Can passive smoking explain the higher radiation-related excess relative risk of lung cancer for women compared to men among atomic bomb survivors?

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Abstract

Can passive smoking explain the higher radiation-related excess relative risk of lung cancer for women compared to men among atomic bomb survivors?

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Analyses of the Life Span Study (LSS) cohort of atomic bomb survivors have shown a sex difference in the incidence of lung cancer in relation to radiation exposure. Specifically, the excess relative risk (ERR) of lung cancer associated with radiation exposure is observed to be higher in women compared to men (the ERR/Gy for females = 1.32; the ERR/Gy for males = 0.34, F:M ratio = 3.91). The basis for this observed difference in ERR is unclear. One possibility is inadequate adjustment for passive smoking exposure in LSS participants. High rates of smoking among men, but not women, in the LSS suggest that non-smoking women in this population could have substantial passive exposure to tobacco smoke. Passive smoke exposure is a known risk factor for lung cancer, but was not measured for study participants. In our analysis, we simulated passive smoking by attributing smoking pack-years to nonsmoking women at various intensities based on male smoking patterns in the cohort. This yielded an increase in the radiation-related ERR/Gy estimates, leading to a higher F:M ratio, and a reduced smoking-related ERR estimate in women. Ultimately, the radiation-associated risks for lung cancer in women did not decrease as we had hypothesized, and our method of simulating passive smoke for women did not attenuate the F:M ratio towards one. However, given the exploratory nature of our simulation and limitations of the data, our results cannot rule out the possibility that passive smoke contributes to the higher radiation risk estimates for women compared to men in the LSS.

Introduction

Exposure to ionizing radiation has long been recognized as a risk factor for cancer.[1] Much of the current knowledge about the long-term health effects of radiation on cancer risk is derived from the Life Span Study (LSS): a study of atomic bomb survivors in Hiroshima and Nagasaki, Japan who have been followed for more than 60 years.[2] The LSS is comprised of approximately 94,000 men and women exposed to ionizing radiation at the time of the atomic bomb detonations in 1945, and a comparison group of 27,000 individuals who were "not-in-city" at the time of the blasts.[2] Through detailed dosimetry, prospective collection of demographic and health data, and linkage with cancer registries, the LSS has made it possible to quantify the effects of ionizing radiation on long-term health outcomes, including cancer.

The LSS has clarified the dose-response relationships of ionizing radiation exposure for various cancer sites, considering important risk modifiers such as sex, age at exposure, and attained age. LSS data have demonstrated an elevated incidence of lung cancer for atomic bomb survivors, with an estimated radiation-related ERR/Gy of 0.83 (95% CI: 0.58, 1.09).[3] However, this relationship differs markedly by sex; the ERR for lung cancer is higher in women compared to men (ERR/Gy = 1.32 and ERR/Gy = 0.34, respectively).[3] The basis for this observed difference is unclear. One possibility is inadequate adjustment for smoking exposure in LSS participants.

Many studies have investigated the relationship between passive smoking and lung cancer in non-smoking women in Japan,[4] and have confirmed that passive smoking is a risk factor for lung cancer among Japanese women, particularly for nonsmoking women married to smokers.[5] While the effect of active smoking was assessed and adjusted for in analyses of radiation exposure in relation to lung cancer risk, no data on passive smoking were collected or utilized. The prevalence of active smoking in the LSS is relatively high in men and low in women – approximately 85% of LSS men with available smoking data indicated that they had ever smoked compared to 18% of LSS women.[3] This smoking behavior is also consistent with trends in the general Japanese population.[7] Thus, passive smoke exposure for nonsmoking LSS female participants (via having grown up with fathers that smoked in the home, having been married to someone that smoked at home, or having worked in smoking environments) is likely a significant contributor to lung cancer risk. Thus, the lack of adjustment for passive smoke exposure may explain the differential dose-response estimated for lung cancer between men and women.

Using simulation methods, we assessed the hypothesis that passive smoking exposure could plausibly explain the higher ERR estimates for lung cancer incidence in women compared to men. Specifically, we hypothesized that simulating the contribution of passive smoke exposure to overall cigarette smoke exposure levels in ERR models for lung cancer would reduce the radiation-related risk estimates for lung cancer, particularly among women.

Materials and Methods

This study was approved by the IRB committee of the Radiation Effects Research Foundation via approval of RP S2-18. The Hiroshima and Nagasaki Prefectures and the city of Hiroshima approved the linkages between data from the Cancer Registries and the LSS cohort members.

