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SHORT COMMUNICATION

The Effect of Prostate-Specific Antigen (PSA) Test on Radiation Risk Estimate for Prostate Cancer Incidence among Atomic-Bomb Survivors

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Following our previous report on the radiation dose-response for prostate cancer incidence rates in the Life Span Study (LSS) cohort of atomic bomb survivors, we re-evaluated the radiation-related risk adjusting for differences in baseline cancer incidence rates among three subsets of the LSS cohort defined by the timing of their first participation in biennial health examinations offered to the Adult Health Study (AHS) sub-cohort members and prostate-specific-antigen (PSA) testing status for AHS participants: 1. non-AHS participants, 2. AHS participants before receiving PSA test, and 3. AHS participants after receiving PSA test. We found a 2.9-fold increase in the baseline incidence rates among AHS participants after receiving PSA test. After adjusting for the PSA-testing-status effects on the baseline rates the estimated excess relative risk (ERR) per Gy was 0.54 (95% CI: 0.15, 1.05), which was almost identical to the previously reported unadjusted ERR estimate (0.57, 95% CI: 0.21, 1.00). The current results confirmed that, while the PSA testing among AHS participants increased the baseline incidence rates, it did not impact the radiation risk estimate, strengthening the previously reported dose-response relationship for prostate cancer incidence in the LSS. As the use of PSA tests continue in screening and medical settings, analyses of possible effects of PSA testing should be an important aspect of future epidemiological studies of the association between radiation exposure and prostate cancer.

INTRODUCTION

The prostate is among the few cancer sites for which the relationship with radiation exposure has not been well established. Epidemiological evidence on the effects of radiation exposure on risk of prostate cancer incidence and mortality has generally been regarded as inconsistent (*1*). Early studies reported increased risks of prostate cancer mortality after X-ray treatment for ankylosing spondylitis (*2*) and prostate cancer incidence among nuclear workers with mixed external and internal exposures (*3*). More recently, studies of nuclear workers have estimated the radiation-related excess relative risk (ERR) per Gy that ranged from below zero (–1.18) to 0.19 in studies of prostate cancer mortality and from below zero (–0.34) to 0.16 in studies of prostate cancer incidence, with none of these estimates being significantly different from zero (*4–9*) (Supplementary Table S1; https://doi.org/10.1667/RADE-22-00089.1.S1). Kondo et al. (*10*) have reported an increased risk of prostate cancer incidence among proximally exposed atomic bomb survivors in Nagasaki followed through 2009, but no dose response analysis was performed. Studies of cancer incidence and mortality data in the Life Span Study (LSS) cohort of Japanese atomic bomb survivors from Hiroshima and Nagasaki, with shorter follow-up, consistently suggested a modestly elevated risk of prostate cancer associated with radiation but without reaching the level of statistical significance (*11, 12*).

Most recently, we reported the significant dose response for prostate cancer incidence found in the latest LSS data for the 1958–2009 period (*13*). During the last two decades of follow-up, there was a sharp increase in the use of prostate-specific antigen (PSA) test for prostate cancer screening in Japan. As Weiss indicated (*14*), the introduction of screening in a population affects the reported incidence rates and can interfere with analyses and interpretations of incidence data over time. Through detection of early-stage cancers and timely treatment, it could also affect patterns of cancer mortality. Furthermore, failure to consider effects of screening can distort the assessment of the association between exposure and risk of

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cancer incidence and mortality. Our age-period-cohort analysis of the LSS data indicated the presence of a significant period effect on the baseline rates of prostate cancer incidence; this corresponded in large measure to the increasing use of PSA tests beginning in the 1990s in Japan (*15*). In addition, there was a marked increase in the baseline incidence rates of prostate cancer among participants of the Adult Health Study (AHS) clinical sub-cohort of the LSS for the period of 2005–2009. This corresponded to the addition of PSA testing in December 2004 to biennial health examinations offered to AHS participants. Allowing for period effects of PSA testing on the baseline incidence rates in the full LSS cohort and among AHS participants, we estimated the ERR for prostate cancer incidence of 0.57 per Gy (95% CI: 0.21, 1.00) (*13*).

The purpose of the present study was to re-evaluate the effect of PSA testing on radiation risk estimate of prostate cancer incidence using a refined baseline risk model and further consider the possible impact of PSA testing. For the re-analysis, we identified individual AHS participants who received PSA tests and timing of PSA tests received. We then used this information to adjust the baseline incidence rates.

