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Risk of Prostate Cancer Incidence among Atomic Bomb Survivors: 1958–2009

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Abstract

Epidemiological evidence for a radiation effect on prostate cancer risk has been inconsistent and largely indicative of no or little effect. Here we studied prostate cancer incidence among males of the Life Span Study cohort of atomic bomb survivors in a follow-up from 1958 to 2009, eleven years more than was previously reported. During this period there were 851 incident cases of prostate cancer among 41,544 male subjects, doubling the total number of cases in the cohort. More than 50% of the cases were diagnosed among those who were less than 20 years of age at the time of the bombings and who were at, or near, the ages of heightened prostate cancer risks during the last decade of follow-up. In analyses of the radiation dose response using Poisson regression methods, we used a baseline-rate model that allowed for calendar period effects corresponding to the emergence of prostate-specific antigen screening in the general population as well as effects of attained age and birth cohort. The model also allowed for markedly increased baseline rates among the Adult Health Study participants between 2005 and 2009, a period during which a prostate-specific antigen test was included in Adult Health Study biennial health examinations. We found a significant linear dose response with an estimated excess relative risk (ERR) per Gy of 0.57 (95% CI: 0.21, 1.00, $P = 0.001$). An estimated 40 of the observed cases were attributed to radiation exposure from the bombings. There was a suggestion of the ERR decreasing with increasing age at exposure ($P = 0.09$). We found no indication of effects of smoking, alcohol consumption and body mass index on the baseline risk of prostate cancer. The observed dose response strengthens the evidence of a radiation effect on the risk of prostate cancer incidence in the atomic bomb survivors.

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INTRODUCTION

Prostate cancer is one of the most common cancers in many Western countries but has been relatively uncommon in Japan and most Asian countries until recently (1). Apart from advancing age, ethnicity and family history, there are no universally established environmental or lifestyle risk factors for prostate cancer (2). Epidemiological studies have provided inconsistent evidence for radiation effects on prostate cancer risk. An increased risk of prostate cancer has been found after X-ray treatment for ankylosing spondylitis (3) and in a subset of nuclear workers who were internally exposed to various radionuclides (4), but with little support from subsequent studies of medically or occupationally exposed populations (5–10).

Previously published analyses of prostate cancer incidence or mortality rates in the Life Span Study (LSS) of Japanese atomic bomb survivors, with a more limited follow-up period, have consistently indicated increased risks with increasing dose, but the estimated radiation-related risks were not statistically significant (11, 12). This may have been due, at least in part, to low prostate cancer rates in Japan and the under-representation of younger adult males at the time of the bombings in this cohort (13). Recently, however, the relatively large portion of male cohort members exposed as children or adolescents have reached ages at which prostate cancer rates are increased. Combined with recently introduced prostate-specific antigen (PSA) screening, this led to a dramatic increase in prostate cancer incident cases in this cohort.

This, together with an elevated risk of prostate cancer reported among proximally exposed atomic bomb survivors in Nagasaki (14), motivated us to evaluate the radiation dose response for prostate cancer in the latest series of LSS solid cancer incidence studies (15). Since the most recent rise in prostate cancer rates in Japan has been linked to increasing use of the PSA test, we examined a possible effect of PSA screening in the radiation risk analysis.

MATERIALS AND METHODS

Life Span Study Cohort

As described in more detail elsewhere (13, 15), the LSS cohort, followed up by the Radiation Effects Research Foundation (RERF), consists of 120,321 persons, including 93,741 atomic bomb survivors in Hiroshima and Nagasaki and 26,580 city residents who were not in either city at the time of the 1945 bombings. The survivor group consists of 54,322 persons who were within 2.5 km of either hypocenter at the time of the bombings and thus exposed to relatively high doses of radiation, and 39,419 city, sex and age-matched persons who were between 2.5 and 10 km of the hypocenter and exposed to lower-to-negligible doses. Less than one half, i.e., 50,175 (42%), of the cohort are males.

Adult Health Study

The Adult Health Study (AHS) cohort is a clinical subset of the LSS cohort. This sub-cohort was created originally in 1958, drawing 19,961 persons from the LSS cohort; approximately one half of these were within 2 km of the hypocenter, one quarter were exposed between 3

and 3.5 km in Hiroshima and between 3 km and 4 km in Nagasaki, and another one quarter were not in either city at the time of the bombings. They were matched on age, sex and city (13, 16). This sub-cohort has been expanded twice, with 2,436 persons added in 1997 and 2008, and currently includes 24,358 persons (of whom 9,440 are males) (13). Surviving AHS members have been invited to biennial clinical health examinations conducted at RERF. Health examinations of the subjects who were not in either city were terminated in 1977.

As described later, the current analysis was restricted to a subset of 41,554 male LSS members (including 8,140 AHS members) aged 45 years or older with known radiation dose. Demographic and dose characteristics of the male AHS and non-AHS members considered in the current study are presented in Appendix Table A1 and described later.

PSA Screening

The PSA test was added to routine laboratory work as part of the AHS clinical examination protocol in December 2004. Participants were informed of their PSA test results; those with elevated PSA levels (4 ng/ml or higher) were advised to consult their primary-care physician or a urologist with assistance or advice from RERF. No further efforts have been made to follow individual participants for whom a PSA test was performed. The AHS program as such does not provide diagnostic services for prostate or any other cancer. As described below, all incident prostate cancers in this study were ascertained by linkage to cancer registries without knowledge of AHS PSA screening participation.

