BioOne COMPLETE

# Effects of Radiation and Lifestyle Factors on Risks of Urothelial Carcinoma in the Life Span Study of Atomic Bomb Survivors

Authors: Grant, E. J., Ozasa, K, Preston, D. L., Suyama, A, Shimizu, Y, et al.

Source: Radiation Research, 178(1) : 86-98

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR2841.1

BioOne Complete (complete.BioOne.org) is a full-text database of 200 subscribed and open-access titles in the biological, ecological, and environmental sciences published by nonprofit societies, associations, museums, institutions, and presses.

Your use of this PDF, the BioOne Complete website, and all posted and associated content indicates your acceptance of BioOne's Terms of Use, available at www.bioone.org/terms-of-use.

Usage of BioOne Complete content is strictly limited to personal, educational, and non - commercial use. Commercial inquiries or rights and permissions requests should be directed to the individual publisher as copyright holder.

BioOne sees sustainable scholarly publishing as an inherently collaborative enterprise connecting authors, nonprofit publishers, academic institutions, research libraries, and research funders in the common goal of maximizing access to critical research.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

RADIATION RESEARCH **177**, 86–98 (2012)
0033-7587/12 $15.00
©2012 by Radiation Research Society.
All rights of reproduction in any form reserved.
DOI: 10.1667/RR2841.1

# Effects of Radiation and Lifestyle Factors on Risks of Urothelial Carcinoma in the Life Span Study of Atomic Bomb Survivors

E. J. Grant,[a,1] K. Ozasa,[a] D. L. Preston,[d] A. Suyama,[a] Y. Shimizu,[a] R. Sakata,[a] H. Sugiyama,[a] T-M. Pham,[a] J. Cologne,[b] M. Yamada,[c] A. J. De Roos,[e] K. J. Kopecky,[f] M. P. Porter,[e] N. Seixas[g] and S. Davis[e]

[a] *Department of Epidemiology,* [b] *Department of Statistics and* [c] *Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Japan;* [d] *Hirosoft International, Eureka, California;* [e] *Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington;* [f] *Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; and* [g] *Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, Washington*

**Grant, E. J., Ozasa, K., Preston, D. L., Suyama, A., Shimizu, Y., Sakata, R., Sugiyama, H., Pham, T-M., Cologne, J., Yamada, M., De Roos, A. J., Kopecky, K. J., Porter, M. P., Seixas, N. and Davis, S. Effects of Radiation and Lifestyle Factors on Risks of Urothelial Carcinoma in the Life Span Study of Atomic Bomb Survivors. *Radiat. Res*. 177, 86–98 (2012).**

**Among the Life Span Study (LSS) of Atomic-bomb survivors, recent estimates showed that unspecified bladder cancer had high radiation sensitivity with a notably high female-to-male excess relative risk (ERR) per radiation dose ratio and were the only sites for which the ERR did not decrease with attained age. These findings, however, did not consider lifestyle factors, which could potentially confound or modify the risk estimates. This study estimated the radiation risks of the most prevalent subtype of urinary tract cancer, urothelial carcinoma, while accounting for smoking, consumption of fruit, vegetables, alcohol and level of education (a surrogate for socioeconomic status). Eligible study subjects included 105,402 (males = 42,890) LSS members who were cancer-free in 1958 and had estimated radiation doses. Members were censored due to loss of follow-up, incident cancer of another type, death, or the end of calendar year 2001. Surveys (by mail or clinical interview) gathered lifestyle data periodically for 1963–1991. There were 63,827 participants in one or more survey. Five hundred seventy-three incident urothelial carcinoma cases occurred, of which 364 occurred after lifestyle information was available. Analyses were performed using Poisson regression methods. The excess relative risk per weighted gray unit (the gamma component plus 10 times the neutron component, $Gy_w$) was 1.00 (95% CI: 0.43–1.78) but the risks were not dependent upon age at exposure or attained age. Lifestyle factors other than smoking were not associated with urothelial carcinoma risk. Neither the magnitude of the radiation ERR estimate (1.00 compared to 0.96), nor the female-to-male (F:M) ERR/$Gy_w$ ratio (3.2 compared to 3.4) were greatly changed after accounting for all lifestyle factors. A multiplicative model of gender-specific radiation and smoking effects was the most revealing though there was no evidence of significant departures from either the additive or multiplicative joint effect models. Among the LSS cohort members with doses greater than 0.005 $Gy_w$ (average dose 0.21 $Gy_w$), the attributable fraction of urothelial carcinoma due to radiation was 7.1% in males and 19.7% in females. Among current smokers, the attributable fraction of urothelial carcinoma due to smoking was 61% in males and 52% in females. Relative risk estimates of smoking risk were approximately two for smokers compared to nonsmokers. After adjustment for lifestyle factors, gender-specific radiation risks and the F:M ERR/$Gy_w$, the ratios of excess urothelial carcinoma risk were similar to the estimates without adjusting for lifestyle factors. Smoking was the primary factor responsible for excess urothelial carcinoma in this cohort. These findings led us to conclude that the radiation risk estimates of urothelial carcinoma do not appear to be strongly confounded or modified by smoking, consumption of alcohol, fruits, or vegetables, or level of education.** **© 2012 by Radiation Research Society**

[1]Address for correspondence: Radiation Effects Research Foundation, Epidemiology, 5-2 Hijiyama Park, Minami-ku, Japan; e-mail: egrant@rerf.or.jp.

## INTRODUCTION

Numerous epidemiological studies have reported associations between ionizing radiation (IR) exposure and bladder cancer (*1–6*), while others have reported associations between lifestyle factors and bladder cancer, particularly smoking (*7–11*). In the most recent cancer incidence report on the Life Span Study (LSS) of A-bomb survivors, the urinary bladder had the highest excess relative risk (ERR) per unit dose of radiation of any of the solid cancers other than the female breast (ERR/gray weighted bladder dose = 1.23) (*1*). Despite the known associations of bladder cancer with lifestyle factors, studies attempting to quantify the risk of bladder cancer after ionizing radiation exposure have often not evaluated the effects of lifestyle factors. Concerns that smoking or other unaccounted for factors may confound or modify established bladder radiation risk estimates have been voiced in recent UNSCEAR and ICRP reports, and in the last LSS cancer incidence report (*1, 12–14*). Recently, evidence of ionizing radiation and smoking joint effects have been reported for lung cancer in the LSS,



Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

which further raises the possibility that lifestyle factors could modify bladder cancer risk estimates (*15*). The purpose of this study was to estimate the ionizing radiation risk of the most common subtype of bladder cancer (urothelial carcinoma) in the LSS cohort using the same methods as those used to derive the most recent ionizing radiation risk estimates, but with the inclusion of lifestyle factors to establish whether urothelial carcinoma radiation risk estimates were either confounded or modified by lifestyle factors.

Rather than use the broader classification of bladder cancer to define our cases, we decided to include only persons diagnosed with urothelial carcinoma. Urothelial carcinomas are more closely associated with lifestyle factors, whereas non-urothelial carcinoma bladder cancers are often associated with infections, foreign bodies or invasive cancers from neighboring organs (*16*). Ninety percent of all cancers that occur in the bladder (*17–19*) and in the urothelium of the upper urinary tract (*20*) are urothelial carcinoma. Due to the common epithelium of origin, all urothelial carcinoma have similar risk factors (*18, 21*).

In Japan, the world age-standardized rate for the incidence of bladder cancer was 8.2/100,000 in males and 2.0/100,00 in females accounting for 2.6% of all cancers estimated to have occurred in 2000 (*22*). A higher incidence in males is seen consistently regardless of country (*23*). Western European and North American rates are generally higher than Asian rates (*17*).

Lifestyle factors reported to be clearly associated with bladder cancer include smoking (*7, 8*), occupational exposures to certain chemicals, particularly aromatic amines (*9, 10*), and excessive use of certain analgesics (*24*). Tobacco from cigarettes is the most common factor in the occurrence of excess bladder cancer, accounting for 30–50% of all cases, with a relative risk of 2–3 for smokers compared to nonsmokers (*17, 18*). A diet that includes fruits and vegetables is generally thought to offer some protection against bladder cancer, although the literature is mixed on the association with vegetables (*11, 25*). Conflicting results on the association between urothelial carcinoma and alcohol intake have been reported, ranging from positive (*26*), to no association (*27–29*) to an inverse association (*30*). Because socioeconomic status is broadly associated with overall health (*31*), we included level of education as a surrogate for socioeconomic status.

To determine if lifestyle factors confound or modify ionizing radiation risks of bladder cancer, this study estimated radiation risks of urothelial carcinomas while adjusting for relevant lifestyle factors where data were available. Lifestyle factors included smoking, level of education, consumption of fruit, vegetables and alcohol. Standard risk factors (e.g., age, gender, etc.) used to model background rates were the same as in the previous incidence study.