Study Population and Follow-up

The LSS cohort consists of 93,741 individuals who were in either Hiroshima or Nagasaki at the time of the bombings (classified as proximally exposed, semi-proximally exposed, and distally exposed depending on distance from bomb hypocenters), as well as a sample of 26,580 people who were designated as "not-in-city" participants, matched on age- and sex- to the proximally exposed group. Survivors received ionizing radiation doses between 0 – 2+ Gy; people who were closer to the hypocenters received higher radiation doses. All participants were born prior to the atomic bombings in August 1945 and still alive on October 1, 1950. LSS participants were excluded if they had died or developed cancer prior to January 1, 1958 (n = 8,317), did not have available radiation dose estimates (n = 6,473), or could not be traced (n = 86). There were 105,444 subjects eligible for this study following these exclusions, including 80,205 survivors and 25,239 not-in-city participants.

Data for the LSS were collected by the Radiation Effects Research Foundation (RERF) - a binational Japan-US scientific organization dedicated to studying health effects of atomic bomb radiation. Study follow-up began on January 1, 1958 and continued until first primary cancer diagnosis, death, or December 31, 2009. Demographic and health data have been collected from participants for over 65 years with the overarching goal of evaluating the long-term health effects of atomic bomb radiation.

Lung Cancer Case Ascertainment

Cancer diagnoses among LSS subjects are ascertained through data linkage to Hiroshima- and Nagasaki-based city and prefecture-wide cancer registry systems. Incident lung cancer cases were ascertained through these tumor registries from the years 1950-2003. Individuals diagnosed with lung cancer upon autopsy were excluded (n = 643).

Radiation Dosimetry

Details regarding the estimation of radiation dose have been described elsewhere.[1] Briefly, Dosimetry System 2002 Revision 1 (DS02R1) was used to estimate the radiation dosage received by individual organs of all LSS subjects (n = 80,205) who were within 10 km of the hypocenters at the time of the bombings. Weighted lung dose estimates were calculated as the sum of the DS02R1 gamma-ray dose estimate and 10 times the DS02R1 neutron dose estimate. Similar to previous analyses, not-in-city participants were assigned zero radiation dose and included in the analysis as a baseline group to improve the characterization of the variation in the unexposed by establishing baseline cancer rates by age, sex, and birth cohort.

Marital Status

Data on the marital status of LSS participants were collected as part of four mailed and three clinic-based questionnaires administered between 1965 and 1991. The 1965 survey was administered to men between the ages of 40 and 69 (n = 8,295). The 1969 survey was administered to only females (n = 14,227). The 1978 and 1991 surveys were mailed to all surviving cohort members who were in the cities at the time of the bombings (n = 31,258 and n = 31,238, respectively). Marital history was summarized as an indicator of marital status (unknown, never married, or ever married). All cohort members were classified by earliest marital status reported from all surveys to which a person responded. Marital status information was available for 47,861 participants (45% of eligible cohort members).

Active Smoking

Smoking data were collected from the same four mailed questionnaires administered between 1965 and 1991 from which marital status data were obtained. Smoking information was available from at least one survey for 64,465 participants (61% of eligible cohort members).

Smoking history was summarized by a time-dependent indicator of smoking status (unknown, never-smoker, past-smoker, or current smoker). To avoid biasing risk estimates by overcounting person years in known smoking status categories, all cohort members were classified as having unknown smoking status until the date at which they first provided information on smoking habits.

More detailed information on smoking included variables such as “age started smoking,” “age stopped smoking,” “average smoking intensity,” and the “year in which data on smoking were first attained”. “Age started smoking” was defined as the lowest starting age of smoking reported from all surveys to which a person responded. “Average smoking intensity” was defined as the average number of cigarettes smoked per day over all surveys in which a person reported having smoked. Smoking duration was defined as the difference between attained age and age started smoking, and time since quitting was defined as the difference between attained age and the age at smoking cessation. Cumulative smoking amount was calculated in pack-years, defined as the product of packs smoked per day (20 cigarettes per pack) and years smoked. Additional details on the smoking variables are available elsewhere.[8]

Passive Smoking Simulation

To investigate the potential role of passive smoking on the relationship between radiation exposure and lung cancer incidence, passive smoke exposure was simulated using individual-level variables and then incorporated into cross-tabulated person-year life tables for analyses. As a measure of passive smoke, we simulated an amount of active smoking pack-years for nonsmoking women, who we hypothesized would be most affected by passive smoke exposure. In other words, we created simulated data sets in which nonsmoking women were treated as “smokers”. Marital status was incorporated into this simulation, as we hypothesized that married nonsmoking women were likely to have passive smoke exposure through their spouses.

The simulation of smoking pack-years was conducted by generating ‘age started smoking’ and ‘average smoking intensity’ variables for nonsmoking women. The product of these two variables was used to estimate the cumulative smoking pack-years and was incorporated into ERR estimates that modeled the joint effect of radiation and smoking on cancer risk. We used male smoking patterns to inform the age at which simulated smoking would start, and varied the proportion of simulated average smoking intensity due to passive smoke exposure. We employed these methods because we hypothesized that women would start to be exposed to passive smoke at the age that men in their birth cohort began smoking. Since we expected that smoking intensity from passive smoke would be less than actively smoking, we represented this simulated smoking intensity as proportions of male smoking intensity. We allowed this adjustment factor to vary from 1-75% to explore various simulation scenarios. We also allowed the proportion to be higher for married versus unmarried women, reasoning that married women are likely to be exposed to a greater intensity of passive smoke through their spouses.