MATERIALS AND METHODS

The LSS cohort 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 (NIC) at the time of the 1945 atomic bombings. As described in more detail in the previous reports (*16, 17*), the survivor group consists of heavily exposed (exposed at $<$2.5 km of the hypocenter) and city-sex and age-matched persons exposed to moderate doses (at 2.5–10 km) and lower-to-negligible doses.

Incident cases of cancer were ascertained through the Hiroshima and Nagasaki local cancer registries. As in the previous study (*13*), we studied male LSS subjects who had estimated radiation doses and were alive and not known to have had any cancer as of 1958. Follow-up began on their 45th birthday or January 1, 1958 and ended on the earliest date of prostate cancer or other cancer diagnosis, date of death, 110th birthday, or December 31, 2009. For the present analyses, we divided the analytic cohort (41,554 males) into three subsets based on when subjects first participated in AHS clinical examination and when they first received a PSA test offered by AHS examination.

AHS Participants and PSA Test

The AHS is a clinical sub-cohort that comprises about 20% of the LSS cohort members, who were sampled more heavily from the high-dose survivors but includes persons in the full dose range. They have been invited to biennial clinical health examinations since 1958. Eighty-three percent (6,735) of 8,140 male AHS subjects participated in one or more of the biennial health examinations.

Beginning in December 2004, AHS participants were offered PSA tests and those with elevated PSA levels ($>$4 ng/mL) were advised to consult their primary-care physicians or urologists. In the present study, we obtained individual data on PSA testing dates and results. Among 6,735 males who participated in AHS examinations at least once since 1958, 1,358 participated in health examinations after December 2004. All but 10 of these males (1,348) received at least one PSA test at various times before the end of the current follow-up period.

Statistical Analyses

For the radiation risk analyses, we estimated the ERR per Gy using Poisson regression methods for grouped survival data. The ERR model can be summarized as λ_0*[1 + ERR], where λ_0 is the baseline incidence rate for unexposed (zero dose) individuals described as a function of city, birth year, attained age and a city-specific indicator of NIC status, plus a city-specific indicator of location whether the subjects were exposed between 3 to 10 km from the hypocenter at the time of bombings to adjust for potential differences in incidence rates due to geographical variation (*18*). We used weighted absorbed dose estimates for the urinary bladder which is located directly adjacent to the prostate in Gy from Dosimetry System 2002 Revision 1 (DS02R1) (*19*), defined as the sum of gamma dose and 10 times the neutron dose. As in all recent analyses in the LSS, the gamma and neutron dose estimates were adjusted to account for implausibly large estimates (shielded *kerma* $>$4 Gy) and random errors in dose assignments (*20*).

The risk model in the previous study allowed baseline rates of prostate cancer incidence to differ between AHS participants between 2005 and 2009 and non-participants for the same period to account for the effect of PSA tests received during AHS examinations (*13*). In the present study, the baseline model also included a three-level time-dependent variable of when (month and year) AHS subjects first visited a biennial clinical examination and when (month and year) they first received a PSA test (before first AHS examination/before first PSA test in AHS/after first PSA test in AHS). In all analyses, we used an age-period-cohort method (*21*) to model the rising baseline incidence rates in the full LSS cohort corresponding to the increasing use of PSA tests in the general population (*13*).

Maximum likelihood parameter estimates and 95% profile-likelihood confidence intervals (CIs) were computed with the AMFIT program of Epicure (version 2.00.02) (*22*). Statistical tests were two-sided and considered significant when $P < 0.05$.

Ethical Considerations

This study was approved by the Institutional Review Board of the RERF. The Hiroshima and Nagasaki prefectures approved linkage of the LSS cohort with the cancer registry data.

RESULTS

There were 851 incident cases with first primary prostate cancer among 41,554 male members of the LSS with 760,477 person-years (PYs) of observation. Timing of first biennial health examination and PSA testing varied between cohort members. Therefore, we constructed the following three cohort subsets:

1. **Non-AHS participants (including pre-AHS period):** This subset of 41,554 males (646,284 PYs of observation) comprised 1. non-AHS subjects (33,414 males, 602,325 PYs), 2. AHS subjects who never participated in AHS health examinations (1,405 males, 23,387 PYs), and 3. AHS subjects before their first AHS examination (6,735 males, 20,571 PYs);
2. **Pre-PSA AHS participants:** This subset included 6,735 male AHS participants, with 111,716 PYs accumulated from the date of first AHS examination to the end of follow-up in those who did not receive an AHS PSA test (5,387 males, 95,461 PYs) and to the date of first PSA test in those who did (1,348 males, 16,255 PYs); and
3. **Post-PSA AHS participants:** The smallest subset of 1,348 male AHS participants with 2,477 PYs accumulated from the date of first AHS PSA test to the end of follow-up.