## METHODS

The RERF LSS cohort consists of 120,321 A-bomb survivors. The cohort includes a substantial fraction of all survivors who were within 2.5 km of the hypocenters at the time of the bombings along with a stratified sample of survivors who were 2.5–10 km away from the hypocenters, and a separate control group who were registered as residents but who were not in the cities (NIC) at the time of the bombings. Eligibility was defined as LSS cohort members who have an individual radiation dose to the bladder assigned by Dosimetry System 2002 (DS02, $N = 7{,}070$ excluded) (*32*), and were alive and not known to have been diagnosed with cancer when comprehensive cancer incidence surveillance was initiated in January 1958 (*33*) (an additional 7,849 excluded).

DS02-assigned gamma and neutron doses from external sources were based on the characteristics of the bombs and an individual's distance and shielding circumstances; no allowance was made for possible doses via fallout or ingestion, the incidence of which were considered to be small (*34*), as well as highly problematic to estimate due to the lack of individual histories for large portions of the cohort in the period immediately following the bombings. Radiation dose estimates used in this analysis were adjusted to account for random errors in the individual radiation dose estimates (*35*) and the total dose was calculated as the gamma component plus 10 times the neutron component to account for the greater biological effectiveness of neutron exposures, as is typically carried out when analyzing the A-bomb survivor cohort.

The total number of eligible subjects was 105,402 (males = 42,890; females = 62,512). An outcome event was the diagnosis of a first primary, malignant urothelial carcinoma [International Classification of Diseases — Oncology Codes 188, 189.1, 189.2 (Revision 2), and C65-C67 (Revision 3) with a morphology code 8010, 8050, 8120, or 8130] detected among persons residing within the catchment areas of the tumor registries. Those diagnosed without histology information (i.e. from death certificates only, $N = 44$ of 695 bladder, ureter or renal pelvis diagnoses) were generally assigned as ''Carcinoma, not otherwise specified'' (morphology code 8010) and were therefore included as cases. Right censoring analysis occurred at the time of a non-urothelial carcinoma cancer diagnosis, death, or end of study period (December, 2001).

Lifestyle factors were ascertained from four mailed questionnaires (1965, 1969, 1979, 1991) (*36–39*) and three clinic-based questionnaires given to a subset of the LSS from 1963–1968 (*36, 40*) (Fig. 1). Despite high participation rates, different questionnaires were targeted at different subgroups (for example, the 1965 survey targeted only males aged 40–69 and the 1979 and 1991 questionnaires did not include the NIC members), resulting in less than 100% coverage of the cohort. The total number of eligible cohort members (cancer-free with a known radiation dose) who participated in a questionnaire was 63,827 and the cumulative total of questionnaires was 118,170. Since questionnaire data were not collected until after cancer surveillance had begun, lifestyle factors were initially assigned to the ''Unknown'' category and continued to be in that category until they were assigned to a derived value one year after the date the survey results were obtained. Methods of calculating the derived survey values are described below.

### *Smoking*

Smoking data were available from all surveys. ''Never'', ''Current'' and ''Former'' smoking categories were assigned for each questionnaire in a logically consistent manner (i.e. a transition from ''Never'' to ''Current'' was allowed, but a transition from ''Current'' to ''Never'' was not allowed). The last known status continued until the end of follow-up. For those who smoked, the earliest start age and the latest stop age were calculated. Smoking intensity was recorded for each questionnaire. Time varying values for ''years since started smoking'', ''years since quitting smoking'' and pack-years (by

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

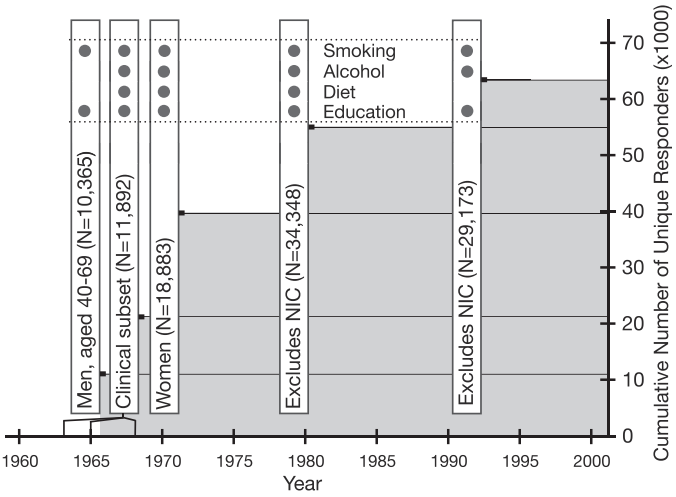



**FIG. 1.** Mail and clinical questionnaires of the Life Span Study cohort conducted by the Radiation Effects Research Foundation. Each survey is shown in a box that details the number of eligible subjects who participated in the survey and the cohort members targeted. The bullets within the dotted box indicate which lifestyle factors were included on each survey. The gray area indicates the total number of persons with known lifestyle data by calendar year while the horizontal lines indicate the cumulative number of unique survey responders (right axis). The clinical subset survey was actually three repeated surveys each of approximately 9,000 persons; the number indicated (11,892) is the total number of unique, eligible responders. Cancer surveillance started in 1958 and the number of eligible cohort members was 105,402. A total of 63,829 unique persons were surveyed.

integrating period-specific smoking intensity) were calculated. When known smokers failed to record start age (or intensity) on all questionnaires, the median value from LSS smoking peers of the same gender and birth year (five-year intervals) was assigned (males = 1,214; females = 709). Values were assigned 1 year after receipt of each questionnaire. For example, a person who started smoking in 1940 (two packs/day) and responded to their first questionnaire in 1965 would be assigned an intensity of two packs/day, 25 ''years since started smoking'', 0 ''years since quitting smoking'', and 50 pack-years as of a year after their questionnaire (1966). Time-dependent values (in this case, ''years since started smoking'' and ''pack-years'') would accumulate with each additional year of follow-up or until (a year after) newer information was ascertained via a later questionnaire; all smoking-related variables would be assigned to ''Unknown'' prior to 1966.

*Fruit and Vegetable Consumption*

Food frequency questions targeting fruit and vegetable consumption (separately) were available from two of the three clinical questionnaires as well as from the 1969 and 1979 LSS mail questionnaires. The clinical questionnaires and the 1969 mail questionnaire used 3-level frequency checkboxes (0–1/week, 2–4/week, almost daily). The 1978 mail questionnaire had 4-level frequency checkboxes (never, 1/week, 2–4/week, almost daily), which was collapsed to three categories by combining the two lowest frequency categories. A single category (0–1/week, 2–4/week, almost daily) was assigned for each person by first assigning a category (0, 1 or 2) for each survey and then taking the median value for each person across all surveys (median values of 0.5 and 1.5 were assigned to the center category 1). The derived category was assigned for the duration of follow-up as of the date of the first questionnaire plus one year; prior to this date, they were assigned to the ''Unknown'' category.

*Alcohol Consumption*

Alcohol consumption data were available from all questionnaires except the 1965 mail survey. For each survey, total grams of ethanol consumption per week were calculated from alcohol type and consumption frequency. The median value across surveys was determined for each individual and this value was assigned as of the date of the first questionnaire plus one year and continued, unchanged, throughout the follow-up period; prior to this date, they were assigned to ''Unknown''. Results are reported in drinks/week (defined as one drink/15 grams of ethanol).

*Education*

Highest obtained level of educational was used as a surrogate for socio-economic status. All questionnaires, except the last clinical survey, included a question on the highest level of education. Three categories were used (less than high school, high school, college or university), and the highest reported category was assigned starting one year after the receipt of the first questionnaire (assigned to ''Unknown'' prior to this date).

*Statistical Analyses*

Poisson regression methods (*41, 42*) were used to model background rates and the effects of ionizing radiation exposure as ERR, and excess absolute rates (EAR). Lifestyle effects were modeled as either a component of the background term or a separate ERR term. The data set was cross-tabulated on city, gender, NIC status, age at exposure (5-year groups, 0, 5, 10,..., $\geq$70 years), attained age (5-year groups, 0, 5, 10, ..., 85–100 years), calendar year (cut points at: 1961, 1966, 1971, 1976, 1981, 1986, 1988, 1991, 1996, 1999), and radiation dose to the urinary bladder (cut points at: 5, 20, 40, 60, 80, 100, 125, 150, 175, 200, 250, 300, 500, 750, 1000, 1250, 1500, 1750, 2000, 2500, $\geq$3000 mGy). NIC members consist of a broad range of nonexposed subjects. Additional cases from the NIC members enhanced stability of the background rates of urothelial carcinoma incidence. For those who smoked, cross-tabulation included time-varying levels of intensity (cut points at: 3, 8, 13, 18, 23, 33, 43> cigarettes/day), duration of smoking, and years since quitting (cut points at: 5, 10, 20, 30> years). Cut points were generally chosen to make counts similar across the groups. Alcohol consumption was also cross-tabulated (cut points at: 0, 100, 200, 300> grams of ethanol/week, roughly 0, 1, 2, 3> drinks/day, respectively). Other lifestyle factors (fruit consumption, vegetable consumption and level of education) were cross-tabulated using the categories described above. Each lifestyle factor included an ''Unknown'' category. For each cross-tabulated cell, totals of person-years and incident cases were also calculated. The final data set contained 466,429 cells. The cancer registries are only able to track cancer cases that occur within the Hiroshima and Nagasaki prefectures, which means that we will not be aware of some portion of cases that occur among those who have migrated outside of the catchment areas. Therefore, adjustments were made to cell-specific person-year totals depending on city, gender, age and calendar year to account for migration into and out of the catchment areas of the cancer registries. Migration estimates are based upon contacting rates within RERF's clinical follow-up cohort and are age, gender and birth-year dependent as described in Sposto *et al.* (*43*).