Cancer Case Ascertainment and Follow-up

Incident cancer cases in the LSS cohort have been ascertained by linkage with the Hiroshima and Nagasaki cancer registries since 1958 (12, 15, 17, 18). The current study, conducted in this framework, involved 42,910 males with dose estimates who were alive and not known to have cancer as of 1958. A total of 851 males had first primary prostate cancers (ICD-10, topography code C61) diagnosed in the cancer registry catchment areas between 1958 and 2009. As indicated elsewhere (15), these excluded prostate cancer cases diagnosed only at autopsy (n = 63) because a large number of autopsies performed under the pathology program during the 1960s and 1970s occurred more often among those who had higher radiation doses and were older. Of the 851 cases, 771 (91%) had histologically verified diagnoses; for 24 (3%), diagnoses were based solely on death certificates.

Since there were no prostate cancer cases in males younger than 45 years of age, we restricted the analysis to a subset of 41,554 males with known radiation dose and followed up after their 45th birthday. Follow-up began on each survivor’s 45th birthday and ended at the earliest date of diagnosis of first primary cancer of the prostate or other organs, date of death or December 31, 2009. Because incident cancers diagnosed outside of the cancer registry’s catchment area were not systematically ascertained, the analysis was restricted to cases with cancer diagnosed in the registry catchment area with person-years of observation adjusted for probability of residence in the catchment area using city-, sex-, age- and period-specific migration-rate estimates obtained from the AHS cohort, as described elsewhere (15, 19).

AHS Subjects in the Current Study

By design, the AHS sub-cohort is more heavily represented by high-dose-exposed individuals but covers the full range of survivor doses in the LSS cohort; 74% of AHS males with known dose were in the dose group that received >0.5 Gy while 15% were in the dose group that received <0.2 Gy (Appendix Table A1). The corresponding figures for all LSS males are 17% and 71%, respectively. The AHS subjects are distributed similarly to the LSS subjects with respect to age, city and follow-up years. A total of 6,850 AHS subjects participated in one or more of the AHS biennial health examinations with an overall participation rate of 84%. The participation rates did not differ by dose: 84%, 87% and 84% for those with dose <0.2, 0.2–0.5 and 0.5+ Gy, respectively.

Radiation Doses and Other Risk Factors

Dosimetry System 2002 (DS02) provided estimated individual organ-specific DS02 Revision 1 (DS02R1) doses received from the bombings (20, 21). We used weighted absorbed doses, to be referred to as “Gy” in this work, for the urinary bladder, located directly adjacent to the prostate, and calculated using a neutron weighting factor of 10. Estimated doses were adjusted to account for implausibly large estimates (shielded kerma >4 Gy) and random errors in dose assignments (22).

Several epidemiological studies of prostate cancer in Japan and elsewhere (23, 24) have suggested smoking, alcohol consumption and body mass index (BMI) as possible prostate cancer risk factors. We used self-reported information on these risk factors obtained from mailed questionnaire surveys conducted in the LSS between 1969 and 1991 (15, 25).

Data Organization

Data were aggregated into a person-year table stratified on attained age (8 five-year categories from 45 to 84 and one of ≥85 to <110), calendar time period (13 categories: 1958–1960, 1961–1965, 1966–1970, 1971–1975, 1976–1980, 1981–1985, 1986–1987, 1988–1990, 1991–1995, 1996–1998, 1999–2000, 2001–2004, 2005–2009), age at exposure (14 five-year categories from 0 to 69 and one category for ≥70) and DS02R1 weighted bladder dose (23 categories with dose cut points at 0, 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1, 1.25, 1.5, 175, 2, 2.5, 3 Gy) and an indicator of high dose (unweighted gamma plus neutron shielded kerma >4 Gy).

Smoking status was characterized as unknown, never-smoker or ever-smoker with information on duration and average intensity for ever-smokers, and time since quitting for past smokers. Alcohol consumption patterns were characterized as unknown, non-drinker, drinker (current or past) and for drinkers, the number of drinks per day (unknown, none, less than 1, 1–2, 2–3, 3 or more). Body mass index [weight (kg)/height $(m)^2$] was categorized as unknown or into four categories with cut-points of 15, 18.5, 25 and 30. The risk factors were considered to be unknown for persons who had never provided any information or prior to the first available information for questionnaire respondents. Smoking, drinking and BMI data were available for approximately 60% of the cohort members.

Analytical Models

Age-period-cohort model.—Because PSA screening was likely to be a major factor in the prostate cancer rate increase in recent years, we characterized and adjusted for effects of calendar period, attained age, and birth cohort on the baseline and excess absolute rates. Because these three factors are collinear (that is, any one can be expressed as the sum or difference of the other two), special methods are required to characterize the joint effects. We did this using a method suggested by Lockenhoff and Carstensen (26) in which one first fits a baseline rate model that includes two of the three effects, then fixes the parameters associated with these two effects and estimates parameters describing the third effect. For these analyses, the initial model for the log of baseline rates was described using log-linear quadratic spline in attained age with a knot at age 70 years and a two-knot quadratic spline in calendar year with knots at 1980 and 2000. After fitting this model, we described the birth-year-related "drift" using a quadratic spline in year of birth with a knot in 1915. The final model was fit by fixing the birth-year drift parameters and re-estimating the age and period effects.

In addition, to account for the effect of AHS PSA screening starting in December 2004, we allowed baseline rates for post-2004 AHS participants to differ from those for non-participants in fitting these models.