Using the male cohort smoking patterns, we generated a Normal distribution of values for the simulated ‘age started smoking’ centered at the mean ‘age started smoking’ for males, specific to city, birth year, radiation dose, and event of lung cancer. Nonsmoking women with known marital status were given a random ‘age started smoking’ value from this distribution. For the ‘average smoking intensity’ variable, we used a lognormal distribution of values that we randomly assigned to women. Similar to the distribution of simulated ‘age started smoking’ values, this distribution was centered around the mean ‘average smoking intensity’ of male smokers and was specific to city, birth year, radiation dose, and event of lung cancer.

Statistical Analysis

We used Poisson regression maximum likelihood methods to estimate parameters, compute confidence intervals, and perform hypothesis tests. To conduct these analyses, a table of person-years and lung cancer cases was created based on the following stratification factors: sex, city, age at exposure, attained age, calendar time, radiation dose, and time-dependent smoking status. The same stratification cut points that have been used in previous analyses of the LSS[2] were implemented to facilitate comparison of findings. The analyses were conducted in R (version 3.4.3) using the RStudio interface (version 1.1.423) and Epicure software.[9]

For each simulated data set, we ran ERR models to estimate radiation and smoking parameters for the various smoking proportions. The analytic approach for modeling the joint effects of radiation and smoking on lung cancer risks was based on the methods used by Cahoon and colleagues.[2] The total risk is characterized in equation (1):

$$\text{(1)} \qquad \mathit{Risk} = \lambda \text{ x } \mathrm{RR}(\mathit{smk, rad}) = \lambda \text{ x } [1 + \mathrm{ERR}(\mathit{smk, rad})]$$

where the *ERR* is the excess risk of lung cancer relative to baseline, *RR* is the relative risk of lung cancer, and *λ* is the baseline risk of lung cancer.

To characterize the joint effects of radiation and smoking on lung cancer, we used both additive and multiplicative ERR models. In the additive model (2), the joint effect of radiation and smoking is equal to the sum of the ERR for smoking and the ERR/Gy:

$$\text{(2)} \qquad \mathit{Risk} = \lambda \text{ x } \mathrm{RR}(\mathit{smk, rad}) = \lambda(1 + \mathrm{ERR}_{\mathrm{smk}} + \mathrm{ERR}_{\mathrm{rad}})$$

In the multiplicative model (3), the joint effect of radiation and smoking is equal to the sum of the radiation and smoking ERRs plus the product of the ERR/Gy and smoking ERR values.

$$\begin{aligned}\text{(3)} \qquad \mathit{Risk} &= \lambda \text{ x } \mathrm{RR}(\mathit{smk, rad}) = \lambda(1 + \mathrm{ERR}_{\mathrm{smk}})\,(1 + \mathrm{ERR}_{\mathrm{rad}}) \\ &= \lambda\,(1 + \mathrm{ERR}_{\mathrm{smk}} + \mathrm{ERR}_{\mathrm{rad}} + \mathrm{ERR}_{\mathrm{smk}}\mathrm{ERR}_{\mathrm{rad}})\end{aligned}$$

The ERR/Gy for lung cancer, $\mathrm{ERR}_{\mathrm{rad}}$, can best be described as the product of a sex-averaged function of dose (d) and an effect modification term that depends on attained age (a) and age at exposure (e):

$$\text{(4)} \qquad \mathrm{ERR}_{\mathrm{rad}} = \beta_g d \times \left(\frac{a}{70}\right) \times e^{\gamma(\frac{e-30}{10})}$$

Sex-specific ERRs/Gy were computed. Attained age and age at exposure were scaled so that the sex-specific dose effect corresponds to the risk for a 70-year-old survivor who was exposed at age 30 years.

The smoking ERR, $\mathrm{ERR}_{\mathrm{smk}}$, can best be described as the product of a function of pack-years and an effect modification term that depends on cigarettes smoked per day (c), smoking duration in years (y), and years since quitting (q) with allowance for birth year (b), sex (g), and unknown smoking status. Among those with information on smoking:

$$\text{(5)} \qquad \mathrm{ERR}_{\mathrm{smk}} = \left(\phi_{0g} \times \frac{p}{50}\right) \times \exp\left[\phi_{1g}\left(\frac{b-1915}{10}\right) + \lambda_1 \ln\left(\frac{y}{50}\right) + \ \lambda_2 \ln(c) + vln(q+1)\right]$$

Smoking duration and birth cohort were centered so that ϕ_{0g} is interpreted as the sex-specific ERR for a current smoker who was born in 1915 (i.e., age 30 years at the time of blast exposure) and smoked one pack per day for 50 years. The excess smoking risk associated with

50 pack-years of smoking was given by a sex-averaged value, ϕ_{0g}, and is defined as the unweighted mean of the 50 pack-years effect parameters for men and women.