The excess relative risk model was written as:

$$\text{Expected rate of urothelial carcinoma} = \text{background rate}\,(c, g, n, e, a[, f]) * (1 + \beta * \text{dose}[* \text{modifiers}]). \quad \text{Eq. (1)}$$

A gender-specific parametric model was used for background rates. This function was the same as the Preston *et al.* model (*1*) except for

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

**TABLE 1**
**Number of Persons, Person-Years and Case Counts**

| | Males | Females | All |
|---|---|---|---|
| All subjects | | | |
| Count | 42,890 | 62,512 | 105,402 |
| Person-years | $108 \times 10^4$ | $180 \times 10^4$ | $288 \times 10^4$ |
| Age at time of bombing (average) | 26.1 | 27.9 | 27.2 |
| Incident cases | 375 | 198 | 573 |
| Responders | | | |
| Count | 24,688 | 39,139 | 63,827 |
| Person-years | $38 \times 10^4$ | $74 \times 10^4$ | $112 \times 10^4$ |
| Age at time of bombing (average) | 23.6 | 24.0 | 23.9 |
| Age at first questionnaire (average) | 52.4 | 52.6 | 52.5 |
| Incident cases | 243 | 121 | 364 |

*Notes*. The upper section is for all subjects over the full duration of the study (1958–2001). The lower section is for subjects who responded to a questionnaire. ''Person-years'' and ''Incident cases'' in the lower section accrue one year after participating in a survey.

the inclusion of optional lifestyle factors. The log of the expected background rate was dependent upon:

c: city (Hiroshima 0, Nagasaki 1);
g: gender (male 1, female 2);
n: not-in-city status (0 in city, 1 NIC), also included an interaction term by city;
e: age at the time of the bombing (piecewise quadratic function, centered at age 30);
a: attained age (piecewise quadratic function of log attained age, centered at age 70);
f: lifestyle factor (optionally included, as defined above).

The ERR term was linear with dose and included optional effect modifiers that could be either continuous or categorical using indictor variables. Optional effect modifiers included gender, age at exposure, attained age, and lifestyle factors. Models that included lifestyle effects used all person-years and all events, but only person-years with known information on lifestyle factors contributed to lifestyle effects estimates. Lifestyle effects were alternatively modeled as ''multiplicative'' or ''additive'' to the radiation risks. If the lifestyle was a component of the background term, the radiation effect was relative to, or ''multiplicative'' of the lifestyle-adjusted background rates. If the lifestyle factor was removed from the background term and included in the ERR term, then the radiation and lifestyle effects were ''additive'' and their summed effects were relative to the background rates. Statistical tests for departures from the preceding multiplicative or additive ERR models were also performed [see Pierce *et al*. for a more complete development of these methods (*44*)]. Sub-analyses included calculations of radiation and smoking attributable fractions using an additive ERR model. Another sub-analysis modeled pack-years of smoking as an additive ERR term to model total smoking exposure as suggested by Lubin *et al*. (*45*).

A separate model form evaluated the excess absolute rates (EAR) of urothelial carcinoma due to radiation exposure, which takes the form:

$$\text{Expected rate of UN} = \text{background rate}(c, g, n, e, a[, f]) + \text{EAR}(d, g, e, a) \quad \text{Eq. (2)}$$

The ''background rate'' term is the same as the ERR model (i.e. a log-linear parametric model that can optionally include lifestyle factors). The EAR term models the excess absolute rate of cases due to radiation exposure (d) and can be modified by any factor that contributes to the background rates, in particular gender (g), age at exposure (e), and attained age (a).

Point estimates and 95% confidence intervals (two-sided) based on Wald statistics were reported for factors modeled in the log-linear background term. Confidence intervals based on the profile likelihood function were reported for ERR, EAR, and female-to-male risk ratio point estimates. Gender-averaged ERR estimates were arithmetic means of the gender-specific risks (not weighted means). ERR and EAR models were fit and evaluated using Epicure (*46*). Trends of lifestyle effects on urothelial carcinoma risks were tested by assigning ordinal values (0, 1, 2, ...) for ordered categories and evaluating the $P$ value for a linear fit (double-sided, significant at $P < 0.05$). Associations of radiation exposure with categories of lifestyle factors were assessed using tertiles of radiation exposure (excluding the NIC group) and testing using the Kruskal-Wallis equality-of-populations rank test as well as a nonparametric test for trends across ordered groups (*47*). Likelihood ratio tests (LRT) were used to quantify statistical improvements of model fit. Akaike Information Criteria (AIC) were used to compare goodness of fits among nonnested models (*48*).

This study was approved by RERF's Human Investigation Committee.

## RESULTS

Of the 105,402 eligible subjects, 57.6% of males and 62.6% of females participated in one or more surveys (Table 1). The total number of incident urothelial carcinoma cases was 573, of which 364 (64%) occurred at least one year after the subject had participated in a questionnaire. Nearly twice as many cases occurred in males as in females. Those who participated in a questionnaire were about 3.6 years younger at the time of the bombing compared to the overall cohort. Crude incidence rates of urothelial carcinoma were similar regardless of whether or not a cohort member ultimately participated in a survey (Nonresponders: 2.06/10,000 person-years; Responders: 1.96/10,000 person-years, data not shown).

The effects of gender-averaged lifestyle factors on urothelial carcinoma risk are shown in Table 2. Lifestyle factors were modeled as components of the background and each was modeled independently using an ERR model [Eq. (1)]. The radiation risk estimates while adjusting for each lifestyle factor, are presented separately (Table 3). A ''baseline model'' that did not include lifestyle factors was used as a null model for likelihood ratio tests. The structure of the baseline model was the same as used by Preston *et al*. (*1*) ERR model, only differing in the case definition, exit date, and lack of age-related radiation effect modifiers; the effect modifiers were removed because neither was statistically significant and their inclusion did not improve model fit ($P > 0.50$; data not shown). In the lifestyle-adjusted models, those suffering an event when their lifestyle information was ''unknown'' were included in a separate category; those results are not reported. Urothelial carcinoma risks generally decreased slightly with increasing levels of education, vegetable and fruit consumption; however none of the trend tests were significant (modeling a single term with the ordinal values and one degree of

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

**TABLE 2**
**Associations of Individual Lifestyle Factors with Urothelial Carcinoma**

| Lifestyle | Cases[a] | Relative risk | Lifestyle-related risks 95% CI | *P* (trend) | LRT |
|---|---|---|---|---|---|
| None (baseline model) | 573 | - | - | - | - |
| Education | | | | | |
| Less than High School | 176 | Ref | - | 0.24 | >0.50 |
| High School | 135 | 0.93 | 0.74–1.17 | | |
| College | 40 | 0.81 | 0.57–1.15 | | |
| Vegetable | | | | | |
| 0–1/week | 81 | Ref | - | 0.11 | 0.07 |
| 2–4/week | 109 | 0.72 | 0.54–0.97 | | |
| 4+/week | 40 | 0.75 | 0.51–1.10 | | |
| Fruit | | | | | |
| 0–1/week | 54 | Ref | - | 0.39 | 0.34 |
| 2–4/week | 85 | 0.71 | 0.51–1.02 | | |
| 4+/week | 103 | 0.81 | 0.58–1.14 | | |
| Alcohol | | | | | |
| 0 drinks/day | 109 | Ref | - | >0.50 | >0.50 |
| 0–1 drinks/day | 65 | 1.17 | 0.86–1.60 | | |
| 1–2 drinks/day | 40 | 0.99 | 0.67–1.47 | | |
| 2–3 drinks/day | 41 | 0.97 | 0.66–1.43 | | |
| >3 drinks/day | 36 | 0.97 | 0.64–1.46 | | |
| Smoking | | | | | |
| Never | 99 | Ref | - | <0.001 | <0.001 |
| Former | 45 | 1.21 | 0.83–1.78 | | |
| Current | 213 | 1.99 | 1.50–2.63 | | |

*Notes*. Relative risk, 95% confidence intervals, *P* value for trend test, and the improvement in model fit as determined by the likelihood ratio test (compared to the ''baseline model'', which was not adjusted for lifestyle factors). All estimates were derived with categories of a lifestyle modeled as part of the background term. Each model also included radiation as a gender-averaged excess relative risk term (ERR/weighted-Gy). Lifestyles were modeled individually and were not adjusted for each other. Radiation estimates adjusted for lifestyle factors are reported in Table 3.