Risk models.—We used Poisson regression to model prostate cancer incidence rates as a function of radiation dose, city, attained age, age at exposure, birth year and other factors. We used excess relative risk (ERR) models primarily in the analysis of the association between radiation dose and incidence of prostate cancer. The ERR model can be expressed as λ_0*[1 + ERR], where λ_0 is the baseline cancer rate for unexposed (zero dose) individuals. The baseline rate was modeled as a function of birth year, attained age, city of exposure and location at the time of the bombings (within 10 km of the hypocenters vs. not-in-city). As described above, we also allowed for calendar-time-period effects on the baseline rates. The effects of smoking and alcohol consumption and BMI on baseline prostate cancer rates were also examined. The radiation-related ERR was modeled as $\rho(d) * \varepsilon(a,e,f)$, where $\rho(d)$ describes the shape of the dose response while $\varepsilon(.)$ describes effect modification as a log-linear function of log attained age (a), age at exposure (e) and other factors (f), e.g., smoking. We considered several forms for the dose-response function, including: linear (βd); linear-quadratic (βd) + d^2); a linear-threshold [$\beta(d - d_{th})I(d > d_{th})$, where d_{th} is the threshold dose] and categorical. Departure from linearity was assessed by testing = 0 in the linear-quadratic model.

We also considered excess absolute rate (EAR) models of the form $\lambda_0 + \rho(d)\in(a,e,f)$. In these models, attained age, period, birth cohort and age at exposure were included as radiation effect modifiers. The period and birth cohort effects on the dose response were constrained to be the same as the corresponding effects in the baseline rates while attained age and age at exposure were unconstrained effect modifiers.

Maximum-likelihood parameter estimates and 95% Wald or profile-likelihood confidence intervals (CIs) were computed based on Poisson regression methods using the AMFIT module of Epicure (27). Parameter estimates were obtained using likelihood methods,

hypothesis tests, confidence intervals and significance test likelihood ratio tests. All statistical tests were two-sided and considered significant when $P < 0.05$.

Ethical Considerations

This study was approved by the Radiation Effects Research Foundation Human Investigation Committee. The Hiroshima and Nagasaki Prefectures approved the linkages between the LSS cohort and data from the Cancer Registries, while the Hiroshima and Nagasaki Medical Associations approved the linkages with their tumor tissue registries.

RESULTS

Baseline Cancer Rates

In Table 1, crude prostate cancer rates are shown by city, age, calendar period of diagnosis and bladder dose among the 41,554 male subjects. The rates were similar in Hiroshima and Nagasaki and increased rapidly after age 65 years, with 88% of prostate cancers diagnosed at age ≥65 years. Almost one half (49%) of the male cohort members were <20 years of age at the time of exposure, and 66% of this group were alive at the end of follow-up (compared to 34% of all LSS males). More than one half (58%) of the prostate cancers were diagnosed among survivors who were <20 years at the time of the bombing. This is a consequence of various factors including the large younger birth cohorts reaching the ages of peak prostate cancer incidence in the recent decades, during which there was increasing PSA screening and increasing age-specific prostate cancer rates among Japanese males. The crude rates increased with decreasing age at exposure as well as increasing calendar time. The rates increased monotonically with increasing bladder dose below 2 Gy.

Table 2 summarizes the crude rates by attained age and calendar period. More than one half (61%) of the cases had occurred since the previous report, i.e., during the last 11 years of follow-up. The rates in the last decade of follow-up were markedly higher than in the earlier period, except for the oldest attained-age group. The largest relative increase in rates during the last decade occurred in the two youngest attained-age groups of 45–64 and 65–74 years. The bottom row in Table 2 presents age-adjusted period-specific rate ratios calculated relative to the earliest period (1958–1979). These show a rising trend of prostate cancer rates over the entire follow-up period, with a marked increase for the last two decades.

Using a simple age-power model with neither period nor birth cohort effects, prostate cancer rates increased rapidly with advancing age, roughly proportional to age to the 7th power peaking around age 80 and then declining slightly. Effects of period and birth cohort were both significant. The results illustrated in Fig. 1 show advancing age as a major determinant of the baseline rates (upper left-side panel) and a modest birth cohort effect (lower left-side panel). The period effect started in 1990–2000 (lower right-side panel) and was seen for all surviving birth cohorts (upper right-side panel). As suggested by the data in Table 2, the plots indicate a marked period effect reflecting, in large measure, the rapid increase in prostate cancer screening activities in Japan between 1990 and 2000.

The introduction of PSA screening in the AHS in December 2004 resulted in a marked increase in the baseline rates in AHS participants. For the period before 2005, the baseline

rates for AHS and non-AHS participants were similar ($P > 0.5$). Between 2005 and 2009, age-specific rates among AHS participants were 2.5 times (95% CI: 1.83, 3.38) those for non-participants. For three decades before 2005, approximately 25% of prostate cancers were in the AHS and this proportion increased to 30% during the 2005–2009 period.

Lifestyle Risk Factors

We found no indication of a difference in the rates for overweight/obese (BMI ≥25 kg/m^2) and underweight/normal weight ($P = 0.25$) nor was there an indication of a trend in prostate cancer risk with increasing BMI ($P = 0.5$). Rates for non-smokers were somewhat higher than those for past or current smokers or males with unknown smoking status (most of whom are likely to have been smokers), and there was no indication of a trend with pack-years ($P = 0.4$). Also, there was no indication of a trend in baseline rates with alcohol consumption levels ($P > 0.5$). Because these lifestyle factors were not significantly associated with baseline rates of prostate cancer, we did not consider any of these factors in the radiation risk analysis. Distributions of prostate cancer cases by smoking status, alcohol consumption and BMI level are presented in Appendix Table A2.

Radiation Effects

Excess relative risk.—We first used a linear dose-response model with age- and birth-cohort-adjusted baseline rates, but with no adjustment for AHS participation. With this model the estimated ERR/Gy for the current follow-up period was 0.65 (95% CI: 0.30, 1.08, $P < 0.001$). To allow for the temporal changes in the baseline rates, we then adjusted for both the general period effect and the effect of post-2004 AHS PSA screening. This resulted in a slightly lower, but significantly elevated ERR/Gy of 0.57 (95%: CI 0.21, 1.00, $P = 0.001$). While the baseline rates increased markedly during the period of AHS PSA screening, the ERR/Gy among AHS participants did not differ significantly ($P > 0.5$) before (0.77, 95% CI: 0.29, 1.37) and after screening (0.86, 95% CI: 0.03, 2.4). Therefore, the impact of PSA screening appeared to be primarily on the baseline rates.

