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Breast Cancer Incidence in a Cohort of U.S. Flight Attendants

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Abstract

Background—Flight attendants may have elevated breast cancer incidence (BCI). We evaluated BCI's association with cosmic radiation dose and circadian rhythm disruption among 6,093 female former U.S. flight attendants.

Methods—We collected questionnaire data on BCI and risk factors for breast cancer from 2002–2005. We conducted analyses to evaluate (i) BCI in the cohort compared to the U.S. population; and (ii) exposure-response relations. We applied an indirect adjustment to estimate whether parity and age at first birth (AFB) differences between the cohort and U.S. population could explain BCI that differed from expectation.

Results—BCI was elevated but may be explained by lower parity and older AFB in the cohort than among U.S. women. BCI was not associated with exposure metrics in the cohort overall. Significant positive associations with both were observed only among women with parity of three or more.

Conclusions—Future cohort analyses may be informative on the role of these occupational exposures and non-occupational risk factors.

Keywords

flight crew; ionizing radiation; cosmic; circadian rhythm disruption; cohort studies

INTRODUCTION

Flight attendants may be at an increased risk of breast cancer due to workplace exposures, including cosmic radiation and circadian rhythm disruption from traveling across multiple

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time zones [Sigurdson and Ron, 2004; IARC, 2010]. Recently published studies of flight attendants and other airline crew populations [Pinkerton et al., 2012; Hammer et al., 2014] have not found elevated risk of breast cancer mortality among flight attendants, nor have they found exposure-related increases in risk. However, mortality studies have limitations for breast cancer etiologic research, given the high survival rates from breast cancer [e.g., 5-year survival was 89–91% from 2000–2004; Howlader et al., 2013]. In addition, records-based mortality studies rarely supply detailed information on important covariates for breast cancer, such as parity, age at first birth, or family history of breast cancer. Earlier cancer incidence studies of airline crew [e.g., Pukkala et al., 1995], summarized in Sigurdson and Ron [2004]; found increased risks of breast cancer in flight attendants that were not fully explained by available data on reproductive risk factors. A cancer incidence study conducted in a pooled cohort of Scandinavian airplane cabin crew [Pukkala et al., 2012] found a 50% increased incidence rate of breast cancer compared to the general public. In a nested case-control study that adjusted for parity and age at first birth, breast cancer was not found to be related to exposure to cosmic radiation or to number of flights with many time zone crossings, a metric of potential circadian rhythm disruption.

In this study, we present findings from a cancer incidence study conducted in a large U.S. cohort of female flight attendants, for which a previous mortality report did not find increased breast cancer risk [Pinkerton et al., 2012], to determine whether the cohort is at increased risk of incident breast and other cancers and whether risk is associated with flying-related cosmic radiation dose or to measures of circadian rhythm disruption. This questionnaire-based cohort represents one of the few among flight attendants to have information on important risk factors for breast cancer, such as reproductive history and family history of breast cancer. This manuscript represents the first report of cancer incidence in this cohort compared to the general U.S. population, and evaluates simple exposure-response associations for breast cancer in stratified analyses that consider family history and some reproductive risk factors (i.e., parity and age at first birth).

MATERIALS AND METHODS

This study was conducted under the review and approval of the Institutional Review Boards of the National Institute for Occupational Safety and Health and the National Cancer Institute [2014]. Informed consent to participate in the study was obtained from all participants (or their next of kin for those who had proxy respondents).

Cohort Description

The incidence cohort for this study is a subset of the mortality cohort of former flight attendants employed by Pan American World Airways (Pan Am) that was described in detail in Pinkerton et al. [2012]. It was assembled from the personnel records of Pan Am, which were available for employees who left employment in 1953 or later. It included employees (male and female) who were employed for at least one year as a flight attendant before Pan Am ceased operation in 1991, were U.S. citizens when they were hired, and who worked at least one day after January 1, 1953 (n = 11,324). In 1981, Pan Am acquired National Airlines. For cohort members who subsequently transferred to Pan Am (n = 1393), the time

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employed as a flight attendant at National Airlines was included in establishing the one year minimum employment criterion for eligibility.

Of the 9617 women in the mortality cohort, 105 were considered ineligible for the incidence study because their last known address was outside the United States. The remaining living female flight attendants in the mortality cohort were invited to participate in the incidence cohort by completing a detailed telephone or mailed questionnaire (administered between August 2002 and July 2005), which contained questions about their demographic information, work history, and non-occupational risk factors for breast cancer (e.g., reproductive history and use of alcohol, tobacco, and hormone replacement therapy). For deceased flight attendants, we attempted to contact next-of-kin, who were invited to complete the questionnaire about the decedent. Repeated attempts were made by telephone and mail to contact all non-respondents.

The incidence cohort includes all the telephone interview and mailed questionnaire respondents (n = 6177), with three exceptions: (i) mailed questionnaire respondents who did not return a signed consent form or who withdrew consent to participate in the study (n = 33); (ii) women with initially unknown citizenship who indicated they were not U.S. citizens in a screening question (n = 49); and (iii) women who were diagnosed with a breast cancer before entry into the cohort (n = 2). The latter two groups were considered ineligible. Thus, the incidence cohort available for analysis includes 6093 women (64.4% of the 9461 eligible women in the mortality cohort). This includes 134 proxy respondents in the survey for decedents or cohort members who were incapable of responding, with the proxies distributed as follows: 62 spouses; 11 daughters; 7 sons; 21 sisters; 11 mothers; 22 others.

Questionnaire Data

The questionnaire administered to living participants is provided in the online supplement. Because the present analysis compares the incidence of breast cancer in the cohort to that in the general population, with adjustment for key factors such as parity, age at first birth, and family history of breast cancer, we focus here on these covariates in our description of the handling of questionnaire data.

In this analysis, the non-exposure-related covariates of interest were age, calendar period, race, parity, age at first birth, and family history of breast cancer. The latter three were selected out of all potential covariates because they are strong risk factors for breast cancer, their various categories had relatively high prevalence in the cohort, and they have been shown to be potential effect modifiers in studies of ionizing radiation and breast cancer risk [Ronckers et al., 2005]. Parity and age at first birth were also selected because we anticipated that their distribution would be substantially different in the cohort than in the U.S. population. The methods by which we obtained data on these variables and how we treated them for analysis are described in online supplemental material.

Breast Cancer Case Ascertainment

Eligible breast cancer cases occurred between the start of follow-up for each cohort member (detailed in the “Statistical analyses” section below) and the questionnaire administration date. To identify incident breast cancers, we first obtained self (or proxy) report of a cancer

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in the questionnaire. We then conducted medical record follow-back of each reported cancer case by contacting the physician's office, hospital, or other health care organization in which the cancer diagnosis was made and obtaining supporting documentation of the diagnosis. Self (or proxy) reported breast cancers that were refuted by a review of the medical records were not included, but we included reported cancers that were neither confirmed nor refuted. We also linked the incidence cohort to cancer registries in six states (California, Florida, New York, Texas, Virginia, and Washington), based on the locations of the domiciles for the airline and on common states of residence for the cohort. Eighty-two percent of breast cancer cases in the cohort were verified using medical record follow-back and/or cancer registry linkage. Seven breast cancer cases (primarily carcinoma in situ) were identified solely by registry linkage. We searched death certificates for all decedents but identified no breast cancers that were not found via the questionnaire.