[a]Case totals in lifestyle-adjusted models are less than the ''baseline model'' as they accrue only after questionnaire data have been ascertained. Also, case totals may not match in lifestyle-adjusted models due to missing data.

freedom), nor did the likelihood ratio tests indicate any improvements in overall model fits (each category modeled independently with three degrees of freedom). There was no suggestion of an association between urothelial carcinoma and alcohol consumption. On the other hand, the relative risk of smokers compared to never smokers was 1.99 (95% CI: 1.50–2.63), while those who indicated that they had quit smoking had a marginally elevated relative risk of 1.21 (95% CI: 0.83–1.78). The trend test for smoking (never, former, current) was highly significant as was the improvement in model fit ($P < 0.001$).

Table 3 shows the radiation risk estimates of urothelial carcinoma while adjusting for lifestyle factors. Gender-averaged ERR estimates of urothelial carcinoma and

**TABLE 3**
**Radiation-Related Risks Adjusted for Lifestyle Factors**

| Adjusted for Lifestyle Factor | Cases[c] | Radiation-related excess relative risks (ERR/$Gy_w$[a]) Gender-averaged | 95% CI | Gender ratio (F:M) | 95% CI | Radiation-related excess absolute rates[b] (EAR/$Gy_w$) Gender-averaged | 95% CI | Gender ratio (F:M) | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| - | 573 | 1.00 | 0.43–1.78 | 3.26 | 0.88–>10 | 3.02 | 1.05–5.40 | 0.70 | 0.19–4.86 |
| Education | 351 | 1.00 | 0.42–1.78 | 3.23 | 0.87–>10 | 2.97 | 0.98–5.35 | 0.71 | 0.19–>10 |
| Vegetable | 230 | 1.03 | 0.44–1.82 | 3.16 | 0.86–>10 | 3.11 | 1.10–5.51 | 0.65 | 0.18–>10 |
| Fruit | 242 | 1.04 | 0.44–1.84 | 3.23 | 0.89–>10 | 3.13 | 1.12–5.54 | 0.71 | 0.20–>10 |
| Alcohol | 291 | 1.00 | 0.42–1.77 | 3.20 | 0.85–>10 | 3.10 | 1.10–5.49 | 0.67 | 0.18–>10 |
| Smoking | 349 | 0.99 | 0.41–1.77 | 3.71 | 0.97–>10 | 2.40 | ND–4.75 | 1.02 | 0.19–>10 |

*Note*. Categories of lifestyle factors (modeled as gender-averaged background terms) were as shown in Table 2.

[a]Weighted gray ($Gy_w$) is the gamma component plus 10 times the neutron component.

[b]Rates are per 10,000 $P \cdot Y \cdot Gy_w$.

[c]Case totals in lifestyle-adjusted models accrue only after questionnaire data have been ascertained and may not match due to missing data.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

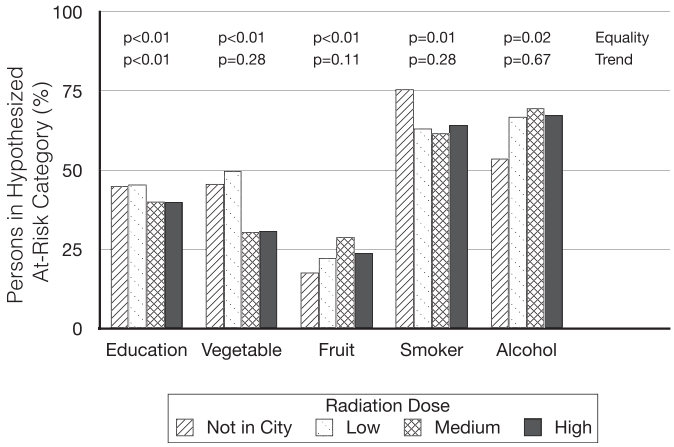



**FIG. 2.** Radiation dose categories compared to lifestyle categories in men. The percentages of men in the hypothesized at-risk categories are shown for 4 levels of radiation exposure. The ''at-risk'' categories were defined as the lowest category of vegetable and fruit consumption (0–1/week), the lowest category of education (less than high school), current smokers (as of the last questionnaire) and more than one drink of alcohol per day. *P* values associated with tests excluded ''not in city'' persons, as they were not included in questionnaires after 1965. ''Equality'' *P* values refer to the null hypotheses that frequencies of lifestyle categories (as defined in Table 2) were the same for each radiation exposure level (tertiles) using the Kruskal-Wallis equality-of-populations rank test. ''Trend'' *P* values were derived from a nonparametric test for a trend across ordered groups.

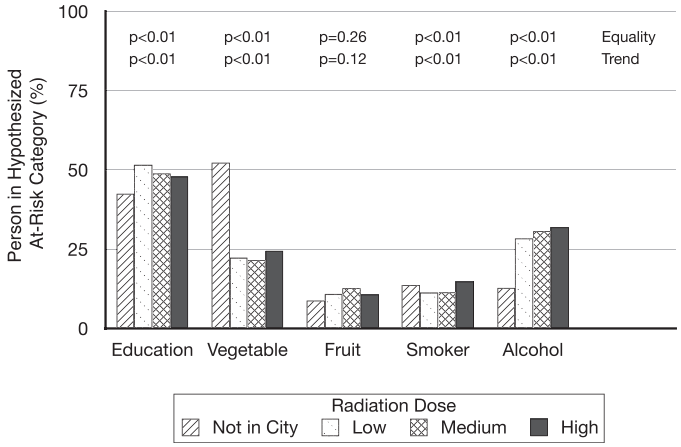



**FIG. 3.** Radiation dose categories compared to lifestyle categories in women. The percentages of women in the hypothesized at-risk categories are shown for 4 levels of radiation exposure. The ''at-risk'' categories were defined as the lowest category of vegetable and fruit consumption (0–1/week), the lowest category of education (less than high school), current smokers (as of the last questionnaire) and more than zero grams of alcohol per day. *P* values associated with tests excluded ''not in city'' persons, as they were not included in questionnaires after 1969. Equality *P* values refer to the null hypotheses that frequencies of lifestyle categories (as defined in Table 2) were the same for each radiation exposure level (tertiles) using the Kruskal-Wallis equality-of-populations rank test. Trend *P* values were derived from a nonparametric test for a trend across ordered groups.

female-to-male ERR per weighted-gray ratio (F:M ERR) are shown in Table 3. Lifestyle categories were the same as in Table 2. ERR risk estimates were largely unchanged when adjusting for each lifestyle factor and ranged from 0.99/$Gy_w$ (95% CI: 0.41–1.77) for the smoking-adjusted model to 1.04/$Gy_w$ (95% CI: 0.44–1.84) for the model adjusted for fruit consumption. These estimates were nearly the same as the ''baseline model'' estimate of 1.00/$Gy_w$ (95% CI: 0.43–1.78). Similarly, the F:M ERR ratios were quite stable ranging from 3.16–3.71 compared to the ''baseline model'' estimate of 3.26 (with very large confidence intervals for all ratio estimates). Only the smoking-adjusted model was significantly improved over the unadjusted model, yet the ERR estimate was nearly unchanged while the F:M ERR estimate increased modestly.

The right panel of Table 3 shows EAR and female-to-male EAR per weighted-gray ratio (F:M EAR) risk estimates with and without adjustments for gender-averaged lifestyle factors. The EAR model is the same as that used by Preston *et al*. (*1*), including the age-related radiation risk modifiers (again differing in case definition and exit date). Gender-averaged EAR/$Gy_w$ estimates ranged from 2.40–3.11 cases/10,000 P-Y-$Gy_w$ (person-years* weighted-gray) for the lifestyle-adjusted models compared to 3.02 (95% CI: 1.05–5.40) cases/10,000 P-Y-$Gy_w$ for the unadjusted model. The F:M EAR estimate was approximately 0.70 for all models except the smoking-adjusted model, in which the female risk was greater than the male risk (1.02), albeit with large confidence intervals (0.19–>10.0).

Figures 2 and 3 show the percentage of persons in the (presumed) most deleterious category of various lifestyles (i.e., lowest fruit, vegetable or education levels; smoker as of the last questionnaire; more than 1 drink per day among men and more than 0 drinks per day among women). To test whether radiation exposure levels possibly led to different choices in lifestyles, gender-specific tertiles of radiation exposure were tested against categories of lifestyle factors (as defined in Table 2). While NIC persons were included in Figs. 2 and 3, they were not included in this sub-analysis as they were excluded from many of the surveys, including the major surveys occurring in the later years of follow-up. For nearly all lifestyles, there was evidence to reject the null hypothesis that radiation exposure levels were not associated with different levels of lifestyle factors. However, there was little evidence to support trends of the ordered categories of lifestyle factors by radiation tertiles, particularly among men. There did appear to be higher levels of education associated with higher levels of radiation exposure among both men and women.