For additive models, the $\mathrm{ERR}_{\mathrm{rad}}$, or ERR/Gy, is among nonsmokers and the $\mathrm{ERR}_{\mathrm{smk}}$, or ERR/50 pack-years, is among zero radiation dose individuals. For multiplicative models, the $\mathrm{ERR}_{\mathrm{rad}}$ is among individuals of the same smoking status as those unexposed to radiation and the $\mathrm{ERR}_{\mathrm{smk}}$ is among individuals with the same radiation dose.

Results

From the 105,444 LSS participants in this study, 2,446 primary lung cancer cases occurred between 1958 to 2009. Sex-specific distributions of lung cancers by city, age at exposure, attained age, radiation dose, and smoking status are shown in Table 1. There were more incident lung cancer cases among men and women at younger ages of exposure as well as at higher attained ages. In addition, there were higher numbers of cancer cases that occurred in those with low radiation dose exposure; however, the majority (94.4%) of people in the LSS were exposed to low dose radiation (<0.5 mGy). The distribution of lung cancers by sex, radiation dose, smoking status, and marital status is shown in Table 2. For men, most lung cancers (56.6%) occurred among current smokers, while among women, most cancers (40.8%) occurred among nonsmokers.

Smoking Data

Data on smoking were available for 60% of men and 62% of women. Among those who provided information on smoking, most men (82.6%) indicated that they had ever smoked while most women (82.1%) indicated that they had never smoked. Male smokers tended to smoke almost twice as many cigarettes per day (mean = 19.1) as female smokers (mean = 10.1), and also tended to start smoking earlier (mean age at start of smoking = 21.5 for men and 32.2 for women).

Marital Status Data

Marital status was available for 46% of men and 45% of women. Among those LSS participants with marital status data, 97.2% of men and 94.8% of women indicated that they had ever been married (i.e. they reported being either currently married, previously married, divorced, or widowed).

Lung Cancer ERR Model estimates

Radiation-related and smoking-related ERR estimates for lung cancers are shown in Table 3. Parameters were estimated from additive and multiplicative models defining the joint effects of radiation and smoking on lung cancer risk.

Background rates: The risk of lung cancer at age 70 for nonsmoking individuals with no radiation exposure was lower in women compared to men with a relative risk of 0.74 (95% CI: 0.55, 0.99).

***Smoking effects**:* Sex-specific smoking effect estimates for lung cancer using additive and multiplicative radiation-smoking interaction are shown in Table 3. Both models included birth year and smoking duration as effect modifiers, and the pack-year effect was allowed to vary with log smoking duration and log packs per day to improve model fit. According to the additive model, among men and women born in 1915 and not exposed to radiation, smoking 20 cigarettes per day for 50 years (i.e. 50 pack-years) was associated with an ERR of 5.75 (95% CI: 4.13, 8.15) and 6.33 (95% CI: 4.83, 8.17), respectively. According to the multiplicative model, the estimated ERR/50 pack-years was 4.40 (95% CI: 3.11, 6.31) among men and 4.81 (95% CI: 3.52, 6.38) among women. The ERR associated with smoking was not markedly different for men and women using either the additive or multiplicative interaction models.

Radiation effects: Radiation exposure effect estimates from ERR interaction models are shown in Table 3. According to the additive model, among 70-year-old nonsmoking men and women exposed to radiation at age 30 years, the ERR/Gy was 0.78 (95% CI: 0.044, 1.51) and 1.53 (95% CI: 0.981, 2.21), respectively, giving a female:male ratio of 1.97 (95% CI: 1.47, 22.1). According to the multiplicative model, among 70-year-old men exposed to radiation at age 30 years with the same smoking status as an unexposed individual is 0.317 (95% CI: 0.126, 0.555) and for a 70-year old non-smoking woman is 1.22 (95% CI: 0.809, 1.71) with a female:male ratio of 3.85 (95% CI: 3.08, 6.43). For both models, the ERR/Gy was significantly higher for women than for men.

ERR Model Estimates from Passive Smoke Simulation

ERR parameters from a range of passive smoke simulations are shown in Table 3. As the adjustment factor relating passive smoke intensity to active smoking intensity is increased, the radiation-related F:M ratio tended to increase in both the additive and multiplicative models (Figure 1). Additionally, the female smoking-related ERR significantly decreased while the male smoking-related ERR did not.

Additive Model: In the additive model, all of the male parameter estimates (the background rate, ERR/50 pack-years, and ERR/Gy) were more variable across simulation scenarios compared to the multiplicative model, in which the male background and smoking parameters remained fairly consistent. The F:M ratio was higher than the reference group ratio at low passive smoke levels and tended to decrease slightly as the adjustment factor was increased for both married and unmarried women. Holding the unmarried group constant at a low level (10%), we observed a similar trend as the married group's passive smoke levels were increased. Keeping the unmarried group constant at a higher level (25%), we found the F:M ratio to be almost unchanged.