In the LSS, a very large proportion of non-AHS members are in low-dose categories (92% at <0.2 Gy) while very few of them are in high-dose categories (2% at doses >0.5 Gy) (Appendix Table A1). Consequently, dose-response analysis among non-AHS members is underpowered and uninformative. The ERR/Gy estimate for non-AHS participants was −0.08 (95% CI: <−0.2, 0.60) while the estimated ERR/Gy for AHS participants was 0.79 (95% CI: 0.36, 1.33).

As described above, we found no significant effect of AHS participation on the baseline rates for prostate cancer before 2005. For sensitivity analysis, we analyzed the pre-2005 data in the full cohort, allowing for the general period effect, and found a significantly elevated ERR/Gy of 0.46 (95% CI: 0.09, 0.94). This provides evidence for the radiation effect before AHS PSA screening in this cohort.

For comparison with previously reported results (12), we applied the simple linear model with age- and birth-cohort-adjusted baseline rates to the current data with a follow-up limited to the end of 1998. This analysis involved 330 cases (Table 2), excluding 63 autopsy-

only cases and one case found to be a non-case while including seven pre-1999 cases that were identified retroactively from updated cancer registry data. The estimated ERR/Gy of 0.21 (95% CI: −0.20, 0.80) was not significant but twice the previous estimate of 0.11 (90% CI: −0.10, 0.54).

There was no indication of ERR effect modification by attained age ($P = 0.3$) or time since exposure ($P = 0.4$). However, there was some suggestion that the ERR/Gy decreases with increasing age at exposure ($P = 0.09$).

Shape of dose response.—Figure 2 shows the fitted linear dose response over the range from 0 to 2 Gy, together with dose-category-specific estimates of the prostate cancer ERR, a smoothed dose-response curve estimated using the category-specific ERR estimates, and upper and lower pointwise 95% bounds on the smoothed curve. There was no indication of non-linearity in a linear-quadratic dose-response model ($P > 0.5$) and the estimated quadratic effect was essentially 0. There was no indication of a statistically significant non-zero threshold effect in the dose response ($P = 0.4$). The threshold estimate in a linear threshold model was 0.06 Gy (95% CI: 0 to 0.67).

Excess absolute rates and excess cases.—The estimated EAR at age 70 for a male exposed at age 30 was 3.5 cases per 10,000 person-year-Gy (95% CI: 0.08 to 8.84, $P = 0.001$). This was higher than the previous estimate of 0.34 (90% CI: −0.064 to 1.6) (12).

Table 3 presents the observed and fitted baseline and radiation-associated excess cases by dose category. Overall, the estimated number of excess cases was approximately 40, accounting for almost 11% of the cases among cohort members with doses in excess of 0.005 Gy. More than one half (23) of the radiation-associated cases were diagnosed since 1999 and most (31) were diagnosed between the ages of 60 and 80 (not shown in Table 3). We estimated that six of the excess cases occurred among AHS participants after 2004.

DISCUSSION

Since the previously published LSS cancer incidence report (12), the number of incident prostate cancer cases in this cohort had increased from 387 to 851. We found that the rising baseline rates starting in 1990–2000 was a period effect, which affected the entire LSS cohort, corresponding to the rising trend of PSA screening in Japan (28). Furthermore, the PSA screening in AHS biennial examinations resulted in a 2.5-fold increase in the baseline rates among AHS participants after 2004. In the analysis allowing for both the general period effect and the post-2004 AHS baseline-rate increase (together with attained age and birth cohort effects), we found a significant linear dose response for prostate cancer with the estimated ERR/Gy of 0.57 (95% CI: 0.21 to 1.00). Approximately 40 of the 851 observed cases were estimated to be excess cases attributed to radiation exposure. There was a suggestion of the ERR decreasing with increasing age at exposure.

The current evidence for a radiation effect on prostate cancer is much stronger than previously found in the LSS. For the previous follow-up period ending in 1998 (12), the estimated ERR/Gy (excluding autopsy-only cases) was 0.24. With an additional six years of

follow-up through 2004, before PSA screening began in the AHS, the ERR/Gy increased to 0.46 and attained statistical significance. With further follow-up through 2009 the ERR/Gy further increased to 0.57. The latest LSS mortality data showed ERR/Gy for prostate cancer increasing from 0.21 (90% CI: <−0.3 to 0.96) in 1997 to 0.33 (95% CI: NA, 1.2) in 2003; neither of these estimates were statistically significant (11, 29), but mortality data may be less powerful for analysis of risk for less fatal prostate cancer.

Potential biases introduced by PSA screening need to be considered carefully (30, 31). Because AHS participants were fully screened regardless of radiation dose (and health conditions or other factors that may influence PSA test outcomes), dose-related selection of screened participants would seem unlikely. Of specific concern in the current study was a possible effect of the markedly increased baseline rates among AHS PSA screening participants on radiation risk estimates. The data indicated that AHS PSA screening elevated both the baseline and radiation-related excess rates proportionally, but did not affect the dose response within the AHS sub-cohort. The dose response could be reliably estimated within the AHS sub-cohort because AHS subjects, though heavily weighted with high-dose survivors, represent the full range of survivor doses. However, in the full cohort analysis, failure to allow for the PSA screening effect on the AHS baseline rates would have biased the radiation risk estimate. In our analysis, therefore, we adjusted the radiation risk for both AHS PSA screening participation and the general period effect on the baseline rates.