Notable results for bladder cancer from Preston *et al*. (*1*) included a female-to-male (F:M) excess relative risk ratio of over 3 and a rise of ERR estimates with increasing attained age with follow-up through 1998 (*1*). Those bladder cancer results are compared to radiation risk estimates of urothelial carcinoma with three additional years of follow-up shown in Table 4 (438 cancers were common to the two studies). Without considering lifestyle factors (''Current Data''), urothelial carcinoma significantly increased with ionizing

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

**TABLE 4**
**Comparison of Previous Analysis of Radiation-Associated Bladder Cancer Risk and Current Risk Estimates of Urothelial Carcinoma**

| Model | Background rates[a] | | Radiation risks | | | | Radiation risk age modifiers | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Gender-averaged | Male | Female | F:M ratio | Age ATB[b] | Age (power)[c] |
| | | | Excess relative risks (ERR/$Gy_w$[d]) | | | | | |
| Preston *et al*. | 7.8 | 1.6 | 1.23 | 0.61 | 1.9 | 3.1 | –3% | 0.33 |
| Current data[e] | 9.1 | 2.1 | 1.00 | 0.47 | 1.5 | 3.2 | –1% | –0.34 |
| Current data, adjusted for all lifestyle factors[f] | 5.0 | 2.6 | 0.96 | 0.44 | 1.5 | 3.4 | –5% | –0.27 |
| | | | Excess absolute risks[g] (EAR/$Gy_w$) | | | | | |
| Preston *et al*. | 7.8 | 1.6 | 3.2 | 3.8 | 2.6 | 0.68 | –19% | 6.3 |
| Current data[e] | 9.2 | 2.2 | 3.0 | 3.6 | 2.5 | 0.70 | –21% | 5.8 |
| Current data, adjusted for all lifestyle factors[f] | 5.0 | 2.9 | 2.7 | 2.9 | 2.5 | 0.87 | –25% | 6.0 |

*Notes*. The previous analysis was for bladder cancer for the period 1958–1998 ($N = 469$ cases) whereas these analyses are for urothelial carcinoma during the period 1958–2001 ($N = 573$ cases). Variables in the background term are identical in all three models except for the inclusion of lifestyle information in the last model. Inclusion of the ''age modifiers'' does not significantly improve any of the ERR models. The 'attained age' modifier in the EAR models was highly significant

[a]Per 10,000 PY (estimated at ATB of 30 years with an attained age of 70 years).
[b]Percentage change per decade increase in age at the time of bombing (ATB). Parameter was centered: (ATB-30)/10.
[c]Power of attained age. Parameter was centered: log(age/70).
[d]Weighted gray (gamma component plus 10 times the neutron component).
[e]Same model as the Preston *et al*. model using urothelial carcinoma as cases and follow-up through 2001.
[f]Same as the Preston *et al*. model but included gender-specific lifestyle categories in background term.
[g]Excess cases per 10,000 P-Y-$Gy_w$.

radiation exposure having a gender-averaged estimate of 1.00 ERR/$Gy_w$, which was slightly less than Preston *et al*. estimated for bladder cancer using a shorter follow-up period and non-urothelial carcinoma bladder cancers (1.23 ERR/$Gy_w$) (*1*). The F:M ERR was nearly the same for urothelial carcinoma and for the value previously reported for all bladder cancer (3.2 compared to 3.1). Age-related radiation effect modifiers (attained age and age-at-exposure) were not statistically different than those derived by Preston *et al*. After adjusting for all lifestyle factors simultaneously, all ERR parameter estimates were nearly unchanged, compared to the unadjusted estimates.

A comparison of the estimates for EAR is shown in Table 4. Again, bladder cancer and urothelial carcinoma risks were similar. Adjustments for lifestyle factors modestly reduced the EAR/$Gy_w$ in males while it had no effect among females. Note that in both the ERR and EAR models, redefining the background to include lifestyle factors resulted in substantial changes to the rates in the reference group, indicating that lifestyle factors (primarily smoking in males) were strongly associated with urothelial carcinoma risk.

The attributable fractions of cases caused by radiation exposure and smoking are shown in Table 5. These fractions are based on fitted background and excess cases using an additive risk model (Eq. 1, with both radiation and smoking modeled as ERR terms without effect modifiers). Among those with radiation dose greater than 0.005 $Gy_w$ (average = 0.21 $Gy_w$), the attributable fraction of urothelial carcinoma due to radiation exposure was 7.1% (11.5/161.4) in males and 19.7% (19.1/97.0) in females, while for the entire cohort, the population attributable fraction of urothelial carcinoma due to radiation was 3.1% in males and 9.7% in females. The population attributable fraction of urothelial carcinoma due to smoking was 53.4% in males and 5.2% in females, while among current smokers (only), the smoking attributable fraction was 61.0% in males and 52.1% in females.

Substituting pack-years of smoking for smoking categories (Never, Former, Current) in the same ERR additive model described in the previous paragraph (Eq. 1), the ERR/pack-year was 0.028 in males and 0.060 in females. By dividing the gender-specific ERR estimates of radiation by the ERR estimates of pack-years of smoking, rough equivalencies can be calculated. We find the risk of 1 $Gy_w$ of radiation exposure to the urothelial carcinoma tract is equivalent to the risk of smoking for about 25 pack-years. This value is roughly the same for both males and females (male: 0.85 $Gy_w^{-1}$/0.028 $PY^{-1} = 30$; female: 1.4 $Gy^{-1}$/0.060 $PY^{-1} = 23$). Said another way, one abdominal CT-scan with 20 mGy dose to the bladder has about the same urothelial carcinoma risk as smoking 10 cigarettes/day for one year.

By including a time-varying modifier of years since quitting for ex-smokers, the estimated reduction in urothelial carcinoma risk for each additional year of smoking cessation was about 5% but this value was not statistically significant.

Table 6 shows the gender-specific effects of smoking on urothelial carcinoma risk using more detailed measures of smoking habits. While the data aren't shown, prevalence of smoking among males was very high (84% ever smokers) and quite low among females (16% ever smokers). As with the results shown in Table 2, smoking measures were included in the background term while the radiation effect was modeled as an excess relative risk. The radiation risks of urothelial carcinoma risks are not shown, but are stable

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

**TABLE 5**
**Attributable Fraction Based on Fitted Counts of Background and Excess (radiation and smoking) Urothelial Carcinoma by Gender and Radiation Dose and Current Smoking Status (all values rounded to one decimal place)**

| Dose category (weighted-Gy[a]) | Fitted total cases | Fitted background | Fitted radiation excess | Fitted smoking excess | Radiation attributable fraction | Smoking attributable fraction |
|---|---|---|---|---|---|---|
| Males by radiation dose | | | | | | |
| NIC[b] | 98.1 | 42.9 | 0.0 | 55.2 | 0.0% | 55.2% |
| 0–<0.005 | 115.5 | 52.4 | 0.0 | 63.0 | 0.0% | 53.0% |
| 0.005–0.1 | 93.9 | 42.1 | 1.1 | 50.7 | 1.2% | 59.6% |
| 0.1–0.2 | 19.9 | 8.6 | 1.0 | 10.4 | 4.8% | 57.9% |
| 0.2–0.5 | 21.6 | 8.8 | 2.2 | 10.6 | 10.4% | 44.0% |
| 0.5–1.0 | 13.3 | 4.8 | 2.7 | 5.8 | 20.3% | 44.8% |
| 1.0–2.0 | 9.4 | 2.8 | 3.0 | 3.6 | 32.0% | 25.5% |
| >2.0 | 3.2 | 0.8 | 1.5 | 1.0 | 45.5% | 50.4% |
| Total (all) | 375.0 | 163.2 | 11.5 | 200.3 | 3.1% | 53.4% |
| Total (dose >0.005) | 161.4 | 67.9 | 11.5 | 82.1 | 7.1% | 52.6% |
| Total (current smokers) | 183.3 | 65.1 | 5.4 | 112.8 | 3.0% | 61.0% |
| Females by radiation dose | | | | | | |
| NIC[b] | 42.9 | 41.0 | 0.0 | 1.9 | 0.0% | 4.4% |
| 0–<0.005 | 58.1 | 55.4 | 0.1 | 2.6 | 0.1% | 4.5% |
| 0.005–0.1 | 49.6 | 44.9 | 2.0 | 2.7 | 4.0% | 5.5% |
| 0.1–0.2 | 12.8 | 9.8 | 2.0 | 1.0 | 15.9% | 7.4% |
| 0.2–0.5 | 15.7 | 9.9 | 4.6 | 1.1 | 29.5% | 7.2% |
| 0.5–1.0 | 10.3 | 4.9 | 4.8 | 0.7 | 46.5% | 6.5% |
| 1.0–2.0 | 6.2 | 2.0 | 3.9 | 0.3 | 62.6% | 5.0% |
| >2.0 | 2.3 | 0.5 | 1.8 | 0.1 | 75.7% | 2.6% |
| Total (all) | 198.0 | 168.5 | 19.2 | 10.3 | 9.7% | 5.2% |
| Total (dose >0.005) | 97.0 | 72.0 | 19.1 | 5.9 | 19.7% | 6.0% |
| Total (current smokers) | 27.4 | 11.2 | 2.0 | 14.3 | 7.3% | 52.1% |

[a]Weighted gray (gamma component plus 10 times the neutron component).
[b]Not in city at the time of the bombing.

and consistent with those obtained in the left panel of Table 3. Those who reported they had quit smoking had a significantly lower risk of urothelial carcinoma than did those who continued to smoke ($P = 0.002$). Point estimates for duration of smoking (by decade) were elevated for all times and for all gender categories, but were generally not significant until smoking $\geq$20 years. The trend test for greater risks with longer smoking duration was highly significant. Similar results were observed when modeling the smoking risk using intensity (cigarettes/day) and pack-years of smoking. Regardless of the measure of smoking (duration, intensity or pack-years), urothelial carcinoma risks of smoking rose quickly, generally reaching a near-maximum level in the first or second ordinal category above the reference category, and then leveling off at a relative risk of roughly 2. Spline models to account for this plateau effect did not significantly improve the model fit over linear models (results not shown). Comparisons of all urothelial carcinoma risk models tested (Tables 3 and 6) found that an ERR model with gender-specific smoking categories in the background term had the lowest AIC value.