TABLE 1
Crude Incidence Rates of Prostate Cancer Among Non-AHS Participants, Pre-PSA AHS Participants and Post PSA AHS Participants by City, Age at Exposure and Attained Age: LSS, 1958–2009

	Non-AHS participants			AHS participants					
				Pre-PSA-test			Post-PSA-test		
	PY[b]	Case	Rate[a]	PY[c]	Case	Rate[a]	PY[d]	Case	Rate[a]
Total	646,284	662	10.2	111,716	146	13.1	2,477	43	173.6
City									
Hiroshima	466,021	493	10.6	77,011	97	12.6	1,589	27	169.9
Nagasaki	180,263	169	9.4	34,706	49	14.1	888	16	180.2
Age at exposure (years)									
0–19	320,398	385	12.0	45,128	74	16.4	2,296	38	165.5
20–39	173,793	165	9.5	42,858	51	11.9	181	5	276.7
40+	152,092	112	7.4	23,730	21	8.8	0	0	-
Attained age (years)									
45–54	180,239	6	0.3	27,475	0	0.0	0	0	-
55–64	210,500	77	3.7	35,545	18	5.1	249	4	160.8
65–74	165,929	293	17.7	30,898	55	17.8	1,084	18	166.0
75–84	73,243	227	31.0	14,589	56	38.4	1,014	18	177.5
85+	16,372	59	36.0	3,209	17	53.0	130	3	231.1

NIC = not in the city of Hiroshima or Nagasaki at the time of the bombings; PY = person year.
[a] Incidence rate per 10,000 PYs; [b] PYs among non-AHS subjects and PYs before the first AHS examination among AHS subjects; [c] PYs from the first AHS examination to the end of follow-up among AHS participants whose last AHS examination was before the introduction of PSA test or to the first AHS examination after the introduction of PSA test since December 2004 among AHS subjects; [d] PYs from the first PSA test to the end of follow-up.

Crude Incidence Rates

Crude incidence rates (per 10,000 PYs) for prostate cancer for the three subsets are presented by city, age at exposure and attained age (Table 1) and by calendar year period and dose (Table 2). The overall incidence rate for post-PSA AHS participants (173.6) was more than ten times higher than for non-AHS participants (10.2, $P < 0.001$) or pre-PSA AHS participants (13.1, $P < 0.001$) (Table 1). The crude incidence rates increased with increasing attained age in all groups and decreased with increasing age at exposure among non-AHS and pre-PSA AHS participants. There were no differences in rates between Hiroshima and Nagasaki in any of the subsets.

By calendar period, the crude incidence rates were similar between the non-AHS and pre-PSA AHS groups before 1986 ($P = 0.7$) (Table 2). The apparently higher crude rates in the pre-PSA AHS group starting from 1986 were not significant when adjusted for attained age ($P = 0.2$). By dose, the rates were similar for non-AHS participants and pre-PSA AHS participants at doses below 0.5 Gy. The rates at higher dose levels for non-AHS participants, based on small numbers of cases, are uninformative; for AHS participants, the highest rates were observed in the highest dose categories.

Relative Risk of Baseline Incidence

We estimated the adjusted relative risk (RR) of baseline incidence for the two sub-sets of AHS participants, using non-AHS participants as the reference group (Table 3). The RR for pre-PSA AHS participants was close to unity (1.14, 95% CI: 0.93, 1.38), but was significantly elevated (2.86, 95% CI: 2.01, 3.99) for post-PSA AHS participants. The latter RR estimate was only slightly higher than that previously estimated for AHS participants for the period of 2005 and 2009 (2.5, 95% CI: 1.83, 3.38) (*13*).

Dose Response Analysis

We used a linear dose response model in which the baseline-rates characterization included an age-period-cohort effect for the full LSS cohort and effect of PSA testing for the AHS indicated in Table 3. The estimated ERR was 0.54 per Gy (95% CI: 0.15, 1.05). This was comparable to the estimate of 0.57 per Gy (95% CI: 0.21, 1.00) with a cruder adjustment for the effect of PSA testing in AHS during the 2005–2009 period that was reported in (*13*).