Multiplicative Model: The multiplicative model provided clearer patterns than using the additive model. The F:M ratio had an increasing trend as passive smoke effects were increased. This trend was consistent when the adjustment factor was applied to both married and unmarried women, as well as when we held the unmarried group constant at a low level (10%). Similar to the additive model, when we kept the unmarried group's passive smoke constant at a higher level (25%), the F:M ratio stayed about the same.

Discussion

We observed that simulating smoking pack years in nonsmoking women led to an increase in the radiation-related ERR/Gy, and a higher F:M ratio. Furthermore, we see that the smoking-related ERR/50 pack-years for women decreased significantly as passive smoke exposure increased. Because this simulation gives women in the LSS additional smoking pack-years without changing the number of cancer events, the primary consequence appears to be a diluting of the ERR of lung cancer for smoking, or that smoking is less detrimental than would be expected. The male smoking-related ERR did not decrease in a similar manner as the female parameter. Since we simulated additional smoking exposure only simulated for women, and it is reasonable that the male estimates were minimally affected. The radiation-associated risks for lung cancer in women did not decrease as we had hypothesized, and our method of simulating passive smoke for women did not attenuate the F:M ratio towards one. However, given the exploratory nature of our simulation, our results cannot rule out the possibility that passive smoke contributes to the high F:M ratio.

We had hypothesized that the high radiation-related F:M ratio seen in our analysis and in previous studies[3,8] came partly as a result of insufficient adjustment for smoking exposure, given the vast differences in smoking behavior amongst men and women in this cohort. We wanted to investigate this issue because there are real-world implications. Risk estimates calculated from LSS data are used to set regulatory limits for exposure to ionizing radiation worldwide. For example, NASA uses the LSS risk estimates to determine the amount of radiation exposure that male and female astronauts can be subjected to in space. Currently, female astronauts are allowed less time in space based on their higher ERR for lung cancer compared to men.

By simulating additional smoke exposure for women in the LSS, we sought to determine if this differential radiation risk by sex could be explained by passive smoke. In non-smoking Japanese women, passive smoking from husbands has previously been associated with a 30% excess risk of lung cancer according to a population-based study.[4] This risk tends to increase with the amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers.[10] Our simulation methods were not able to account for such dose-response trends, which likely would have represented the effects of passive smoke exposure more accurately.

Further work should investigate the effect of passive smoke by histological type of lung cancer. There is evidence that passive smoking exposure increases the risk for adenocarcinoma, the predominant lung cancer type in nonsmoking women.[4] Another study has shown that the relative effect of radiation may be larger for adenocarcinoma than for other lung cancer types in the LSS,[11] suggesting that adenocarcinomas may be more sensitive to radiation. While the present analysis considered all lung cancer types together, passive smoking and radiation may have different effects on different subtypes of lung cancer, and thus further research is needed to understand these relationships.

This analysis was an exercise in simulating passive smoke exposure, as no actual data on passive smoke were available for analysis. Our simulation model was simple and possibly insufficient. While we relied on available cohort data to inform how we designated the smoking patterns in our simulations, these assumptions are based on partial information since smoking data were available for only ~60% of the cohort. A more recent LSS survey captured data on passive smoke. However, given that completion of those passive smoke survey items was confined to participants who had survived almost 50 years after the atomic bombs, those data are limited and unlikely to be representative of the experiences of the full LSS cohort. In addition, this analysis was focused on passive smoke acquired from husbands by using marital status in our simulation methods. Women also could have acquired passive smoke through parental smoking, although a previous case control study on passive smoking in LSS women did not find increased risk for lung cancer associated with parental smoking,[10] and so we did not incorporate this into our simulation.

In summary, our approach to simulating passive smoke in the LSS yielded a higher F:M ratio, contrary to our hypothesis. The differential radiation risks for men and women persist throughout all of our simulation scenarios, and it remains an open question for investigation. Future research should explore other underlying factors for this observed difference, whether they be statistical artifacts, biological mechanisms, or some other factor.

Table 1: Lung cancer cases among Japanese Atomic Bomb Survivors from 1958 to 2009