All cancer diagnoses obtained from the questionnaire or medical record follow-back were coded using the International Classification of Diseases revision in effect at the time of diagnosis. Breast cancer cases were identified based on ICD-8 and -9 code 174, and ICD-10 code C50 (malignant neoplasm of breast) and on ICD-8 code 233, ICD-9 code 233.0, and ICD-10 code D05 (carcinoma in situ of breast). For cancer registry data, diagnoses were available from ICD-O-3 codes for site, behavior, and histology. Breast cancer cases were identified using behavior code 3 and site code C50.0–C50.9. We also included carcinoma in situ of breast (behavior code 2 and site code C50.0–C50.9). No cases of breast neoplasm of uncertain behavior were identified in the cohort. For the statistical analyses, we used only the first diagnosis of a breast cancer for each cohort member. Date of diagnosis was obtained preferentially from medical records, then registry data, then self (or proxy) reported age (choosing the midpoint of the age year) for the first reported breast cancer.

Exposure Assessment

We used self-reported work history data to estimate duration of employment for every cohort member except those who did not provide work history data (n = 195, which includes proxies). For the latter group, we used work history records from Pan Am and (in some instances) National Airlines to estimate employment duration. We estimated cosmic radiation dose for each self-respondent based on her occupational dose received during work flights and during commuter flights (taken to the domicile to which the flight attendant was assigned), as described in detail in Anderson et al. [2011]. Briefly, questionnaire data consisted of airline of employment, assigned domicile, start/end dates of employment at the domicile, number of block hours (flight time plus taxi time) worked per month, and number of commuter flights flown per month. These data were combined with domicile-and/or era-specific dose rates to estimate daily absorbed dose from occupational exposure to cosmic radiation. The cosmic radiation dose is expressed as absorbed dose in mGy (i.e., no radiation or tissue weighting factor applied).

The quality of the questionnaire data regarding circadian rhythm disruption was poor for some respondents, so we calculated the cumulative number of time zones crossed and time spent working as a flight attendant during the standard sleep interval using algorithms described elsewhere [Grajewski et al., 2003; Waters et al., 2009].

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Complete work history questionnaire data were available for 99% of living women in the incidence cohort, and data on commuter travel were available for 98%. For cohort members (including proxy respondents) with no self-reported work history data (n = 195), cosmic radiation dose, time zones crossed, and travel in the standard sleep interval were estimated using the methods of Waters et al. [2009] in combination with work history information obtained from Pan Am records.

The cosmic radiation dose and circadian rhythm disruption exposure metrics incorporate exposure incurred during all employment as a flight attendant at Pan Am and National and (for self-respondents) exposure during commuter flights and from flight attendant jobs at other airlines, but not exposure from air travel associated with non-flight attendant jobs or personal air travel.

Statistical Analyses

Statistical analyses were conducted using the NIOSH Life Table Analysis System for Windows [LTAS.NET; Schubauer-Berigan et al., 2011] to compare the incidence of breast cancer in the cohort to the incidence of breast cancer that would be expected based on comparison to the U.S. population. All analyses were planned *a priori*. The U.S. general population rates were estimated based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population for the period 1970–2005. SEER represents cancer diagnosis and population data for a non-randomly selected 28% of the U.S. population [NCI, 2014]. Data are more representative for urban areas and for races other than white and for those of Hispanic ethnicity. The rate numerator was based on the combination of invasive female breast cancer (ICD-10 code C50) and in situ breast neoplasms (ICD-10 code D05), which were recoded from ICD-O-3 data in the same way as for the cohort. The SEER rate file included the number of new cases of female breast cancer (i.e., both first and subsequent primaries) as the numerator and the total female population (i.e., including prevalent cases) as the denominator. While the numerator can be adjusted to include the first primary cancer only, the number of prevalent cases is unknown and (for early years) can be only estimated based on data from the Connecticut Tumor Registry, which began in 1935. Because uncertainty is inherent in rates adjusting for prevalent cases, we chose to use unadjusted rate denominators. In this situation, overall error is minimized and the SIR is not overestimated by retaining second or subsequent primary breast cancers in the rate numerator [Merrill and Feuer, 1996]. The rate file was stratified by race (white, all other races), age (15–19, 20–24, …, 80–84, 85 +), and calendar year (1970–74, 1975–79, …, 2000–04, 2005).

Time-dependent variables were used for covariates that could change through the period of follow-up and for which temporal information was available (e.g., parity, age at first birth), as well as for the main exposure variables of interest (cosmic radiation dose, number of time zones crossed, and time spent working during the standard sleep interval).

Person-time at risk for each cohort member began on the latest of the following dates: (i) January 1, 1970 (the date the SEER rate file begins); (ii) the date the one year employment eligibility period was met; or (iii) (for flight attendants who transferred to Pan Am from National) the date of transfer to Pan Am. Person-time at risk ended at the earliest date

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among the following events (i) first diagnosis of breast neoplasm; (ii) death; and (iii) interview or questionnaire completion.

Person-time was stratified by the LTAS.NET program into age and calendar time strata and then multiplied by the appropriate race-specific breast cancer rates for women to calculate the expected number of breast cancer cases, which were summed across all strata. The ratio of observed to expected number of breast cancer cases was expressed as the standardized incidence ratio (SIR). Ninety-five percent confidence intervals (CI) were computed for the SIRs assuming a Poisson distribution for observed cases. The exact Poisson distribution was used for number observed less than 11; otherwise, Byar's approximation was used [Breslow and Day, 1987].

We evaluated SIRs for the overall cohort and for each potential confounder (race, family history of breast cancer, parity, and age at first birth). SIRs for breast cancer were also stratified by each exposure variable (cumulative absorbed cosmic dose, cumulative number of time zones crossed, and cumulative time spent working during the standard sleep interval), divided into quintiles based on the exposure distribution among cases. For the primary analyses, we applied a 10-year lag period to the exposure metrics, to account for a delay between exposure and the diagnosis of breast cancer. A 10-year lag is consistent with the National Academies' recommendations [National Academy of Sciences (NAS), 1990] and recent breast cancer incidence studies among Nordic flight crew [e.g., Kojo et al., 2005; Pukkala et al., 2012]. We evaluated alternative lags (5, 15, and 20 years) in a sensitivity analysis.