DISCUSSION

The introduction of PSA testing/screening in Japan had the period-effect on the baseline prostate cancer incidence rates in the entire LSS cohort beginning in the 1990s while the addition of PSA test to AHS biennial health examinations further affected the subset of AHS participants examined during the 2005–2009 period. In our previous analysis, the radiation-related risk was estimated based on the model that included adjustment for the period-dependent effects on the baseline rates (*13*). Although nearly all AHS participants examined after 2004 received the PSA tests, they did so at various times over the last five-years of the follow-up period. In the present study, we refined the baseline model in which the baseline incidence rates varied according to the timing of individual subjects first AHS examination and the

TABLE 2
Crude Incidence Rates of Prostate Cancer Among Non-AHS Participants, Pre-PSA AHS Participants and Post-PSA AHS Participants by Calendar Year Period and Radiation Dose: LSS, 1958–2009

				AHS participants					
	Non-AHS participants			Pre-PSA-test			Post-PSA-test		
	PY[b]	Case	Rate[a]	PY[c]	Case	Rate[a]	PY[d]	Case	Rate[a]
Calendar period									
1958–1965	109,141	24	2.2	15,311	3	2.0	0	0	-
1966–1975	112,164	39	3.5	24,595	6	2.4	0	0	-
1976–1985	126,491	63	5.0	28,333	18	6.4	0	0	-
1986–1995	145,173	93	6.4	24,801	31	12.5	0	0	-
1996-Nov 2004	106,479	241	22.6	15,121	63	41.7	0	0	-
Dec 2004–2009	46,836	202	43.1	3,555	25	70.3	2,477	43	173.6
Radiation dose (Gy)									
NIC	166,597	155	9.3	30,568	35	11.4	0	0	0.0
<0.005	214,932	238	11.1	34,477	37	10.7	1,055	11	104.2
0.005–0.1	187,653	187	10.0	7,902	12	15.2	379	12	316.4
0.1–0.2	32,084	36	11.2	6,097	7	11.5	170	2	117.5
0.2–0.5	28,697	36	12.5	10,828	11	10.2	278	5	179.7
0.5–1	10,610	7	6.6	11,608	23	19.8	351	3	85.4
1–2	4,436	2	4.5	8,038	19	23.6	181	8	441.9
2+	1,275	1	7.8	2,198	2	9.1	61	2	326.2

NIC = not in the city of Hiroshima or Nagasaki at the time of the bombings; PY = person year.
[a] Incidence rate per 10,000 PYs; [b] PYs among non-AHS subjects and PYs before the first AHS examination among AHS subjects; [c] PYs from the first AHS examination to the end of follow-up among AHS participants whose last AHS examination was before the introduction of PSA test or to the first AHS examination after the introduction of PSA test since December 2004 among AHS subjects; [d] PYs from the first PSA test to the end of follow-up.

first PSA test in AHS health examination. The resulting ERR estimate of 0.54 per Gy (95% CI: 0.15, 1.05), which is essentially the same as the previous estimate of 0.57 per Gy (95% CI: 0.21, 1.00), suggests that the apparent dose response relationship for prostate cancer incidence in the LSS is unlikely to be a consequence of bias related to inadequate adjustment for the impact of PSA testing.

The incidence rates of prostate cancer in Japan increased gradually between 1985 and late 1990s, rapidly accelerated between 2000 and 2004 and slowed down thereafter (*23*). The increase in rates was most prominent for localized prostate cancer, suggesting early detection of cancers through dissemination of PSA testing (*24*). Since the PSA test is used mainly for screening of older males without symptoms, a potential for over-diagnosis, i.e., cancer which would not have been diagnosed and caused harm during the person's lifetime without screening, is considerable (*25*). Despite the possibility of over-diagnosis, prostate cancer mortality in Japan showed a small but significant decrease during 2005–2018 (*23*). Overall, the merits and harms of PSA screening continue to be debated. In 2008, the Japanese Urological Association recommended PSA screening for men 50 years or older (*26*) while the research group funded by the Ministry of Health, Labor and Welfare of Japan concluded a year later that there was insufficient evidence to support population-based PSA screening and decisions about opportunistic screening should be made at the individual level (*27*).