		Lung Cancer Cases n (%)		
	Subjects	**Males**	**Females**	**Both**
City				
Nagasaki	32,043	448 (31.0)	293 (29.3)	741 (30.3)
Hiroshima	73,401	997 (69.0)	708 (70.7)	1705 (69.7)
Age at exposure				
0-19	45,159	588 (40.7)	277 (27.7)	865 (35.4)
20-39	30,071	429 (29.7)	476 (47.6)	905 (37.0)
40-49	16,232	305 (21.1)	167 (16.7)	472 (19.3)
50+	13,982	123 (8.5)	81 (8.1)	204 (8.3)
Attained age				
0-39		4 (0.3)	3 (0.3)	7 (0.3)
40-49		21 (1.5)	16 (1.6)	37 (1.5)
50-59		150 (10.4)	101 (10.1)	251 (10.3)
60-69		463 (32.0)	247 (24.7)	710 (29.0)
70-79		546 (37.8)	344 (34.4)	890 (36.4)
80+		261 (18.1)	290 (29.0)	551 (22.5)
Radiation Dose (Gy)				
NIC	25,239	373 (25.8)	227 (22.7)	600 (24.5)
0-0.005	35,172	476 (32.9)	297 (29.7)	773 (31.6)
0.005-0.1	27,441	338 (23.4)	242 (24.2)	580 (23.7)
0.1-0.2	5,631	68 (4.7)	65 (6.5)	133 (5.4)
0.2-0.5	6,050	78 (5.4)	76 (7.6)	154 (6.3)
0.5-1	3,411	53 (3.7)	43 (4.3)	96 (3.9)
1-2	1,806	40 (2.8)	39 (3.9)	79 (3.2)
2+	694	19 (1.3)	12 (1.2)	31 (1.3)
Smoking status				
Never		41 (2.8)	408 (40.8)	449 (18.4)
Past		159 (11.0)	43 (4.3)	202 (8.3)
Current		817 (56.5)	185 (18.5)	1002 (41.0)
Unknown		428 (29.6)	365 (36.5)	793 (32.4)
Total		**1445**	**1001**	**2446**

Table 2: Lung cancer cases by sex, smoking status, marital status and radiation dose from 1958 to 2009

	Radiation Dose (Gy)					
	NIC	0-0.1	0.1-0.5	0.5-1	1+	Total
Smoking status	**Men**					
Never	8 (2.1)	30 (3.7)	2 (1.4)	1 (1.9)	0 (0.0)	41
Past	16 (4.3)	114 (14.0)	20 (13.7)	4 (7.5)	5 (8.5)	159
Current	180 (48.3)	468 (57.5)	94 (64.4)	35 (66.0)	40 (67.8)	817
Unknown	169 (45.3)	202 (24.8)	30 (20.5)	13 (24.5)	14 (23.7)	428
Marital Status						
Never	0 (0.0)	4 (0.5)	2 (1.4)	0 (0.0)	1 (1.7)	7
Ever	87 (23.3)	525 (64.5)	87 (59.6)	27 (50.9)	30 (50.8)	756
Unknown	286 (76.7)	285 (35.0)	57 (39.0)	26 (49.1)	28 (47.5)	682
Total	**373**	**814**	**146**	**53**	**59**	**1445**
Smoking status	**Women**					
Never	76 (33.5)	222 (41.2)	57 (40.4)	29 (67.4)	24 (47.1)	408
Past	3 (1.3)	31 (5.8)	6 (4.3)	1 (2.3)	2 (3.9)	43
Current	36 (15.9)	90 (16.7)	38 (27.0)	8 (18.6)	13 (25.5)	185
Unknown	112 (49.3)	196 (36.4)	40 (28.4)	5 (11.6)	12 (23.5)	365
Marital Status						
Never	0 (0.0)	18 (3.3)	3 (2.1)	2 (4.7)	0 (0.0)	23
Ever	30 (13.2)	271 (50.3)	62 (44.0)	20 (46.5)	20 (39.2)	403
Unknown	197 (86.8)	250 (46.4)	76 (53.9)	21 (48.8)	31 (60.8)	575
Total	**227**	**539**	**141**	**43**	**51**	**1001**

Table 3A: Lung cancer parameter estimates and confidence intervals for smoking and radiation effects from 1958 to 2009

Additive Model							
	Background Rates		Radiation parameters ERR/Gy (age 70, age at exposure 30, nonsmoker)			Smoking Parameters ERR/50 pack-years (born in 1915)	
Adjustment Factor* (married, unmarried)	Male	Female	Male[a], β_m	Female[a], β_f	F:M ratio, β_m/β_f	Male, $e^{\varphi 0m}$	Female, $e^{\varphi 0f}$
Reference	1.91	1.66	0.778	1.53	1.97	5.75	6.33
1,1	1.96	1.60	0.813	1.71	2.10	5.44	6.72
5,5	2.00	1.54	0.835	1.84	2.20	5.15	6.84
10,10	2.04	1.51	0.846	1.91	2.26	4.88	6.37
20,20	2.04	1.51	0.870	1.95	2.24	4.84	4.15
25,25	2.01	1.52	0.892	1.93	2.16	5.02	3.16
30,30	1.95	1.58	0.908	1.86	2.04	5.39	2.00
40,40	1.91	1.64	0.909	1.78	1.96	5.66	1.15
50,50	1.89	1.72	0.891	1.64	1.84	5.82	0.626
20,10	2.04	1.51	0.871	1.94	2.23	4.87	4.11
30,10	1.95	1.58	0.909	1.85	2.04	5.40	1.99
40,10	1.91	1.65	0.910	1.77	1.95	5.68	1.13
50,10	1.88	1.73	0.890	1.62	1.82	5.84	0.595
50, 25	2.01	1.52	0.898	1.95	2.17	5.02	3.17
75, 25	2.00	1.53	0.900	1.93	2.14	5.10	2.92