We calculated standardized rate ratios (SRRs) to compare female breast cancer among cohort members in higher exposure categories with those in the lowest exposure category for each 10-year lagged exposure metric, adjusting for age, race, and calendar year. A linear trend test for the directly standardized rates was calculated in LTAS.NET using weighted least squares regression with weights estimated from the Poisson variance of the cancer counts; statistical significance of each trend was determined using a two-tailed *Z*-test with $\alpha = 0.05$ [Rothman, 1986; Schubauer-Berigan et al., 2011].

Analyses were also conducted for each 10-year lagged exposure variable, stratifying on parity (0, 1, 2, 3 +), age at first birth category (<25, 25–<30, 30–<35, 35 +), or family history of breast cancer in a first degree relative, in addition to the standard stratification variables of race, age, and calendar time. These analyses excluded women for whom parity, age at first birth, or family history of breast cancer was unknown. A parity-, age-at-first-birth-, or family history-adjusted pooled slope value was calculated (weighted by the inverse of the variance of the stratum-specific slope estimates) if the estimates were not found to vary substantially by strata (i.e., no substantial effect modification).

We used indirect adjustment [Axelson and Steenland, 1988] to evaluate the impact on the breast cancer SIR of differences in parity and age at first birth (separately) in the cohort, compared to the female U.S. population. For parity, we assumed that parity was the only reason the Pan Am cohort had an elevated risk of breast cancer and estimated the cohort's expected breast cancer incidence rate using the fraction in each parity group and known

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breast cancer rate ratios compared to uniparous women (from Ewertz et al. [1990], adapted slightly to account for different parity cutpoints used in that study compared to ours): 1.30 for nulliparity, 1 for uniparity, 0.92 for parity of 2, and 0.70 for parity of 3 or more. We compared this rate to the expected breast cancer incidence rate in the female U.S. population estimated using analogous fractions of the U.S. population (obtained as a weighted mean of birth cohorts 1943, 1947, and 1953 from Hamilton and Cosgrove [2010]) and the same breast cancer rate ratios. The two estimated rates were divided to obtain an estimate of the bias factor (i.e., the amount of confounding produced by differences in the parity distributions). The estimated bias in the breast cancer SIR due to differences in parity was calculated as the quotient of this ratio in the cohort and that in the female U.S. population. We estimated a bias-adjusted 95% CI by dividing the lower and upper bounds of the cohort CI by the bias factor, which should produce an interval that is at least as wide as the true bias-adjusted CI.

We calculated an indirect adjustment for age at first birth using similar methods, obtaining U.S. population data on this metric from Kirmeyer and Hamilton [2011] (averaging the closest available birth cohorts, which were 1935 and 1960), and relative risks for age at first birth of 3% for each year of delay past age 20 from Parkin [2011]. For the age at first birth analysis, we assumed that the percentage of parous women was the same in the cohort and the U.S. population, because data on age at first birth for the latter excluded nulliparous women and we wanted to evaluate the effects of parity and age at first birth independently.

RESULTS

The flight attendant cohort characteristics are described in Table I. Cohort members had a median year of birth of 1947, and breast cancer cases were born on average three years earlier. Only 2% of the cohort overall and 8% of the breast cancer cases were deceased. More than 90% of the cohort and of breast cancer cases were white. A family history of breast cancer was reported by 14% of the cohort and 21% of cases. The distribution of parity was similar among cases and the general cohort, but a slightly higher percentage of cases had an age at first birth of 25–29 and a slightly lower percentage had age at first birth of 30–34. Cumulative exposure metrics (including employment duration, absorbed radiation dose, time zones crossed, and hours spent flying during the standard sleep interval) were all slightly lower, but with wide variability, among cases than among the cohort. Correlations among all four cumulative exposure metrics were very high (Spearman ρ ranged from 0.94 to 0.99).

We observed 344 first primary breast cancers in the cohort. For the LTAS analyses, beginning follow-up in 1970 (the rate file begin date) eliminated one woman (a breast cancer case) from the cohort; thus, the total number of breast cancers included in this analysis was 343, with an accrual of 162,477 woman-years. The overall incidence of breast cancer in the cohort was 37% higher (95% CI: 23%, 52%) than in the U.S. population, adjusting for race, age and calendar year (Table II). Nulliparous and uniparous women had similar SIRs compared to the general population, at about the overall cohort value. Women with parity of two had a nearly 60% higher breast cancer rate than the general population, and those with higher parity had an SIR of near unity. Among parous women, those who

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first gave birth before age 25 did not exhibit an elevated SIR, while women who first gave birth at older ages exhibited significantly elevated breast cancer rates (34% to 56% higher) compared to the general population (Table II).

The Pan Am cohort had much lower parity (Fig. 1) and older age at first birth (Fig. 2) than U.S. women of similar birth cohorts. The indirect adjustment for the differences in parity and age at first birth gave a parity-adjusted overall SIR of 1.19 (95% CI: 1.07, 1.32) and an age-at-first-birth-adjusted SIR of 1.17 (95% CI: 1.05, 1.30). If parity and age at first birth act independently (leading to multiplicative independent effects), the adjusted SIR for both would be 1.02 (95% CI: 0.92, 1.13).

In 10-year lagged analyses, cumulative cosmic radiation exposure, hours spent flying during the standard sleep internal, time zones crossed, and employment duration all showed SIRs that did not vary substantially across exposure groups (Table III). Internal comparisons showed that in no higher exposure group did any of these exposure metrics show elevated SRRs compared to the lowest exposure groups. The trend slope was non-significantly negative for each cumulative exposure metric (Table III). In sensitivity analyses, changing the exposure lag did not affect these results (Appendix Tables A1–A3).

The exposure-response slopes for the four workplace exposure variables stratified by family history are shown in Table IV. There were no substantive differences in the slopes (i.e., in their direction or statistical significance) by family history (indicating little important effect modification), and the pooled slope estimate was similar to the unadjusted slope estimate (indicating little confounding by family history).

The exposure-response slopes for the occupational exposure metrics stratified by parity are shown in Table V. Nulliparous women had non-significantly negative breast cancer incidence trends for absorbed radiation dose, time zones crossed, and employment duration and a non-significantly positive trend for hours spent in the standard sleep interval. Uniparous women showed significant negative trends (P <0.01) for absorbed dose and time zones crossed, and non-significantly negative trends for the other exposure metrics. Women with parity of two or greater showed positive trends in breast cancer incidence with each exposure metric, although only absorbed dose, hours spent flying in the standard sleep interval, and number of time zones crossed among women with parity of three or more were statistically significant (P <0.05).

Stratification of exposure metrics by age at first birth (among parous women) gave slopes that were consistently negative for women with age at first birth of 30 or greater, although few were statistically significant (Table VI). All exposure measures showed a substantially (and usually significantly) increased SIR and SRR in the highest exposure category for the parous women who gave birth younger than age 25 (data not shown). Women who first gave birth younger than age 30 had positive slopes for absorbed radiation dose (non-statistically significant) and time zones crossed (statistically significant only for the youngest age at first birth category). A non-significant positive trend was observed for hours spent traveling during the standard sleep interval among women who first gave birth between age 25 and 29. The slopes for employment duration were consistently negative among all age at first

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birth categories, although only statistically significant for the oldest group. The pooled estimate for employment duration slope across age-at-first-birth strata was of different direction than the unadjusted slope, indicating substantial confounding.