In Japan, municipal governments began community-wide PSA screening in the 1990s. Participation rates in municipal screening have been low, approximately 20% of the targeted population, having little effect on annual cancer detection rates (0.54–1.13%) (32); they are unlikely to be influenced by survivor dose, as the survivors are generally not informed of radiation dose. However, those survivors who were close to the explosion may have participated more actively in screening. Since all proximally exposed LSS subjects who had acute radiation symptoms are included in the AHS (16), they are likely to have been screened, together with other survivors, as part of AHS examinations. Cancer screening for atomic bomb survivors was enacted in the mid-1960s in Hiroshima and Nagasaki (33), but has not included prostate cancer screening. Therefore, the impact of screening activities outside the AHS on radiation risk would appear negligible. On an individual level, increasing awareness of the PSA test may have led some to voluntarily seek a PSA test (32); it is difficult to assess the impact of such cases, the size and characteristics of which are unknown.

The study by Kondo *et al.* of the Nagasaki atomic bomb survivors found a significantly increased relative risk (~1.5) of prostate cancer (excluding those diagnosed by screening) for proximally compared with distally exposed survivors (14). No dose-response analysis was performed. The subjects in the Kondo study were largely young at the time of the bombings (mean exposure age of 11–14 years) and followed up during the same decade as in our study. Some of the cases that study are likely to overlap with ours.

Studies of populations having received medical radiation exposure have provided variable evidence of a radiation-related risk of prostate cancer. In early published studies of patients treated with high-dose X rays (mean, 1.41 Gy) for ankylosing spondylitis (3, 34, 35),

increased prostate cancer mortality was found, but only within five years after treatment; it was noted that prostate cancer, which frequently presents with pain in the back due to direct spread or spinal secondaries, was prone to be confused with ankylosing spondylitis. In an extended follow-up of this cohort, prostate cancer mortality was elevated more than five years after treatment and there was a significant dose response with an estimated excess relative risk of 0.14 at 1 Gy (3). A follow-up study of patients treated with X rays for peptic ulcer disease (mean, 80 mGy) found no indication of increased mortality for prostate cancer (36, 37). Several follow-up studies of patients who received radiotherapy for rectal cancer (5, 38–41) reported a decreased risk of prostate cancer, but this may be explained by a cell-killing effect of high therapeutic doses.

In published occupational studies, early data from UK Atomic Energy Authority (UKAEA) employees showed an increased risk of prostate cancer (diagnosed before 1987) associated with external radiation exposure among those who had probable environmental internal exposure to one or more of several radionuclides (4); however, a further follow-up of the UKAEA workforce through 1997 presented no evidence of a continuing elevation of the risk of prostate cancer in any subset of the workers (10). More recently reported studies of nuclear-worker populations provide quantitative risk estimates (Appendix Table A3). While the NRRW-3 update (9), INWORKS (6) and Wismut German uranium miner cohorts (8) represent low-dose exposure (mean, 23–34 mGy), the Mayak population was exposed to moderately high dose (350–540 mGy) (42, 43). None of the ERR/Gy estimates in these nuclear worker studies are significantly different from zero, although the Mayak estimates tend to be higher than the others. It should be noted that nearly one half of the INWORKS data are from the NRRW-3 cohort (44), which was subsequently updated in the NRRW-3 update (9). The current LSS incidence ERR/Gy estimate (0.58) is higher than the estimates from any of these nuclear worker studies (ranging between −1.18 and 0.16). The higher ERR for the LSS may in part be related to the fact that the current LSS data are largely driven by the large proportion of the youngest birth cohort of survivors. Given the wide confidence intervals, however, the LSS risk data are not inconsistent with those of nuclear worker cohorts, with the exception of the Wismut cohort.

Most recently, a long-term follow-up study of U.S. nuclear weapons test participants has reported an increased standardized mortality ratio (1.13) for prostate cancer, but no evidence of a dose response with an ERR per 100 mGy of 0.03 (95% CI: −0.27, 0.33). Estimated mean doses were low (6 mGy for red bone marrow) and approximately 25% of the cohort subjects first participated in the test between 16 and 19 years of age (45). Similarly, an increased relative risk for prostate cancer incidence and mortality was found among UK atmospheric nuclear weapons test participants, but no dose-response analysis was performed (46). Doses were considered low (mean gamma, 9.9 mGy for those with recorded dose).

The current study suggested increased radiation-related risk of prostate cancer associated with younger exposure age. Recent LSS data on female breast and endometrial cancers suggested heightened risk associated with radiation exposure around puberty for these hormone-related cancers (25, 47). The number of prostate cancer cases in the current study was still insufficient for detailed analysis of the possible age effect.

The time-dependent impact of PSA screening complicated the analysis and interpretation of the radiation risk of prostate cancer in the LSS. We used the linear dose-response model including a population-wide period effect beginning in 1990–2000 augmented with additional PSA-associated period effects for post-2004 AHS participants and obtained a statistically significant radiation dose response with an estimated ERR/Gy of 0.57 for the full cohort for the current follow-up period. This, together with the significant dose response that existed prior to AHS PSA screening, is the strongest evidence to date of a radiation effect on prostate cancer in the LSS. The extent to which the younger birth cohort may have contributed to the recent increase in the risk will become clearer with future follow-up. Unfortunately, because of the nature of the linkage-based incidence data used in the current study, we were unable to identify screening-detected prostate cancers at individual levels. However, efforts are underway to ascertain individual screening-detected cancers to further assess the implications of PSA screening on the radiation risk estimate.