*Adjustment factor is the proportional multiplier (c) that is applied to the male average smoking intensity in calculating a simulated average smoking intensity value for women

[a] Risk for a nonsmoker at age 70 after an exposure at 1 Gy at age 30

[b] Risk at age 70 for an individual with no radiation exposure who was born in 1915 and smoked a pack of cigarettes per day for 50 years

Table 3B: Lung cancer parameter estimates and confidence intervals for smoking and radiation effects from 1958 to 2009

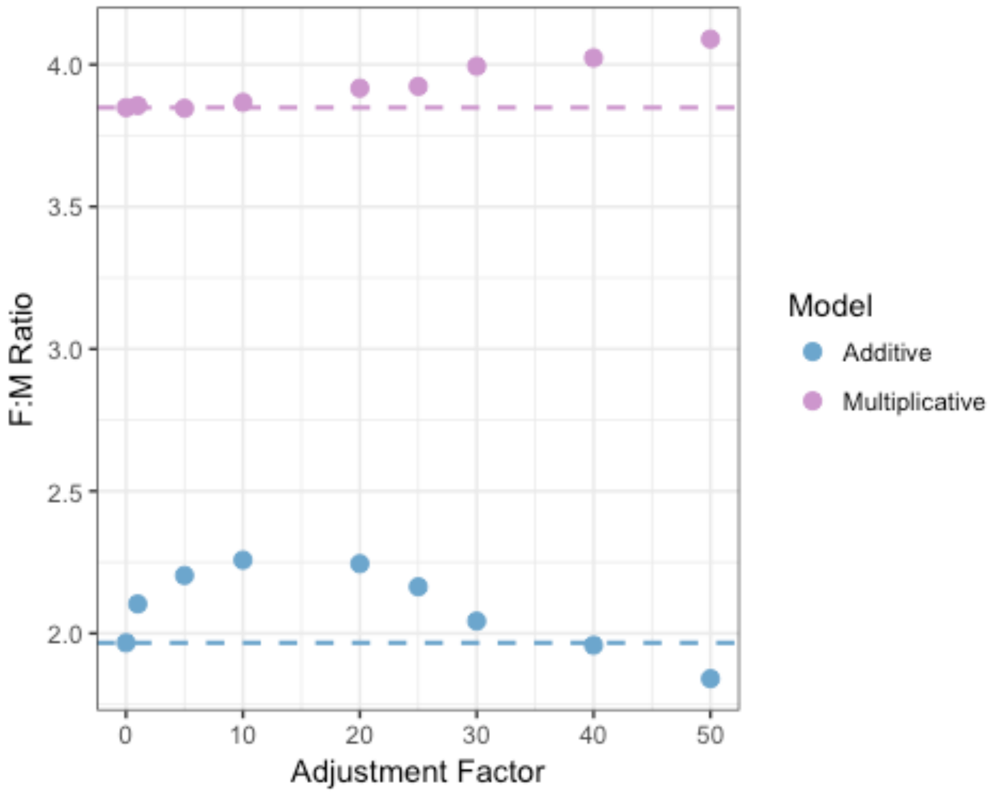
Multiplicative Model							
	Background Rates		Radiation parameters ERR/Gy (age 70, age at exposure 30)			Smoking Parameters ERR/50 pack-years (born in 1915)	
Adjustment Factor (married, unmarried)	Male	Female	Male[a], β_m	Female[a], β_f	F:M ratio, β_m/β_f	Male[b], $e^{\varphi 0m}$	Female[b], $e^{\varphi 0f}$
Reference	1.97	1.67	0.317	1.22	3.85	4.40	4.81
1,1	1.98	1.67	0.319	1.23	3.86	4.33	4.34
5,5	1.98	1.59	0.325	1.25	3.85	4.32	4.52
10,10	1.98	1.53	0.331	1.28	3.87	4.33	4.19
20,20	1.96	1.53	0.337	1.32	3.92	4.39	2.87
25,25	1.95	1.53	0.339	1.33	3.92	4.49	2.43
30,30	1.95	1.59	0.338	1.35	3.99	4.49	1.79
40,40	1.95	1.64	0.338	1.36	4.02	4.49	1.18
50,50	1.93	1.71	0.335	1.37	4.09	4.58	0.703
20,10	1.96	1.53	0.337	1.32	3.92	4.40	2.88
30,10	1.94	1.59	0.338	1.35	3.99	4.50	1.80
40,10	1.94	1.64	0.337	1.36	4.04	4.51	1.17
50,10	1.92	1.72	0.335	1.36	4.06	4.62	0.681
50, 25	1.95	1.53	0.34	1.34	3.94	4.46	2.42
75, 25	1.96	1.54	0.34	1.34	3.94	4.43	2.29