Using Lubin's suggested model for total smoking exposure,[2] a parametric dose-response curve [β: 0.023 (NS), $\phi_1 = 0.74$ (NS), $\phi_2 = -0.17$ (NS)] as well as point estimates for different values of smoking intensity were derived and plotted in Fig. 2 (point estimates were plotted at the average intensity for each group). Due to the model structure, the shape of the curve in Fig. 4 is predictably consistent with Lubin's results. However, the apparent modification of smoking risk by intensity was not significant (LRT $P = 0.24$).

Joint effects of radiation and smoking were also investigated. There was no evidence ($P = 0.46$) of a statistically significant departure from a model in which the joint effect of radiation and smoking was assumed to be multiplicative (AIC = 6216.9). However an additive model described the data equally well (AIC = 6214.6), and a test for a departure from additivity was also not significant ($P = 0.13$).

## DISCUSSION

High radiation risks of urothelial carcinoma were evident in both males and females with a high F:M ERR ratio. Models that estimated urothelial carcinoma risks after radiation exposure while simultaneously adjusting for all considered lifestyle factors did not appreciably change the ionizing radiation risk estimates. Although a number of other lifestyle factors were considered as additional urothelial carcinoma risk factors, a model with gender-specific smoking categories (Never, Former, Current) in the

[2] $ERR_2 = \beta * \text{pack·years} * e^{intensity}$ where intensity is: $\varphi_1 \log_e(\text{cigs/day}) + \varphi_2(\log_e(\text{cigs/day}))^2$.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

**TABLE 6**
**Urothelial Carcinoma Risks by Gender and Various Measures of Smoking**

| | Males | | | | Females | | | | Both Sexes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Relative risk | CI | *P* | Cases | Relative risk | CI | *P* | Cases | Relative risk | CI | *P* |
| Smoke | | | | | | | | | | | | |
| Never | 17 | Ref | - | - | 82 | Ref | - | - | 99 | Ref | - | - |
| Former | 39 | 1.68 | 0.95–2.98 | 0.07 | 6 | 1.24 | 0.54–2.86 | >0.5 | 45 | 1.21 | 0.83–1.78 | 0.32 |
| Current | 185 | 2.74 | 1.67–4.52 | <0.001 | 28 | 2.20 | 1.43–3.38 | <0.001 | 213 | 1.99 | 1.50–2.65 | <0.001 |
| Duration (years) | | | | | | | | | | | | |
| Never | 17 | Ref | - | - | 82 | Ref | - | - | 99 | Ref | - | - |
| >0–<10 | 6 | 1.82 | 0.72–4.63 | 0.21 | 4 | 1.71 | 0.63–4.69 | 0.29 | 10 | 1.48 | 0.77–2.87 | 0.24 |
| ≥10–< 20 | 9 | 1.59 | 0.71–3.58 | 0.26 | 6 | 2.24 | 0.97–5.13 | 0.06 | 15 | 1.44 | 0.82–2.51 | 0.20 |
| ≥20–<30 | 25 | 2.58 | 1.39–4.80 | 0.003 | 7 | 2.07 | 0.95–4.47 | 0.07 | 32 | 1.90 | 1.25–2.89 | 0.003 |
| ≥30–<40 | 41 | 2.43 | 1.37–4.31 | 0.002 | 4 | 1.17 | 0.43–3.21 | >0.50 | 45 | 1.66 | 1.13–2.43 | 0.01 |
| ≥40–<50 | 64 | 2.64 | 1.54–4.52 | <0.001 | 8 | 2.50 | 1.20–5.18 | 0.01 | 72 | 1.95 | 1.38–2.75 | <0.001 |
| ≥50 | 79 | 2.76 | 1.62 −4.70 | <0.001 | 5 | 2.32 | 0.93–5.76 | 0.07 | 84 | 2.05 | 1.45–2.91 | <0.001 |
| Intensity (cigarettes/day) | | | | | | | | | | | | |
| 0 | 56 | Ref | - | - | 88 | Ref | - | - | 144 | Ref | - | - |
| ≥1–<8 | 14 | 1.77 | 0.93–3.02 | 0.08 | 6 | 1.40 | 0.61–3.22 | 0.42 | 20 | 1.51 | 0.95–2.44 | 0.08 |
| ≥8–<13 | 48 | 2.15 | 1.45–3.17 | <0.001 | 13 | 2.66 | 1.48–4.76 | 0.001 | 61 | 2.10 | 1.53–2.87 | <0.001 |
| ≥13–<18 | 13 | 1.42 | 0.78–2.61 | 0.25 | 5 | 3.20 | 1.30–7.87 | 0.01 | 18 | 1.56 | 0.95–2.58 | 0.08 |
| ≥18–<23 | 76 | 2.03 | 1.44–2.88 | <0.001 | 3 | 1.65 | 0.52–5.22 | 0.40 | 79 | 1.85 | 1.37–2.49 | <0.001 |
| ≥3 | 34 | 2.06 | 1.33–3.18 | 0.001 | 1 | 2.70 | 0.38–19.4 | 0.32 | 35 | 1.88 | 1.27–2.78 | 0.002 |
| Pack-years | | | | | | | | | | | | |
| 0 | 17 | Ref | - | - | 82 | Ref | - | - | 99 | Ref | - | - |
| ≥1–<10 | 10 | 2.44 | 1.11–5.33 | 0.02 | 10 | 1.58 | 0.82–3.06 | 0.17 | 20 | 1.74 | 1.07–2.82 | 0.02 |
| ≥10–<20 | 14 | 1.76 | 0.87–3.57 | 0.12 | 16 | 2.40 | 1.40–4.11 | 0.001 | 30 | 1.74 | 1.14–2.64 | 0.01 |
| ≥20–<30 | 42 | 2.50 | 1.42–4.41 | 0.001 | 5 | 1.43 | 0.58–3.53 | 0.44 | 47 | 1.75 | 1.20–2.54 | 0.003 |
| ≥30–< 40 | 67 | 2.54 | 1.49–4.34 | <0.001 | 2 | 2.74 | 0.67–11.2 | 0.16 | 69 | 1.84 | 1.29–2.61 | <0.001 |
| ≥40–< 50 | 47 | 2.34 | 1.34–4.08 | 0.003 | 1 | 8.69 | 1.20–62.6 | 0.03 | 48 | 1.73 | 1.16–2.56 | 0.006 |
| ≥50 | 44 | 3.21 | 1.82–5.65 | <0.001 | 0 | - | | - | 44 | 2.38 | 1.57–3.62 | <0.001 |

*Note*. Smoking was modeled as part of the background term while radiation was modeled as an excess relative risk (radiation estimates not shown).

background term and ERR ionizing radiation effects with no dependence on age-at-exposure or attained age, had the lowest AIC value. The estimated number of excess cases attributable to radiation exposure was approximately 11 in males and 19 in females, corresponding to an attributable fraction of 7.1% and 19.7%, respectively, among those exposed to more than 0.005 $Gy_w$. The estimated number of excess cases due to smoking was 200 in males and 10 in females. We calculated that one abdominal CT scan with 20 mGy dose to the bladder has about the same urothelial carcinoma risk as smoking 10 cigarettes/day for one year.

Urothelial carcinoma is the dominant form of bladder, ureter and renal pelvis cancers. Of the three cancer sites, bladder cancer is by far the most frequent. Therefore, comparisons of urothelial carcinoma to bladder cancer in other studies should be valid in most situations. The primary advantages of defining the cases as urothelial carcinoma were to exclude cases that may not be related to lifestyle factors and to increase the case counts by using additional sites.