DISCUSSION

In this study, we observed that female flight attendants employed at Pan American World Airways in 1953 or later exhibited a 37% increased risk of age-, race-, and calendar-year-adjusted breast cancer (95% CI: 23–52%) compared to the U.S. population. This elevated risk was not explained by any of the workplace exposure metrics, including cosmic radiation and the two variables used to characterize potential circadian rhythm disruption: number of flight hours during the standard sleep interval, and number of time zones crossed during flying. The most likely explanation for the higher risk of breast cancer among this cohort is the difference in reproductive risk factors compared to the general population. The Pan Am flight attendants' cohort had far lower parity, on average, than U.S. women in the same birth cohorts (Fig. 1) and a later age at first birth (Fig. 2). The indirect adjustments that were conducted for the independent effects of parity and age at first birth suggest that these two factors in combination could have explained the excess risk that was observed in the Pan Am cohort. Research on other cohorts [e.g., Ewertz et al., 1990; Kelsey et al., 1993] suggests that the effects of these two reproductive risk factors are independent. A relatively high percentage of the cohort (14%) reported a family history of breast cancer. This estimate is similar to recent estimates from the Nurses' Health Study [12.8%; Yaghjyan et al., 2012] and population-based studies in the United States [e.g., 10.9%; Mai et al., 2010] and may reflect increasing breast cancer diagnoses over time among U.S. women.

Our lack of observed association between occupational exposures and breast cancer incidence is consistent with most published studies of flight attendants. An early, small case-control study [Rafnsson et al., 2001] found a significant four-fold elevation in breast cancer risk among flight attendants hired after 1971, when doses among young flight attendants were presumed to be highest. Based on the prevalence of reproductive factors in the general population and flight attendants, those authors concluded that parity and age at first birth did not explain the increase in risk compared to the general population. However, they did not observe differences in parity and age at first birth compared to the general population as large as were observed in our study. A study of flight crew in Sweden [Linnersjö et al., 2003] found a 30% increased breast cancer risk compared to the general population, but it was not related to duration of employment, and differences in parity and age at first birth did not seem to fully explain the excess. In a nested case-control study [Linnersjö et al., 2003], breast cancer incidence was higher among those with over 5000 block hours of high-altitude, long-distance flights, but this was based on a small number of cases and the result was uncertain and not statistically significant. Another small nested case-control study [Kojo et al., 2005] found a positive association between self-reported sleep rhythm disruption and breast cancer incidence, but confidence intervals were very wide. They observed no association with cosmic radiation. A more comprehensive pooled study among air crew in four Nordic countries [Pukkala et al., 2012], of comparable size to our study, found a significant 50% elevation in breast cancer risk compared to the general population. The authors saw no association between cosmic radiation or the number of flights crossing six or

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more time zones and breast cancer risk. They did not estimate the percentage of the elevation that was due to differences in parity and age at first birth in the cohort and the general population; however, they also concluded that none of the known risk factors for breast cancer, including parity and age at first birth, seemed to explain the excess.

For a small percentage of the Pan Am cohort (the 15% who had three or more live or still births), a significant positive trend was observed for cosmic radiation and the two circadian rhythm disruption metrics. It is unclear why this group would exhibit greater sensitivity to the effects of cosmic radiation or circadian rhythm disruption than women with lower parity. The sensitivity of the breast to radiation and other exogenous (and endogenous) agents is thought to be lessened after the breast cell differentiation that occurs following first and subsequent births [Colditz et al., 2006]. Other research suggests breast cancer risk from ionizing radiation is lower for those with high parity and young age at first birth [Land et al., 1994; Ronckers et al., 2005]. Thus, our finding seems suspect for cosmic radiation. However, flight attendants have reported much higher rates of disrupted sleep in cross-sectional surveys, as compared to the general population [McNeely et al., 2014]. It is possible that circadian rhythm disruption could also be affected by the spacing of multiple births and parity. A recent study showed that the frequency of reported sleep insufficiency among U.S. women increases linearly with the number of children in the home [Chapman et al., 2012]. It is possible that our subgroup of high-parity cohort members, already sleep-stressed from the home environment, was more sensitive to the effects of occupational circadian rhythm disruption. To our knowledge, this is the first time that risks of occupational exposures among flight crew have been stratified by parity and age at first birth.

Studies of other shift workers (such as military employees and nurses) have observed a significant trend of increased risk of breast cancer with duration of night shift work among women; however, these studies did not evaluate effect modification by parity or age at first birth [Lie et al., 2006; Schernhammer et al., 2006; Hansen and Lassen, 2012]. Furthermore, most of these studies observed associations with shift work and breast cancer only after very long durations of shift work employment. We could not evaluate whether the circadian rhythm disruption metrics were associated with breast cancer risk among long-term workers (e.g., those who worked for longer than the cohort median of 7.7 years) because no cases occurred in the low-exposure groups among these long-term workers, due to the strong correlation between employment duration and exposure.

Strengths

This cohort of female Pan Am flight attendants, with over 6000 participants and 344 breast cancer cases, is among the largest in which a questionnaire-based incidence study has been conducted. Its large size and long follow-up period make it potentially highly informative on the association between cosmic radiation or circadian rhythm disruption metrics and breast cancer. This is the first study to evaluate work at night, although the ability to uniquely evaluate the effect of this metric was limited by its high correlation with other exposure metrics. Additional strengths include its use of questionnaire data to obtain information on other risk factors for breast cancer (to be explored in future analyses), as well as medical

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record follow-back and registry linkage for verification of diagnosis. We also had a high response rate for individual questions on the questionnaire, reducing the need to rely on imputation for missing data. Although questionnaire data were collected retrospectively (with respect to breast cancer diagnosis), the occupational exposure metrics other than self-reported duration of employment as a flight attendant (which corresponded well with workplace records) were developed using objective external sources [Anderson et al., 2011], by researchers who were blinded to case status.

Limitations

The follow-up end date was 2005 or earlier for all cohort members, and it is unknown whether the results we observed over the studied time period are representative of current levels of breast cancer risk in this cohort. The incidence cohort had a response rate of only 64% after repeated contact attempts by telephone and mail. The response rate (e.g., by proxies) was lower among decedents (41%) in the mortality study than among living cohort members (65%). Among breast cancer decedents, the response rate was similarly low, at 46%. The impact of low response rate on the generalizability of our observed results is uncertain. However, median duration of Pan Am employment (based on workplace records) among the respondents (5.8 years) was slightly longer than for the mortality cohort (5.0 years), suggesting that long-term employees of Pan Am were more likely to respond to the questionnaire.