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APPENDIX

Table A1

Distribution of Male Subjects, Person-Years by Age at Exposure, Attained Age, Calendar Period and Urinary Bladder Dose among LSS, Non-AHS and AHS Participants

	LSS				Non-AHS				AHS			
	Persons	**(%)**	**Person-years**	**(%)**	**Persons**	**(%)**	**Person-years**	**(%)**	**Persons**	**(%)**	**Person-years**	**(%)**
Total	41,554	100.0	760,508	100.0	33,414	100.0	602,327	100.0	8,140	100.0	158,181	100
Age at exposure (years)												
0–19	20,367	49.0	367,817	48.4	16,417	49.1	294,682	48.9	3,950	48.5	73,134	46.2
20–39	8,390	20.2	216,844	28.5	6,345	19.0	163,704	27.2	2,045	25.1	53,140	33.6
40+	12,797	30.8	175,847	23.1	10,652	31.9	143,941	23.9	2,145	26.4	31,906	20.2
Bladder dose category (Gy)												
NIC	10,209	24.6	197,177	25.9	8,386	25.1	160,015	26.6	1,823	22.4	37,162	23.5
<0.005	14,088	33.9	250,474	32.9	11,576	34.6	200,696	33.3	2,512	30.9	49,778	31.5
−0.1	10,787	26.0	195,936	25.8	9,824	29.4	178,161	29.6	963	11.8	17,775	11.2
−0.2	2,087	5.0	38,353	5.0	1,616	4.8	29,520	4.9	471	5.8	8,832	5.6
−0.5	2,201	5.3	39,806	5.2	1,447	4.3	25,358	4.2	754	9.3	14,448	9.1
−1	1,245	3.0	22,572	3.0	416	1.2	6,459	1.1	829	10.2	16,113	10.2
−2	714	1.7	12,657	1.7	115	0.3	1,674	0.3	599	7.4	10,983	6.9

	LSS				Non-AHS				AHS			
	Persons	(%)	Person-years	(%)	Persons	(%)	Person-years	(%)	Persons	(%)	Person-years	(%)
2+	223	0.5	3,534	0.5	34	0.1	446	0.1	189	2.3	3,089	2.0
Attained age (years)												
45–54			207,723	27.3			163,911	27.2			43,812	27.7
55–64			246,306	32.4			194,244	32.2			52,061	32.9
65–74			197,920	26.0			157,161	26.1			40,759	25.8
75–84			88,847	11.7			70,934	11.8			17,914	11.3
85+			19,712	2.6			16,078	2.7			3,634	2.3
Period												
1958–1964			119,048	15.7			96,607	16.0			22,441	14.2
1965–1974			139,822	18.4			108,529	18.0			31,293	19.8
1975–1984			153,695	20.2			118,716	19.7			34,978	22.1
1985–1994			170,055	22.4			135,049	22.4			35,006	22.1
1995–2004			125,998	16.6			101,257	16.8			24,741	15.6
2005–2009			51,891	6.8			42,170	7.0			9,721	6.1

NIC = not in either city.

Table A2

Distribution of Male Subjects and Prostate Cancer Cases by Smoking Intensity, Alcohol Consumption and Body Mass Index (BMI)

	Persons	Cases	Rate[a]
Total	41,554	851	11.2
Smoking intensity			
Unknown	16,228	192	5.7
Never-smoker	3,601	117	19.4
1–14 CPD	8,346	229	16.5
15–25 CPD	9,327	224	15.1
25+ CPD	4,052	89	14.5
Alcohol consumption (g/week)			
Unknown	21,727	290	6.6
None	3,351	91	16.8
1–49	1,850	52	19.3

	Persons	Cases	Rate[a]
50–249	7,943	231	18.9
250+	6,683	187	18.5
BMI category			
Unknown	16,481	203	8.8
Underweight (<18.5)	3,158	73	11.3
Low normal (−21.4)	9,416	236	11.9
High normal (−24.9)	9,111	245	12.6
Overweight (−29.9)	3,154	89	13.4
Obese (30+)	234	5	10.9

[a]Per 10,000 person-years.

Abbreviation: CPD = cigarettes per day

Table A3

Comparisons of ERRs for Prostate Cancer from Occupationally Exposed Populations and LSS

Cohort	Deaths/cases	ERR/Gy	(95% CI)	Mean gamma dose (mGy)
Prostate cancer mortality				
NRRW-3 update (9)	1,115	0.072	(−0.63, 1.04)	28
INWORKS (6)	1,685	−0.11	(−0.71, 0.67)[a]	23
Wismut German uranium miners (8)	263	−1.18	(−2.4, 0.02)	34
Mayak (43)	80	0.11	(<, 0.63)	354
LSS	130	0.33	(NA, 1.25)	125
Prostate cancer incidence				
NRRW-3 update (9)	3,809	−0.268	(−0.68, 0.24)	28
Mayak (42)	70	0.16	(−0.12. 0.73)	540
LSS	851	0.59	(0.21, 1.07)	125

[a]90% confidence interval (CI).