Of the five lifestyle factors considered, only smoking was significantly associated with urothelial carcinoma risk, however, some suggestion of a lowered background risk was evident for higher levels of education, fruit and vegetable consumption. The lack of significant associations with dietary factors were somewhat surprising as Nagano *et al*. found protective effects for vegetable consumption and marginal protective effects for fruit consumption in the same cohort (*49*). Our results, however, were not qualita-

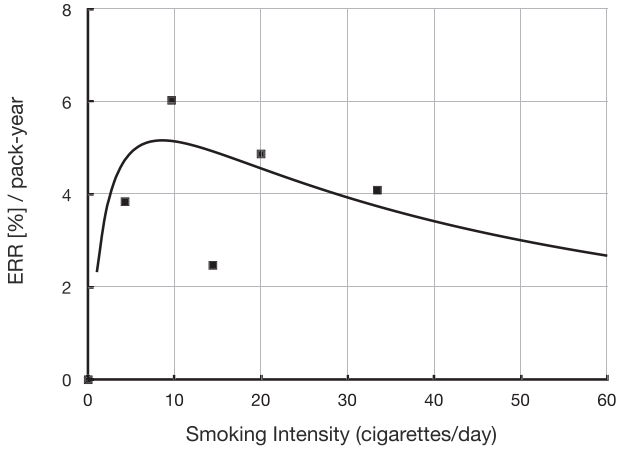



**FIG. 4.** Gender-averaged excess relative risk of urothelial carcinoma per pack-year of smoking, modified by intensity. The ''total exposure'' model suggested by Lubin *et al*.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

tively inconsistent with those findings and there were a number of differences between the two studies that may account for the lack of full agreement. In particular, Nagano *et al*. limited their study to only those who participated in the 1979 LSS mail questionnaire (114 incident cases) with 13 years of follow-up.

Preston *et al*. reported high ionizing radiation risks of bladder cancer with a high F:M ERR ratio (*1*). We observed slightly lower gender-specific point estimates and a similar F:M ERR ratio using urothelial carcinoma as an end point and 3 years of additional follow-up data. While the finding was not significant, Preston *et al*. noted that ERR increased with attained age, a finding that was not consistent with most solid organs. Our point estimate indicated a decreased risk with attained age that was not significant. Generally speaking, radiation excess relative risk estimates tend to decrease with attained age, but only a limited set of organs are strongly age dependent. Also of note is the similarity of our findings to the mortality-based ERRs reported among the A-bomb survivors for the follow-up period 1950–1997 (*50*). In that report, the ERR/Gy for bladder cancer deaths among males was 1.1, while it was 1.2 in females (compared to 0.44 and 1.5, respectively, in this report).

Women treated for cervical cancer with high doses of radiation (30–60 Gy bladder dose) were reported to have a high relative risk of bladder cancer (as well as renal pelvis and ureter cancers). They also noted that controlling for smoking did not alter the radiation risk, and that there was no evidence that ionizing radiation and smoking effects interacted multiplicatively (*3*). Weiss *et al*. reported a relative risk of bladder cancer death of approximately 2 after exposure to an average of 2.2 Gy with no dependence on years since exposure; the study did not attempt to control for smoking (*6*). In studies of lung cancer incidence and smoking among the A-bomb survivors, Pierce *et al*. (*44*) reported statistical evidence to reject an additive model, but not a multiplicative model, while Furukawa *et al*. (*15*), using additional follow-up data, rejected both additive and multiplicative models in favor of a generalized interaction model in which multiplicative effects were observed among light smokers, but additive effects were observed among heavy smokers. Lung cancer, however, is more strongly associated with smoking than urothelial carcinoma and those studies had many more incident cases, which afforded greater power to detect interactions. Both Pierce and Furukawa reported a reduction of the F:M ERR in models that included smoking. In this study, it was not possible to reject either additive or multiplicative joint effects but the results suggest that the combined effects lay somewhere between additive and multiplicative.

Lifestyle factors could conceivably confound the relation of radiation exposure and urothelial carcinoma if a factor is associated with both radiation exposure and outcome. The city centers were more urban than surrounding areas and therefore, it is not unreasonable that the education level in the city centers may be higher than in the surrounding areas (this is supported by Figs. 2 and 3), indicating a higher socioeconomic status and likely better access to healthcare with a higher estimated radiation dose. If this scenario were true, the radiation risk estimate may be underestimated if the level of education was ignored. It is also conceivable that surrounding areas may have had more agricultural land and local farming, raising their intake of vegetables and fruits in their diet (possibly resulting in an overestimation of health care radiation risk by preferentially lowering the background risk among the distal survivors). Lifestyle factors could also conceivably be on a causal pathway between radiation exposure and outcome. This could happen if a person decided to smoke or drink more after surviving the A-bombing. In these cases, unadjusted health care radiation risk estimates would be a combination of both risk factors. The adjusted risk estimates would be ''over and above'' the risks incurred by the resultant lifestyle change, and more appropriate models would be required to assess the total and mediated risks for radiation.

Despite the heterogeneity of lifestyle factors by radiation exposure tertiles, and the plausibility that lifestyle factors could confound or modify urothelial carcinoma radiation risks, we did not observe any major changes in either the gender-averaged or gender-specific radiation risk estimates of urothelial carcinoma after adjusting for lifestyle factors (Table 4). This indicates that the gender-averaged, gender-specific and F:M ERR and EAR ratio estimates of bladder cancer risks reported in previous incidence studies of the LSS cohort were unlikely to have been strongly affected by ignoring smoking effects or other considered lifestyle factors. The primary impact on the models is the change in background rates for the reference group. When adjusting for lifestyle factors, the background rate for nonsmokers dropped by about 40% in males compared to all men, regardless of smoking status. This difference does not greatly affect the radiation risks, but it does alter the attributable fraction (i.e., shifting the cause of cases to smoking and away from radiation exposure). Preston *et al*. reported that the radiation attributable fraction of bladder cancers was 16.4% among those with greater than 0.005 $Gy_w$ exposure (*1*). Among the same group, we calculate the attributable fraction of urothelial carcinoma due to radiation was 11.8% overall, and only 7.1% among males (Table 5).

This study has a number of strengths and limitations. In terms of strengths, all data were collected prospectively. Cancer incidence and censoring due to mortality were carried out using consistent methods over a period of 45 years. The cohort was large and radiation doses to the bladder were well characterized. In terms of study weaknesses, recorded lifestyle factors were not collected in a consistent manner (self-reported or recorded during a clinical interview) and some categories of lifestyle habits were not consistent across questionnaires. Collection of lifestyle factors began in 1963 and the last update of lifestyle data was collected in 1991; NIC members were not included in the last two major questionnaires. Cancer

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

follow-up did not begin until 1958, 13 years after the bombings. Dietary questionnaires were fairly crude by today's standards, simply using food frequency of broad categories of foods without any regard to portion size. Accounting for migration into and out of the catchment areas is difficult to validate and may not be free of bias. Finally, another known risk of urothelial carcinoma is occupational exposure to certain chemicals and these were not considered in this analysis. However, none of these limitations is likely to greatly impact the results or invalidate the conclusions of the research.

Due to the size and long follow-up period of this Japanese cohort, the estimated effects of smoking on urothelial carcinoma risk may be of general interest. We found the risk of urothelial carcinoma increased with increasing levels of intensity, duration, and pack-years of smoking, consistent with other published studies. When modeling the effects of radiation and smoking as gender-specific additive excess relative risks (Eq. 1), the ERR/pack-year of smoking was 0.028 in males and 0.060 in females. Risk estimates using any measure of smoking intake level quickly plateaued. The population (i.e. the full cohort) attributable fraction of urothelial carcinoma due to smoking in males was 53% while it was only 5% in females. The prevalence of ever having smoked among females, however, was small (16%). Among current smokers, the gender-specific attributable fractions were similar: 61% in males and 52% in females.

The smoking-related risk of urothelial carcinoma has been reported to be similar for both males and females (*51*) while some have reported that the risk is higher in females (*52*). A recent report among the Japanese ages 40–69 at the start of follow-up (1990) and followed over 15 years showed an relative risk of 1.7 for male smokers and an relative risk of 5.4 for female smokers (compared to never smokers) (*53*). Our results indicated that male smokers had a slightly higher risk compared to female smokers. With regard to quitting smoking, we found that smokers who quit had lower risks than those who continued to smoke which is consistent with other reports, the time-course of the reduced risks is unclear in this study. Some reports have indicated that beyond 15 years, the risk in former smokers is the same as in those who never smoked (*51*) whereas others have reported an immediate decrease in risk (*54*) that never reaches nonsmoker levels (*18*). We found no dependence on the years of cessation, but if the risk reduction occurred rapidly, the timing of our questionnaires may not have allowed us to detect time trends.

At least two studies have applied Lubin's total smoking exposure model (pack-years modified by intensity) to case-control bladder cancer data. Lubin (*45*) and Baris (*55*) found increased excess odds ratios per pack-year of smoking at lower levels of smoking intensity. We found no statistical evidence that smoking intensity modified pack-years of smoking risk estimates.

With our findings generated from a cohort of A-bomb survivors, there may be some concern as to whether the smoking findings are affected by the unique nature of the cohort. However, as most of the excess urothelial carcinoma cases were attributable to smoking and not radiation, the smoking findings detailed above should not be largely influenced by the radiation exposure.