This cohort of flight attendants had low estimated cumulative cosmic radiation absorbed dose (7.5 mGy was the median dose) and narrow exposure distribution (90% of the incidence cohort had dose between 1 and 34 mGy), which limits the ability to detect a significant dose-response association. Contrary to previous studies that used estimated effective dose [e.g., Pinkerton et al., 2012; Pukkala et al., 2012], we used units of absorbed dose that do not incorporate a “quality factor” (Q) or radiation weighting factor that accounts for the greater relative biological effectiveness (RBE) of high-linear energy transfer radiation. In part, this was because the recently recommended weights for proton and neutron radiations are reduced compared to weights used in previous studies. For example, the International Commission on Radiological Protection [2003], in its most recent guidance, advocates the use of an RBE of 2 for protons and 6 for the combination of neutrons of different energies resulting from cosmic radiation [ICRP, 2003, p. 80]. Because about 50% of the dose equivalent [ICRU, 2010] or 13–25% of absorbed dose [e.g., Anderson et al., 2011] of cosmic radiation under commercial aviation conditions is from neutrons, while the largest contribution is from photons, electrons, and positrons (i.e., low-linear-energy-transfer radiation), the overall RBE of cosmic radiation would be expected to be still lower. This is supported by recent studies of empirical microdosimetry for total cosmic radiation on board actual aircraft at a range of altitudes and latitudes, which suggest values of Q for total cosmic radiation of approximately 2–2.5 [Meier and Hubiak, 2010; Burda et al., 2013]. The attenuated Q was thought to be due partially to shielding of occupants (from low-energy neutrons) provided by the aircraft, fuel, and cargo [Ferrari et al., 2005; Burda et al., 2013]. The impact of a low RBE for cosmic radiation is the persistence of the limitation in power of air crew studies to be informative on risk of low-dose radiation exposure.

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An additional limitation is that the four primary occupational exposure metrics (employment duration, cosmic radiation dose, number of time zones crossed, and number of hours spent flying during the standard sleep interval) are all highly correlated, which complicates the interpretation of positive findings. The correlation between the first three metrics was noted to be very high in the mortality analysis of this cohort [Spearman ρ of 0.96–0.99; Pinkerton et al., 2012]. This high correlation persists in the incidence cohort and is equally high for the standard sleep interval metric. As noted in the mortality study, this high correlation derives from the tendency for long-haul flights (which confer the highest cosmic radiation dose) to cross multiple time zones and to overlap the standard sleep interval of 10 pm–8 am. All three metrics are obviously also closely related to duration of employment as a flight attendant. Furthermore, because we did not have individual flight records for each cohort member, there was likely to be misclassification in exposure estimates. Neither the airline nor the flight attendants kept records of individual flight histories, and so the radiation and time-zone metrics may be quite markedly in error. However, such exposure misclassification will probably introduce Berksonian error into assessments of exposure for both metrics. As such this will not (to first order) bias the regression estimates, although it will inflate their variances [Carroll et al., 2006]. The available flight data (domicile-specific averages applied to each individual) likely contributed to the high correlation between metrics and affected our ability to detect an association with breast cancer incidence. However, it should be noted that a more individualized exposure assessment approach used in a recent study of airline pilots for whom lifetime records of flights were available [Grajewski et al., 2011] also found that cumulative cosmic radiation dose was highly correlated with cumulative time zones crossed (Spearman $\rho = 0.91–0.92$), though not as highly with employment duration (Spearman $\rho = 0.66$). For flight attendants, it is very unlikely that individualized lifetime flight records could be reconstructed because such data are not retained either by the airlines or by the flight attendants themselves.

Another limitation is that we used a population rate file with “prevalent cases” included in the denominator and “second primaries” included in the numerator, which has been found to increase population rates by 3.5% [Merrill and Feuer, 1996]. This would lead to a slight underestimate in our SIRs for breast cancer. The small group of women (n = 38) in the cohort who indicated they were multiracial (with white as one of the races) were classified differently than in the cancer incidence rate file. However, this limitation is unlikely to have influenced these findings, given the small number of affected women. Lastly, in this analysis, we did not adjust for all reproductive (and other) risk factors simultaneously in regression models of the association between cosmic radiation or circadian rhythm disruption metrics and breast cancer incidence, although little evidence of confounding was seen for the metrics evaluated. Future analyses of this cohort, which focus on internal comparisons through Cox regression modeling, are being conducted to address this limitation and to consider a wider range of potential confounders and effect modifiers.

CONCLUSIONS

This large study of breast cancer incidence in a cohort of U.S. flight attendants formerly employed at Pan Am found increased risk compared to the general population; however, breast cancer incidence was not related to cosmic radiation or to two metrics of circadian

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rhythm disruption in the overall cohort. The excess risk in the cohort compared to the U.S. population appeared to be largely explained by differences in parity and age at first birth, which were lower and later (respectively) in the Pan Am cohort. However, an association of one or more of the occupational exposure metrics with breast cancer risk cannot be ruled out for the small subgroup of women with parity of 3 or more or age at first birth below 25. We recommend that additional research be carried out in populations with extensive shift work exposure to determine whether this finding is observed elsewhere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

TABLE AI

Five-year Lagged Results for Exposure-related Variables, Using Quintile Cutpoints for Each Metric[a]

Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), *P*
Absorbed dose (mGy)							2.35E-05[b](9.09E-06), 0.0097
0 to <1.79	68	48,701	1.37	1.07, 1.74	1.0	—	
1.79 to <4.04	70	35,688	1.33	1.04, 1.68	0.98	0.68, 1.41	
4.04 to <8.12	67	31,901	1.45	1.12, 1.84	1.04	0.72, 1.49	
8.12 to <16.0	70	28,710	1.37	1.07, 1.73	1.08	0.75, 1.56	
16.0+	68	17,477	1.34	1.04, 1.70	1.54	0.57, 4.13	
SSI travel (hours)							−8.02E-08 (1.04E-07), 0.44
0 to <395	68	56,625	1.15	0.89, 1.46	1.0		
395 to <873	69	31,394	1.52	1.18, 1.92	1.30	0.92, 1.86	
873 to <1585	69	26,247	1.76	1.37, 2.23	1.52	1.06, 2.17	
1585 to <2996	69	28,588	1.30	1.01, 1.64	1.26	0.88, 1.80	
2996+	68	19,623	1.28	0.99, 1.62	0.95	0.67, 1.35	
Time zones crossed (n)							−2.88E-08 (2.41E-08), 0.23
0 to <933.9	69	52,838	1.21	0.94, 1.54	1.0	—	
933.9 to <1902	69	30,270	1.56	1.22, 1.98	1.24	0.86, 1.77	
1902 to <3740	68	31,195	1.51	1.17, 1.92	1.22	0.85, 1.76	
3740 to <7998	70	31,619	1.23	0.96, 1.56	1.16	0.80, 1.68	

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Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), *P*
7998+	67	16,555	1.41	1.09, 1.79	0.94	0.65, 1.36	
Empl. duration (days)							−3.70E-08 (1.88E-08)[b], 0.049
0 to <853	68	51,313	1.37	1.06, 1.74	1.0		
853 to <1829	69	36,417	1.30	1.01, 1.65	0.97	0.68, 1.39	
1829 to <3229	68	29,256	1.52	1.18, 1.93	1.13	0.79, 1.61	
3229 to <6659	71	31,797	1.20	0.93, 1.51	0.97	0.67, 1.38	
6659+	67	13,694	1.54	1.19, 1.95	0.85	0.60, 1.22	

PY, person-years at risk; SIR, standardized incidence ratio; CI, confidence interval; SRR, standardized rate ratio; SE, standard error; SSI, standard sleep interval.