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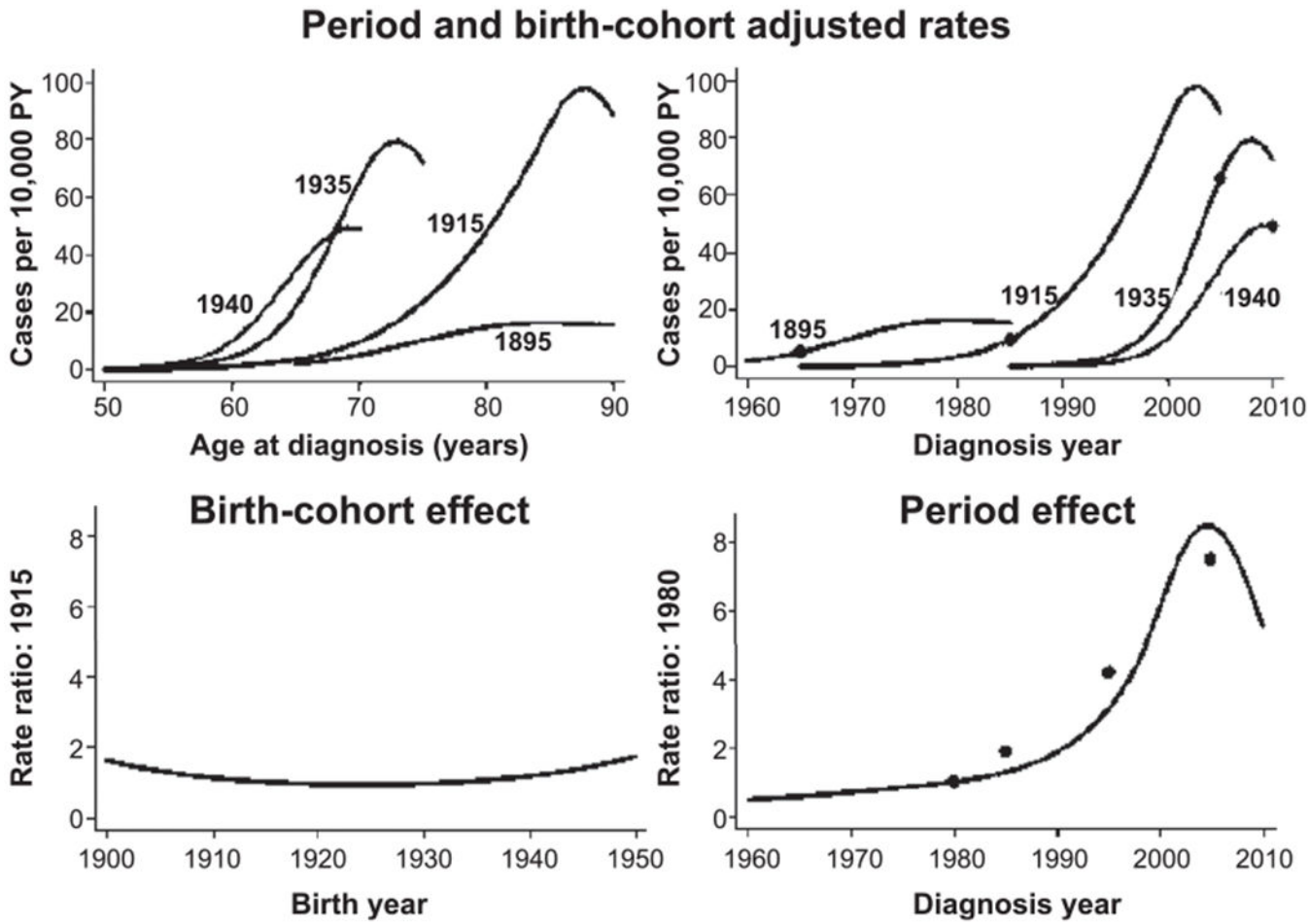

FIG. 1.

Summary of age, period and birth cohort effects on LSS prostate cancer rates. The upper panels present age-specific prostate cancer incidence rates for men born in 1895, 1915, 1935 and 1940. In the left-side panel the rates are plotted against age while in the right-side panel they are plotted against year of diagnosis. The fitted rates are the product of a (fitted) standard age curve (for someone born in 1915 and an exam in 1990) times the appropriate period and birth cohort effects. The points in the upper right-side panel indicate the risk at age 70 for the different birth cohorts. The plots in the bottom row display the birth cohort effect (left-side panel) and the fitted period effect (right-side panel). The points on the period effect plot are categorical estimates of the age-adjusted period effect (see Table 2). The same vertical scale was used for the birth cohort (rate ratio relative to birth year 1915) and period (rate ratio relative to year 1980) effects to provide a better indication of the relative magnitudes of these effects. PY = person-years.