As part of health examinations offered by the AHS, nearly all AHS participants eligible for PSA testing in December 2004 received at least one PSA test before the end of follow-up (1,348/1,358), representing a small fraction of the LSS males: 9% of those remaining under observation in December 2004 or 3% of those at the beginning of follow-up. Outside AHS health examinations, there are several settings in which the LSS cohort members may have received PSA tests. In Japan, municipal governments across the country began PSA-based screening in the 1990s, but screening participation rates

TABLE 3
Numbers of Males, Cases, Crude Rates and Baseline Relative Risk for Prostate Cancer Incidence

	Males	PYs[b]	Cases	Crude rates[c]	Baseline relative risk
Non AHS participants[a]	41,554	646,284	662	10.2	Ref
Pre-PSA AHS participants	6,735	111,716	146	13.1	1.14 (0.93, 1.38)
Post-PSA AHS participants	1,348	2,477	43	173.6	2.86 (2.01, 3.99)

[a] Includes AHS subjects before first AHS health examinations; [b] Some AHS participants contributed PYs to more than one subset; for example, persons in the post-PSA AHS subset contributed PYs to the pre-PSA AHS subset before receiving PSA tests and to the pre-AHS subset before their first AHS examination; [c] Incidence rate per 10,000 PYs.

are reportedly low (about 20%) (*15*). Annual health check-ups, which include PSA tests in recent years, are also offered by large companies to their employees; however, the magnitude of their impact on population cancer rates is unknown. In Japan, older persons often voluntarily seek comprehensive health-examination services including PSA tests. In the medical care setting, the PSA test is one of the first tests performed in persons with symptoms suggestive of prostate cancer. However, it is often difficult to determine whether the PSA test was done among apparently healthy (asymptomatic) males or those who are symptomatic of prostate cancer; so this raises considerable possibility for misclassification of screening status (*14*). Given these situations and scarcity of reliable information, it would be extremely challenging to ascertain screening status for epidemiological evaluations. Here, the key question for our study is whether motivation to enroll in PSA-based screening outside of the AHS is influenced by radiation exposure among the survivors. This seems unlikely because survivors are unaware of radiation dose received from the bombings. The participation rates for AHS health examinations did not differ by dose: 84%, 87% and 84% for those with dose <0.2, 0.2–0.5 and 0.5+ Gy, respectively (*13*). Cancer screening programs targeted at atomic-bomb survivors in Hiroshima and Nagasaki do not include prostate cancer screening (*13*). Nonetheless, the extent to which PSA testing outside of the AHS may have affected the dose response analysis remains uncertain.

Because prostate cancer is generally less fatal than most major cancers, incidence rates are a better measure of risk than mortality rates, but the dormant nature of prostate cancer makes incidence studies more prone to screening bias. To our knowledge, a study by Kondo et al. (*10*) of the Nagasaki atomic bomb survivors has been the only other radiation study that considered the possible effect of PSA tests in that the analysis excluded prostate cancer cases diagnosed by screening. That study found an increased incidence risk of prostate cancer for proximally compared with distally exposed survivors. Among the most recently reported studies of occupationally exposed cohorts (NRRW-3 update, INWORKS, Mayak, Wismut German uranium minors, and Eldorado uranium workers), as summarized in Supplementary Table S1 (https://doi.org/10.1667/RADE-22-00089.1.S1), three examined cancer incidence data (NRRW-3 update, Mayak and Eldorado uranium workers) (*4, 5, 9*) with null findings regarding dose-response association with radiation; possible effects of PSA testing were not considered in any study although PSA tests may have affected the incidence rates toward the end of their follow-up periods.

In general, the effects of PSA testing in observational studies are likely to depend on fraction of tested individuals, how it depends on dose and magnitude of true dose response. In the present LSS study, the number of post-PSA AHS participants and their observed PYs would be too small (3% of total subjects and 0.3% of total PYs) to impact the risk estimates among the whole LSS. The number of post-PSA AHS participants is not expected to increase, however person-years and prostate cancer cases will continue to accumulate among the post-PSA AHS subgroup as follow-up continues. The impact of PSA tests in AHS examinations appears to be primarily on the baseline incidence rates with almost no impact on the magnitude of the ERR dose response to date with little likelihood of a marked impact with increased follow-up. Despite this, adjustment of baseline incidence rates for PSA testing in AHS examination is important in obtaining unbiased risk estimates for prostate cancer incidence especially if one is interested excess rate estimation.

Advanced age is the major risk factor for prostate cancer. As the follow-up of the LSS and other radiation-exposed cohorts continue, increasing numbers of male subjects enter into age groups eligible for PSA screening. Despite changes in recommendations for prostate cancer screening, diagnosis and management, PSA tests will likely continue to be used in various forms and settings. Therefore, it will be necessary that future epidemiological studies of the radiation risk for prostate cancer incidence and mortality consider how PSA screening practiced during the follow-up period may influence the baseline rates and dose response analysis in other radiation-exposed cohorts as well as the atomic-bomb survivors.

SUPPLEMENTARY INFORMATION

Supplementary Table S1. ERRs for prostate cancer from occupationally exposed and LSS cohorts.[a]

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