[a]The date of diagnosis was changed for one subject to reduce the influence of a single cell with one event and little person-time.

[b]Note that this significant slope appears to be a result of a single influential cell and is highly susceptible to cutpoint choice.

TABLE AII

Fifteen-year Lagged Results for Exposure-related Variables, Using Quintile Cutpoints for Each Metric

Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), *P*
Absorbed dose (mGy)							−1.40E-05 (3.12E-05), 0.65
0 to <1.09	69	81,758	1.42	1.10, 1.79	1.0	—	
1.09 to <3.00	69	28,353	1.12	0.87, 1.42	0.69	0.46, 1.02	
3.00 to <5.41	68	19,374	1.52	1.18, 1.93	1.03	0.69, 1.54	
5.41to <10.7	70	19,847	1.38	1.07, 1.74	0.94	0.58, 1.53	
10.7+	67	13,145	1.50	1.17, 1.91	0.71	0.47, 1.09	
SSI travel (hours)							−8.31E-08 (9.77E-08), 0.40
0 to <208	69	84,859	1.25	0.97, 1.58	1.0	—	
208 to <599	69	26,466	1.20	0.93, 1.52	0.94	0.64, 1.38	
599 to <1146	68	18,737	1.58	1.23, 2.00	1.25	0.86, 1.83	
1146 to <2232	70	19,138	1.37	1.07, 1.73	0.93	0.64, 1.37	
2232+	67	13,277	1.55	1.20, 1.96	0.89	0.59, 1.32	
Time zones crossed (n)							2.10E-08 (6.36E-08), 0.74
0 to <479	68	80,995	1.44	1.12, 1.83	1.0	—	
479 to <1339	70	27,756	1.16	0.90, 1.47	0.71	0.47, 1.07	
1339 to <2602	68	21,099	1.40	1.09, 1.78	0.87	0.58, 1.32	
2602 to <5046	69	19,362	1.38	1.08, 1.75	0.87	0.56, 1.36	
5046+	68	13,266	1.53	1.19, 1.94	0.84	0.49, 1.43	
Empl. duration (days)							2.29E-08 (6.68E-08), 0.73
0 to <607	69	83,903	1.34	1.04, 1.69	1.0	—	
607 to <1338	68	26,059	1.19	0.93, 1.51	0.82	0.56, 1.20	
1338 to <2436	68	21,582	1.37	1.06, 1.73	1.04	0.69, 1.57	
2436 to <4230	69	17,687	1.49	1.16, 1.88	0.92	0.62, 1.38	

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Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), *P*
4230+	69	13,247	1.51	1.17, 1.91	0.96	0.54, 1.71	

PY, person-years at risk; SIR, standardized incidence ratio; CI, confidence interval; SRR, standardized rate ratio; SE, standard error; SSI, standard sleep interval.

TABLE AIII

Twenty-year Lagged Results for Exposure-related Variables, Using Quintile Cutpoints for Each Metric

Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), *P*
Absorbed dose (mGy)							−2.19E-05 (3.96E-05), 0.58
0 to <0.52	69	96,854	1.17	0.91, 1.48	1.0	—	
0.52 to <1.94	68	20,847	1.27	0.98, 1.61	0.77	0.44, 1.35	
1.94 to <3.94	68	17,676	1.39	1.08, 1.76	1.11	0.51, 2.40	
3.94 to <6.85	70	13,287	1.76	1.37, 2.22	0.93	0.53, 1.63	
6.85+	68	13,813	1.39	1.08, 1.77	0.69	0.37, 1.30	
SSI travel (hours)							−1.23E-07 (2.26E-07), 0.59
0 to <78.4	67	96,494	1.14	0.89, 1.45	1.0	—	
78.4 to <439.6	71	25,718	1.07	0.83, 1.35	0.79	0.44, 1.40	
439.6 to <841.3	68	14,303	1.69	1.32, 2.15	1.13	0.63, 2.03	
841.3 to <1457	69	11,879	1.91	1.49, 2.42	1.36	0.72, 2.57	
1457+	68	14,084	1.39	1.08, 1.76	0.73	0.40, 1.32	
Time zones crossed (n)							1.51E-08 (1.15E-07), 0.90
0 to <161	69	95,509	1.22	0.95, 1.54	1.0	—	
161to <954	69	23,857	1.13	0.88, 1.43	0.65	0.37, 1.16	
954 to <1874	68	16,337	1.50	1.17, 1.90	0.84	0.46, 1.53	
1874 to <3307	69	13,444	1.71	1.33, 2.17	1.07	0.56, 2.05	
3307+	68	13,330	1.44	1.12, 1.83	0.69	0.36, 1.32	
Empl. duration (days)							4.86E-09 (7.28E-08), 0.95
0 to <366	68	98,223	1.11	0.86, 1.41	1.0	—	
366 to <975	69	21,116	1.25	0.97, 1.59	0.80	0.43, 1.48	
975 to <1826	68	16,820	1.45	1.13, 1.84	0.89	0.48, 1.66	
1826 to <3015	69	13,337	1.72	1.34, 2.17	0.91	0.49, 1.69	
3015+	69	12,982	1.47	1.14, 1.86	0.75	0.33, 1.58	

PY, person-years at risk; SIR, standardized incidence ratio; CI, confidence interval; SRR, standardized rate ratio; SE, standard error; SSI, standard sleep interval.