In conclusion, a number of models incorporating radiation exposure and different measures of lifestyles were examined and compared. Radiation risk estimates for urothelial carcinoma were largely unchanged when incorporating all of the lifestyle factors into the analyses. Smoking was associated with urothelial carcinoma risk, but the nature of the joint effects of smoking and ionizing radiation on urothelial carcinoma risks could not be determined precisely. Some evidence of heterogeneity of lifestyle factor categories was evident among different radiation dose categories, which will require further investigation. Researchers and others concerned that RERF radiation risk estimates for urothelial carcinoma or bladder cancer may be markedly biased by unaccounted for lifestyle factors should be reassured by these findings.

## ACKNOWLEDGMENTS

We thank the members of the LSS for their participation. The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, nonprofit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through DOE Award DE-HS0000031 to the National Academy of Sciences. This publication was supported by RERF Research Protocol RP A7-08. The views of the authors do not necessarily reflect those of the two governments.

Received: October 24, 2011; accepted: February 7, 2012; published online: May 25, 2012

## REFERENCES

1. Preston DL, Ron E, Tokuoka S, et al. Solid Cancer Incidence in Atomic Bomb Survivors: 1958–1998. Radiat Res 2007; 168:1–64.
2. Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 1994; 137:S17–67.
3. Boice JD, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 19881; 116:3–55.
4. Inskip PD, Monson RR, Wagoner JK, et al. Cancer mortality following radium treatment for uterine bleeding. Radiat Res 1990; 123:331–44.
5. Darby SC, Reeves G, Key T, Doll R, Stovall M. Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. Int J Cancer 1994; 56:793–801.
6. Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer 1994; 59:327–38.
7. Alberg AJ, Kouzis A, Genkinger JM, et al. A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. Am J Epidemiol 2007; 165:660–6.
8. Puente D, Hartge P, Greiser E, et al. A pooled analysis of bladder cancer case-control studies evaluating smoking in men and women. Cancer Causes & Control 2006; 17:71–9.
9. Friesen MC, Demers PA, Spinelli JJ, Lorenzi MF, Le ND.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

Comparison of two indices of exposure to polycyclic aromatic hydrocarbons in a retrospective aluminium smelter cohort. Occup Environ Med 2007; 64:273–8.

10. Reulen RC, Kellen E, Buntinx F, Zeegers MP. Bladder cancer and occupation: a report from the Belgian case-control study on bladder cancer risk. Am J Ind Med 2007; 50:449–54.
11. Silberstein JL, Parsons JK. Evidence-based principles of bladder cancer and diet. Urology 2010; 75:340–6.
12. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of Ionizing Radiation, UNSCEAR 2006 Report; Vol I, Scientific Annex A: Epidemiological Studies of Radiation and Cancer. 2008.
13. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Annals of the ICRP 2007; 37:1–332.
14. Hall P. Radiation-associated urinary bladder cancer. Scand J Urolo Nephrolo Suppl 2008; 85–8.
15. Furukawa K, Preston DL, Lönn S, et al. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. Radiat Res 2010; 174:72–82.
16. Kakehi Y, Hirao Y, Kim WJ, et al. Bladder Cancer Working Group report. Jpn J Clin Oncol 2010; 40 Suppl 1:i57–64.
17. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66:4–34.
18. Silverman DT, Morrison AS, Devesa SS. Bladder Cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York (NY): Oxford University Press; 1996. P. 1156–79.
19. Wilbourn JD, Partensky C, Rice JM. Agents that induce epithelial neoplasms of the urinary bladder, renal cortex and thyroid follicular lining in experimental animals and humans: summary of data from IARC monographs vol 1–69. IARC Scien Publi 1999; 191–209.
20. Korkes F, Silveira TS, Castro MG, Cuck G, Fernandes RC, Perez MD. Carcinoma of the renal pelvis and ureter. Intern Braz J Urolo 2006; 32:648–53.
21. McLaughlin J, Blot WJ, Devesa S, Fraumeni J. Renal cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. 2nd ed. 1996; 1142–55.
22. Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2000: Estimates based on data from 11 population-based cancer registries. Japan J Clin Oncolo 2006; 36:668–75.
23. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology, diagnosis, and management. Cancer Pract 2002; 10:311–22.
24. Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br J Cancer 2000; 82:1364–9.
25. Zeegers MP, Kellen E, Buntinx F, van den Brandt PA. The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. World J Urolo 2003; 21:392–401.
26. Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S. Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. Eur J Epidemiol 1997; 13:795–800.
27. Brownson RC, Chang JC, Davis JR. Occupation, smoking, and alcohol in the epidemiology of bladder cancer. Am J Public Health 1987; 77:1298–1300.
28. Zeegers MP, Volovics A, Dorant E, Goldbohm RA, van den Brandt PA. Alcohol consumption and bladder cancer risk: results from The Netherlands Cohort Study. Am J Epidemiol 2001; 153:38–41.
29. Pelucchi C, Negri E, Franceschi S, Talamini R, La Vecchia C. Alcohol drinking and bladder cancer. J Clin Epidemiol 2002; 55:637–41.
30. Djoussé L, Schatzkin A, Chibnik LB, D'Agostino RB, Kreger BE, Ellison RC. Alcohol consumption and the risk of bladder cancer in the Framingham Heart Study. J Natl Cancer Inst 2004; 96:1397–1400.
31. Adler NE, Boyce WT, Chesney MA, Folkman S, Syme SL. Socioeconomic inequalities in health. No easy solution. JAMA 1993; 269:3140–5.
32. Young RW, Kerr GD, editors. Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki–Dosimetry System 2002. Hiroshima, Japan: Radiation Effects Research Foundation; 2005.
33. Mabuchi K, Soda M, Ron E, et al. Cancer incidence in atomic bomb survivors. Part I: Use of the tumor registries in Hiroshima and Nagasaki for incidence studies. Radiat Res 1994; 137:S1–16.
34. Roesch WC, editor. US-Japan joint reassessment of atomic bomb radiation dosimetry in Hiroshima and Nagasaki, Final Report. Hiroshima, Japan: Radiation Effects Research Foundation; 1987.
35. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 1990; 123:275–84.
36. Study of cardiovascular disease, Hiroshima and Nagasaki: Mortality related to family history and habits. Hiroshima: Radiation Effects Research Foundation. Research Protocol No. 9–65; 1965.
37. Mail questionnaire survey for epidemiologic data on females in the JNIH-ABCC Life Span Study sample. Hiroshima: Radiation Effects Research Foundation. Research Protocol No. 11–69; 1969.
38. Mail questionnaire survey for epidemiologic data on the Life Span Study extended sample, 1978. Hiroshima: Radiation Effects Research Foundation. Research Protocol No. 14–78; 1978.
39. Mail survey on epidemiologic factors in the Extended Life Span Study sample, 1991. Hiroshima: Radiation Effects Research Foundation. Research Protocol No. 4–91; 1991.
40. Epidemiologic survey, Adult Health Study sample, Hiroshima and Nagasaki Study of cardiovascular disease Hiroshima and Nagasaki: Mortality related to family history and habits. Hiroshima: Radiation Effects Research Foundation. Research Protocol No. 26–63; 1963.
41. Breslow NE, Day NE. Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. Lyon: International Agency for Research on Cancer; 1987.
42. Clayton D, Hills M. Statistical models in epidemiology. New York: Oxford University Press; 1993
43. Sposto R, Preston DL. Correcting for catchment area nonresidency in studies based on tumor-registry data. Hiroshima: Radiation Effects Research Foundation; 1992. Report No. CR 1–92.
44. Pierce DA, Sharp GB, Mabuchi K. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. Radiat Res 2003; 159:511–20.
45. Lubin JH, Alavanja MC, Caporaso N, et al. Cigarette smoking and cancer risk: modeling total exposure and intensity. Am J Epidemiol 2007; 166:479–89.
46. Preston DL, Lubin J, Pierce DA, McConney ME. Epicure Users Guide. Seattle: Hirosoft International Corporation; 1993.
47. StataCorp. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP; 2009.
48. Akaike H. A new look at the statistical model identification. IEEE Trans Autom Control 1974; 19:716–23.
49. Nagano J, Kono S, Preston DL et al. Bladder-cancer incidence in relation to vegetable and fruit consumption: a prospective study of atomic-bomb survivors. Intern J Cancer 2000; 86:132–38.
50. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use

cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 60:381–407.

*51*. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press; 2004.

*52*. Castelao JE, Yuan JM, Skipper PL et al. Gender- and smoking-related bladder cancer risk. J Natl Cancer Inst 2001; 93:538–45.

*53*. Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S, Group JPHCJPHC)S. Coffee, green tea, and caffeine consumption and subsequent risk of bladder cancer in relation to smoking status: a prospective study in Japan. Cancer Sci 2009; 100:294–1.

*54*. Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer 2000; 86:289–94.

*55*. Baris D, Karagas MR, Verrill C et al. A case-control study of smoking and bladder cancer risk: emergent patterns over time. J Natl Cancer Inst 2009; 101:1553–61.

Downloaded From: https://bioone.org/journals/Radiation-Research on 29 Mar 2024
Terms of Use: https://bioone.org/terms-of-use