrued 40+ years		2000 hour increase	0.60	0.31-1.05	3.39	0.33-14.8
Birth windows:	accrued prior to 1st birth	5,369.587	2000 hour increase	0.94	0.79-1.11	1.23	0.60-1.93
	accrued at 1st birth or later		2000 hour increase	1.07	0.71-1.47	2.16	0.90-4.00
<u>Time zones crossed (zones)</u>							
Quintile	Category mean	5,374.517					
<720	360		Q1 vs. Q1	1		1	
720-<1700	1200		Q2 vs. Q1	0.94	0.64-1.40	0.88	0.37-2.09
1700-<3200	2400		Q3 vs. Q1	1.08	0.73-1.59	1.69	0.68-4.10
3200-<6400	4600		Q4 vs. Q1	0.92	0.62-1.38	2.30	0.91-5.65
6400+	9300		Q5 vs. Q1	0.94	0.63-1.42	2.49	0.56-8.05
Trend p[d]							*0.02*
Log-linear		5,365.378	4600 zone increase	1.00	0.85-1.15	1.81	1.05-2.78

Power	5,364.831	4600 vs. 360 zones	1.10	0.91-1.36	2.23	1.04-5.09
Age windows: accrued 0-<30 years	5,370.728	4600 zone increase	0.86	0.54-1.33	1.91	0.54-5.62
accrued 30-<40 years		4600 zone increase	1.21	0.87-1.61	1.31	0.36-3.95
accrued 40+ years		4600 zone increase	0.76	0.45-1.20	3.20	0.62-9.21
Birth windows: accrued prior to 1st birth	5,369.275	4600 zone increase	0.98	0.82-1.17	1.70	0.62-3.87
accrued at 1st birth or later		4600 zone increase	1.04	0.72-1.37	1.86	0.93-3.00

Abbreviations: AIC, Akaike Information Criterion; HR, hazard ratio; CI, profile-likelihood based confidence interval; Q, quintile; p, p-value

[a] 6001 subjects including 340 cases were included in the analysis; all models excluded subjects with missing height, alcohol status, or birth information. Results are adjusted for age (since risk sets were created based on attained age), age at menarche, height, alcohol status, age at first birth, menopausal status, use of hormone replacement therapy, and family history of breast cancer. Covariate categories are indicated in Table 3. The models also included terms for parity, exposure, and the product of parity and exposure.

[b] Hazard ratios (HRs) for the log-linear, age window, and birth window models are for a 10-mGy increase in absorbed dose, a 2000 hour increase in standard sleep interval travel, or a 4600 zone increase in time zones crossed. Power model HRs are relative to the mean of the lowest category of exposure based on quintiles to avoid taking the logarithm of zero.

[c] Under the stratified model, the hazard function for the j^{th} individual in the i^{th} risk set is expressed as $\lambda_{ij}(t) = \lambda_{i0}(t)\exp[Z'_{ij}\beta]$. For covariates $X_1, \ldots, X_p$ (assume X_p is an indicator of 3+ births versus 0/1/2 births) and exposure variable X_e:

Log-linear model: $\lambda_{ij}(t) = \lambda_{i0}(t)\exp[\beta_1 X_1 + \ldots + \beta_p X_p + \beta_e X_e + \beta_{pe} X_p X_e]$

Power model: $\lambda_{ij}(t) = \lambda_{i0}(t)\exp[\beta_1 X_1 + \ldots + \beta_p X_p + \beta_e \mathit{ln}(X_e) + \beta_{pe} X_p \mathit{ln}(X_e)]$

$= \lambda_{i0}(t)\exp[\beta_1 X_1 + \ldots + \beta_p X_p]\, X_e^{\beta e + \beta ep\ Xp}$

[d] The trend p-value is for exposure among the 3+ parity group. For the quintile model, the trend p-value was obtained by running a separate log-linear model on the mean level for each quintile-based group.

Supplementary Table S4. Excess relative risks for 10-year lagged cumulative exposure variables among women with parity of three or more stratified by age at diagnosis[a]

Cumulative exposure metric Comparison	Age at diagnosis in years (number of cases) <50 (12)		50+ (30)		
	ERR	95% CI	ERR	95% CI	p^b
Absorbed dose					
10 mGy increase	0.046	NF-3.4	2.2	0.39-7.8	0.18
SSI travel					
2000 hour increase	0.23	NF-3.7	1.2	0.025-4.7	0.41
Time zones crossed					
4600 zone increase	0.12	NF-3.5	2.2	0.39-7.6	0.21

Abbreviations: CI, profile-likelihood based confidence interval; ERR, excess relative risk; NF, not found; p, p-value for three way interaction model compared to two way interaction model; SSI, standard sleep interval

[a] 6001 subjects including 340 cases were included in the analysis; all models exclude subjects with missing height, alcohol status, or birth information. Results are based on linear ERR models that were adjusted for age (since risk sets were created based on attained age), age at menarche, height, alcohol status, age at first birth, menopausal status, use of hormone replacement therapy, and family history of breast cancer and included terms for parity, age at diagnosis, exposure, and the product of parity, age at diagnosis, and exposure. Covariate categories are indicated in Table 3.

[b] p-value for model with three way interaction for exposure, parity, and age at diagnosis compared to model with two way interaction for exposure and parity