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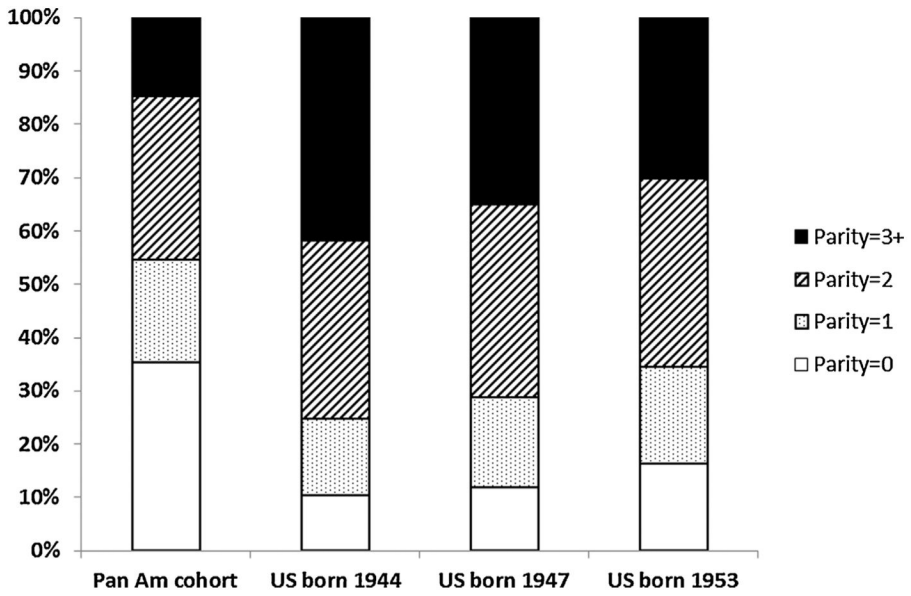

FIGURE 1.

Parity (defined as live birth or still birth in the Pan Am cohort and as live birth in the U.S. population) in the Pan Am cohort (median year of birth 1947 interquartile range 1944–1953) compared to U.S. women born in 1944, 1947, and 1953 (Data for U.S. women from Hamilton and Cosgrove 2010).

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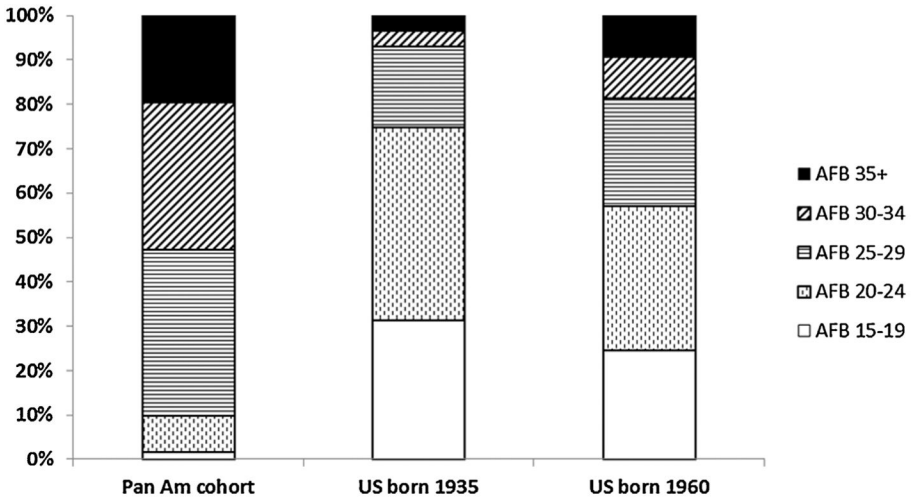

FIGURE 2.

Age at first birth (AFB) (defined as age at first live birth or still birth in both the Pan Am cohort and in the U.S. population) in the Pan Am cohort (median year of birth 1947 interquartile range 1944–1953) compared to U.S. women born in 1935 and 1960 (Data for U.S. women from Kirmeyer and Hamilton, 2011).

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TABLE I

Cohort Characteristics

Characteristic	Questionnaire respondents	Breast cancer cases
Number	6093	344
Age at end of follow-up for breast cancer[a]		
Median	55.2	51.3
IQ range	48.6–59.0	46.3–56.3
Year of birth		
Median	1947	1944
IQ range	1944–1953	1939–1947
Vital status[b]		
Alive	5972 (98%)	315 (92%)
Deceased	121 (2%)	29 (8%)
Race		
White	5568 (91%)	322 (94%)
All other races	525 (9%)	22 (6%)
Family history of breast cancer		
No	5062 (83%)	256 (74%)
Yes	846 (14%)	71 (21%)
Unknown	185 (3%)	17 (5%)
Parity[c]		
None	2125 (35%)	124 (36%)
1	1162 (19%)	63 (18%)
2	1846 (30%)	111 (32%)
3+	884 (15%)	42 (12%)
Unknown	76 (1%)	4 (1%)
Age at first birth[d]		
<25	380 (10%)	17 (8%)
25–29	1455 (37%)	93 (43%)
30–34	1293 (33%)	65 (30%)
35+	764 (20%)	41 (19%)
Cumulative absorbed radiation dose (mGy)		
Median (IQ range)	7.2 (2.7–17)	5.5 (2.6–16)
Mean (std dev)	12 (11)	10 (10)
Cumulative number of time zones crossed		
Median (IQ range)	3600 (1300–8600)	2700 (1200–7400)
Mean (std dev)	5800 (5900)	5000 (5200)
Cumulative hours flying in the standard sleep interval		
Median (IQ range)	1500 (510–3200)	1300 (520–3000)
Mean (std dev)	2200 (2200)	2000 (2000)
Cumulative employment duration (years)		
Median (IQ range)	7.7 (3.1–17)	6.8 (3.1–16)

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Characteristic	Questionnaire respondents	Breast cancer cases
Mean (std dev)	12 (10)	11 (10)

IQ, interquartile.

[a] Defined as the age at the earliest of: date of first breast cancer diagnosis, date of interview (for living subjects), and date of death (for decedents).

[b] At questionnaire completion.

[c] Number of live or still births.

[d] Among participants with one or more live or still births.

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TABLE II

Standardized Incidence Ratios of Breast Cancer for Women in Overall Pan Am Cohort (n = 6092[a]) and for Covariates of Interest

Analysis description	Person-years	SIR	95% CI
Overall cohort[a]	162,477	1.37	1.23, 1.52
Race			
White	149,064	1.37	1.23, 1.53
All other races	13,414	1.31	0.82, 1.98
Family history of breast cancer			
No	134,104	1.25	1.11, 1.42
Yes	23,547	1.89	1.47, 2.38
Unknown	4826	2.02	1.18, 3.23
Parity[b,c]			
0	76,121	1.35	1.12, 1.60
1	29,458	1.38	1.06, 1.76
2	37,232	1.58	1.30, 1.90
3+	17,725	1.05	0.75, 1.42
Age at first birth[c]			
<25	9856	1.03	0.60, 1.65
25–29	37,008	1.44	1.16, 1.77
30–34	26,105	1.34	1.03, 1.70
35+	11,446	1.56	1.12, 2.12

SIR, standardized incidence ratio, adjusted for age, race and calendar year; CI, confidence interval.

[a] One woman was excluded from the cohort because she had a breast cancer diagnosis before the rate begin date.

[b] Parity indicates number of live or still births.

[c] 76 women, including 4 breast cancer cases, were excluded due to missing parity and age at first birth.