*Adjustment factor is the proportional multiplier (c) that is applied to the male average smoking intensity in calculating a simulated average smoking intensity value for women

[a] Risk among individuals of the same smoking status at age 70 after an exposure at 1 Gy at age 30

[b] Risk at age 70 for individuals with the same radiation dose exposure who were born in 1915 and smoked a pack of cigarettes per day for 50 years

Figure 1: Estimates for the radiation-related Female:Male ratio across passive smoke simulation scenarios



*Adjustment factor applied equally to married and unmarried women

Appendix: Alternative methods for passive smoke approximation

Methods

Our approach to simulating passive smoke exposure was to use the cross-tabulated person-year life tables and match men and women of similar birth cohorts, and then give women some proportion of the average male smoking. We hypothesized that a proxy for passive smoke exposure in women could be some portion of male smoking patterns for men of the same birth cohort. To do this, we created birth cohort groups defined by the categorical variables: age at exposure (0-5 yrs, 5-10 yrs, 10-15 yrs, 15-20 yrs, 20-25 yrs, 25-30 yrs, 30-35 yrs, 35-40 yrs, 40-45 yrs, 45-50 yrs, 50-55 yrs, 55-60 yrs, 60-65 yrs, 65-70 yrs, 70+ yrs), attained age (0-5 yrs, 5-10 yrs, 10-15 yrs, 15-20 yrs, 20-25 yrs, 25-30 yrs, 30-35 yrs, 35-40 yrs, 40-45 yrs, 45-50 yrs, 50-55 yrs, 55-60 yrs, 60-65 yrs, 65-70 yrs, 70-75 yrs, 75-80 yrs, 80-85 yrs, 85+ yrs) city (Hiroshima or Nagasaki), and radiation dose (0-150 mGy, 150-1000 mGy, 1000-3000+ mGy, not in city).

A weighted average of smoking pack years was calculated for each birth cohort of males (n = 815 birth cohort groups). Then, we matched men and women of the same birth cohort group and simulated additional smoking in women with a known smoking status as a proportion of the male smoking patterns. The proportion of male smoking attributed to women by birth cohort varied between 1-75%. This resulted in a higher F:M ratio, but eventually the model was unable to cover past 40%.

In addition, we tried another scenario in which we increased smoking for just women where were exposed to higher dose radiation (1-3+ Gy). By doing so, we noticed that the F:M ratio decreased and came closer to 1 at higher proportions.

Preliminary Results

Increased smoking in all women with known smoking status

Multiplicative Model							
	Background Rates		Radiation parameters ERR/Gy (age 70, age at exposure 30)			Smoking Parameters ERR/50 pack-years (born in 1915)	
Adjustment Factor (% of mpy50)	Male	Female	Male[a], β_m	Female[a], β_f	F:M ratio, β_m/β_f	Male[b], $e^{\varphi 0m}$	Female[b], $e^{\varphi 0f}$
Reference	1.919	1.673	0.3215	1.2317	3.832	4.680	4.972
1	1.916	1.203	0.3229	1.249	3.867	4.682	7.833
5	1.918	1.462	0.3222	1.240	3.848	4.681	6.120
10	1.916	1.203	0.3229	1.249	3.867	4.682	7.833
15	1.915	0.878	0.3237	1.259	3.889	4.682	10.644
20	1.914	0.441	0.324	1.269	3.912	4.683	16.057
30	1.912	-2.178	0.3255	1.289	3.961	4.685	205.59
40	NA	NA	NA	NA	NA	NA	NA

Increased smoking in just women exposed to higher dose radiation (1000-3000 mGy)

Multiplicative Model							
	Background Rates		Radiation parameters ERR/Gy (age 70, age at exposure 30)			Smoking Parameters ERR/50 pack-years (born in 1915)	
Adjustment Factor (% of mpy50)	Male	Female	Male[a], β_m	Female[a], β_f	F:M ratio, β_m/β_f	Male[b], $e^{\varphi 0m}$	Female[b], $e^{\varphi 0f}$
Reference	1.919	1.673	0.3215	1.2317	3.832	4.680	4.972
1	1.919	1.673	0.3206	1.2491	3.772	4.679	4.987
5	1.920	1.674	0.3170	1.125	3.548	4.679	5.014
10	1.922	1.678	0.3126	1.031	3.297	4.679	5.002
15	1.923	1.682	0.3079	0.9467	3.075	4.679	4.959
20	1.924	1.687	0.3030	0.8721	2.878	4.678	4.902
30	1.926	1.697	0.2930	0.7462	2.547	4.678	4.769
40	1.928	1.706	0.2829	0.6445	2.278	4.677	4.631
50	1.930	1.715	0.2728	0.5612	2.057	4.677	4.497
75	1.933	1.733	0.2490	0.4096	1.645	4.675	4.185

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