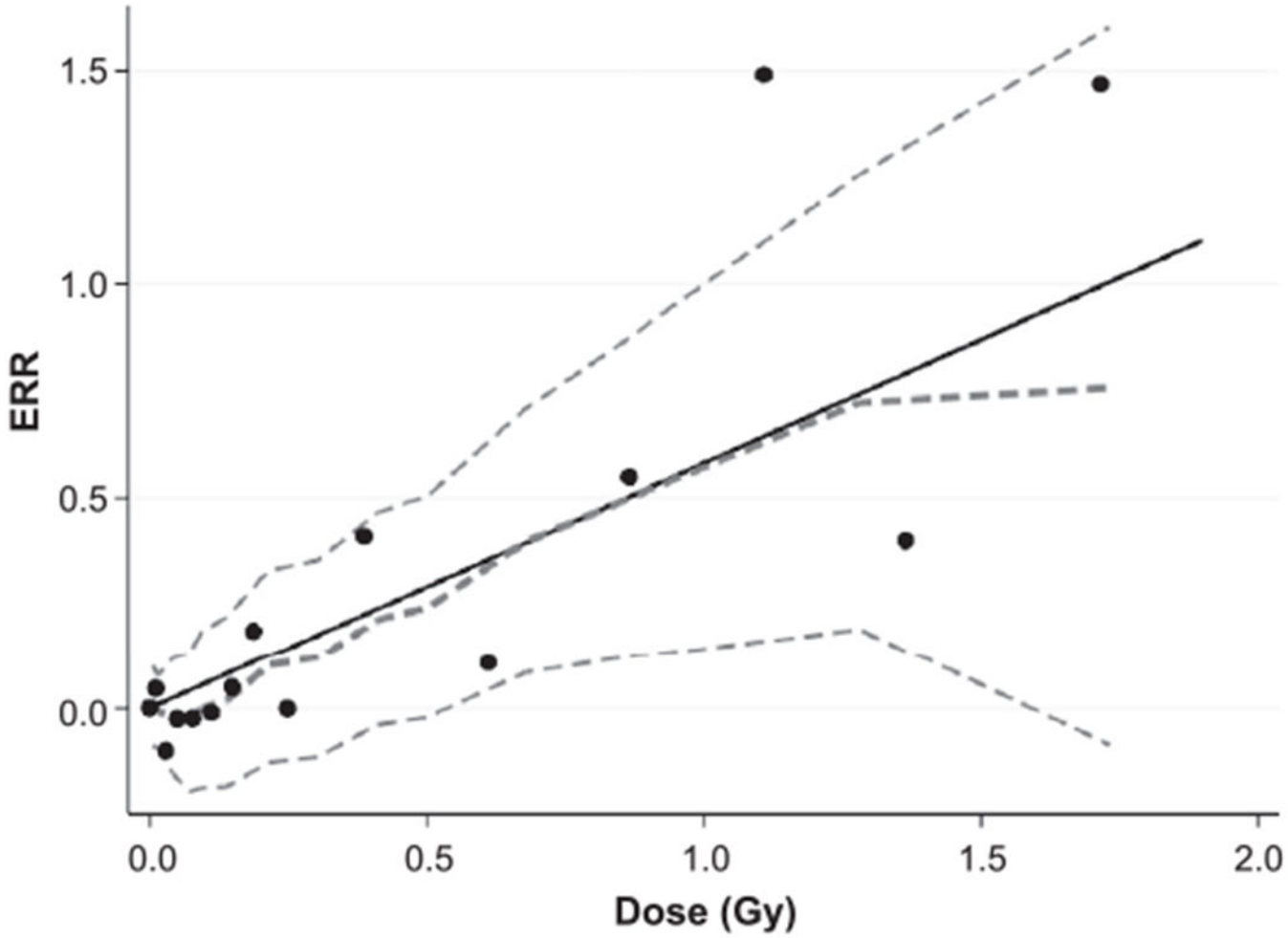

FIG. 2.

Prostate cancer excess relative risk (ERR) in relationship to weighted absorbed DS02R1 bladder dose. Shown are the fitted linear ERR dose-response function (black solid line), the ERR estimates for 16 dose categories (black points) and nonparametric smoothed estimate with pointwise 95% confidence intervals (dashed curves) over the entire dose range.

TABLE 1

Number of Persons, Person-Years of Follow-up, Prostate Cancer Cases and Crude Incidence Rates by City, Age at Exposure, DS02R1 Weighted Bladder Dose, Attained Age and Calendar Period of Diagnosis

	Men	Person-years	Cases	Crude rate[a]
Total	41,554	760,508	851	11.2
City				
Hiroshima	28,650	544,642	617	11.3
Nagasaki	12,904	215,866	234	10.8
Age at exposure				
0–19	20,367	367,817	497	13.5
20–39	8,390	216,844	221	10.2
40+	12,797	175,847	133	7.6
Attained age				
45–54		207,723	6	0.3
55–64		246,306	99	4.0
65–74		197,920	366	18.5
75–84		88,847	301	33.9
85+		19,712	79	40.1
Calendar period				
1958–1964		119,048	27	2.3
1965–1974		139,822	44	3.1
1975–1984		153,695	80	5.2
1985–1994		170,055	118	6.9
1995–2004		125,998	319	25.3
2005–2009		51,891	263	50.7
Bladder dose category (Gy)				
Not in either city	10,209	197,177	190	9.6
<0.005	14,088	250,474	286	11.4
−0.1	10,787	195,936	211	10.8
−0.2	2,087	38,353	45	11.7
−0.5	2,201	39,806	52	13.1

	Men	Person-years	Cases	Crude rate[a]
−1	1,245	22,572	33	14.6
−2	714	12,657	29	22.9
2+	223	3,534	5	14.1

[a] Per 10,000 person-years.

TABLE 2

LSS Incident Prostate Cancer Case Counts and Crude Rates by Attained Age and Period: 1958–2009

		Calendar period				
Age		**1958–1979**	**1980–1989**	**1990–1998**	**1999–2009**	**Total**
45–64	Cases[a]	12	10	15	68	105
	Rate	0.5	0.7	1.2	10.5	1.9
65–74	Cases	46	24	41	255	366
	Rate	4.9	8.4	13.3	34.2	16.1
75–84	Cases	40	44	53	164	301
	Rate	10.5	19.8	38.9	67.8	30.6
85+	Cases	7	14	24	34	79
	Rate	16.5	22.7	45.4	37.9	36.6
Total	Cases	105	92	133	521	851
	Rate	3.0	4.4	7.5	30.8	9.3
Period effect (RR)[b]		1	1.9	3.5	7.8	
		(Ref)	(1.4; 2.5)	(2.7; 4.5)	(6.3; 9.7)	

[a] Cases per 10,000 person-years.

[b] Attained-age adjusted risk relative to the pre-1980 period.

TABLE 3

Observed and Fitted Incident Prostate Cancer Cases:[a] LSS, AHS Participants and Non-participants, 1958–2009

Dose category (Gy)	Men	Person-years	Cases	Fitted cases[a]		Attributable fraction[b]
				Background	Excess	
Not in either city	10,209	197,194	190	190	0.0	
<0.005	14,088	250,479	286	274.4	0.1	
−0.1	10,787	195,941	211	216.6	4.1	2%
−0.2	2,087	38,351	45	42.8	3.5	8%
−0.5	2,201	39,803	52	43	7.9	16%
−1	1,245	22,570	33	26	10.7	29%
−2	714	12,656	29	13.6	10.4	44%
2+	223	3,534	5	3.8	3.4	48%
Total	41,554	760,508	851	810	40.0	11%

[a] Estimated background and fitted excess cases based on an ERR model including age and period effects.

[b] Fraction attributable to radiation exposure among those with doses in excess of 0.005 Gy.