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TABLE III

Ten-year Lagged SIR and SRR Results for Exposure-Related Variables, Using Quintile Cutpoints Among the Breast Cancer Case Distribution for Each Metric

Analysis description	N cases	PY	SIR	95% CI on SIR	SRR	95% CI on SRR	Trend slope (SE), P^a
Absorbed dose (mGy)							
0 to <1.55	68	66,838	1.35	1.05, 1.71	1.0	—	−1.67E-05 (1.11E-05), 0.13
1.55 to <3.57	70	30,453	1.32	1.03, 1.67	1.01	0.71, 1.45	
3.57 to <6.61	68	24,355	1.54	1.20, 1.96	1.19	0.82, 1.71	
6.61to <13.9	69	26,380	1.21	0.94, 1.54	0.95	0.65, 1.38	
13.9+	68	14,452	1.48	1.15, 1.87	0.88	0.60, 1.29	
SSI travel (hours)							
0 to <318	69	71,301	1.21	0.94, 1.54	1.0	—	−5.27E-08 (1.06E-07), 0.62
318 to <792	69	30,732	1.29	1.00, 1.63	1.00	0.69, 1.45	
792 to <1435	67	21,341	1.70	1.32, 2.16	1.41	0.98, 2.05	
1435 to <2642	70	22,865	1.35	1.05, 1.70	1.13	0.78, 1.63	
2642+	68	16,238	1.40	1.09, 1.78	0.93	0.64, 1.36	
Time zones crossed (n)							
0 to <724	69	66,871	1.35	1.05, 1.71	1.0	—	−2.96E-08 (2.59E-08), 0.25
724 to <1716	70	30,598	1.31	1.02, 1.66	0.94	0.66, 1.36	
1716 to <3201	67	24,822	1.50	1.16, 1.90	1.17	0.81, 1.68	
3201to <6399	68	24,520	1.29	1.00, 1.63	1.01	0.69, 1.47	
6399+	69	15,667	1.42	1.11, 1.80	0.87	0.60, 1.26	
Employment duration (days)							
0 to <731	68	66,605	1.45	1.12, 1.83	1.0	—	−4.54E-08 (4.45E-08), 0.31
731to <1614	68	32,710	1.19	0.92, 1.50	0.78	0.54, 1.12	
1614 to <2831	69	24,614	1.52	1.18, 1.92	1.02	0.71, 1.48	
2831to <5369	70	24,641	1.28	1.00, 1.62	0.96	0.65, 1.41	
5369+	68	13,909	1.48	1.15, 1.88	0.74	0.51, 1.08	

PY, person-years at risk; SIR, standardized incidence ratio; CI, confidence interval; SRR, standardized rate ratio; SE, standard error; SSI, standard sleep interval.

[a]Slope units are breast cancers per person-year · exposure unit.

P-values are two-sided.

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TABLE IV

Effect Modification of Trend Slope[a] for 10-Year Lagged Exposure Variables, by Family History

Family history	Absorbed dose (mGy) slope (SE)	Hours flying in standard sleep interval slope (SE)	Time zones crossed slope (SE)	Employment duration (days) slope (SE)
Yes	−1.15E-05 (2.17E-05)	−2.32E-07 (2.21E-07)	−6.28E-08 (4.51E-08)	−8.86E-08 (1.17E-07)
No	−1.05E-05 (1.04E-05)	−5.01E-09 (7.24E-08)	−9.42E-09 (2.13E-08)	−4.84E-09 (5.39E-08)
Pooled estimate[b]	**−1.07E-05**	**−2.69E-08**	**−1.92E-08**	**−1.94E-08**
Unadjusted estimate	**−1.05E-05 (8.27E-06)**	**−4.34E-08 (9.39E-08)**	**−1.63E-08 (1.98E-08)**	**−2.07E-08 (5.43E-08)**

SE, standard error.

[a] Slope units are breast cancers per person-year · exposure unit.

[b] Inverse-variance weighted.

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TABLE V

Effect Modification of Trend Slope[a] for 10-Year Lagged Exposure Variables, by Parity.

Parity (number of births)	Absorbed dose (mGy) slope (SE)	Hours flying in standard sleep interval slope (SE)	Time zones crossed slope (SE)	Employment duration (days) slope (SE)
0	−2.95E-05 (1.75E-05)	9.93E-09 (1.55E-07)	−6.74E-08 (3.48E-08)	−6.24E-08 (6.87E-08)
1	−3.90E-05* (1.37E-05)	−4.65E-08 (2.50E-07)	−7.43E-08* (2.88E-08)	−5.89E-08 (7.86E-08)
2	2.17E-05 (6.39E-05)	1.52E-07 (2.74E-07)	9.98E-08 (1.31E-07)	6.15E-09 (5.39E-08)
3+	2.62E-04** (1.23E-04)	7.00E-07** (2.89E-07)	6.22E-07** (2.53E-07)	5.11E-07 (4.88E-07)
Pooled estimate[b]	**NR**	**NR**	**NR**	**NR**
Unadjusted estimate	**−1.71E-05 (1.20E-05)**	**−4.07E-08 (1.05E-07)**	**−2.52E-08 (2.81E-08)**	**−3.90E-08 (4.77E-08)**

SE, standard error; NR, a pooled estimate is not reported given the strong apparent effect modification.

[a] Slope units are breast cancers per person-year · exposure unit.

[b] Inverse-variance weighted.

* P <0.01.

** P <0.05.

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TABLE VI

Effect Modification of Trend Slope for 10-year Lagged Exposure Variables, by Age at First Birth

Age at first birth	Absorbed dose (mGy) slope (SE)	Hours flying in standard sleep interval (SE)	Time zones crossed slope (SE)	Employment duration (days) slope (SE)
14–<25	1.02E-05 (8.00E-05)	Not reported[b]	2.18E-07** (1.01E-07)	−1.29E-08 (2.08E-07)
25–<30	4.42E-05 (1.00E-04)	2.58E-09 (4.22E-07)	1.44E-07 (1.86E-07)	−2.51E-07 (2.45E-07)
30–<35	−7.83E-05** (3.41E-05)	−2.83E-08 (2.12E-07)	−1.07E-07 (6.98E-08)	−4.17E-09 (7.14E-08)
35+	−2.39E-05 (5.06E-05)	−6.13E-08 (1.65E-07)	−3.16E-08 (1.18E-07)	−1.70E-07** (8.39E-08)
Pooled estimate[a]	**NR**	**NR**	**NR**	**−7.80E-08**
Unadjusted estimate	**3.94E-05 (3.53E-05)**	**1.57E-07 (2.13E-07)**	**8.86E-08 (6.73E-08)**	**6.38E-08 (7.47E-08)**

SE, standard error; NR, a pooled estimate not reported given the strong apparent effect modification.

[a] Inverse-variance weighted.

[b] Zero-cells present in one exposure category.

** P <0.05.