cluded in the earlier solid cancer incidence analyses. As noted in the Material and Methods section, the baseline rate models used here allow baseline rates for the NIC to differ from those for other cohort members. Baseline rates for the Hiroshima NIC group were significantly lower (SIR 0.93, 90% CI, 0.89; 0.97, $P < 0.001$) than those for other Hiroshima cohort members. Rates for the Nagasaki NIC group were slightly lower (SIR 0.97) than those for other Nagasaki cohort members, but the SIR was not significantly different from 1 (90% CI 0.89; 1.04, $P = 0.3$). The dose–response parameter estimates are virtually unchanged when the NIC group is excluded from the analyses. When the NIC group was included in analyses without adjustment of the baseline rates, the point estimate of the standardized ERR was increased by about 8% relative to those given in Table 10 with almost no change in the effect modification estimates.

Comparison of Site-Specific Excess Risk Patterns

As has been noted in reports on cancer mortality risks in the LSS (*20, 21*), one must be careful in interpreting the variation in the levels and patterns of excess risk across sites. With follow-up through 1990, Pierce *et al.* (*21*) show that the hypothesis of a common standardized ERR value for all solid cancer sites could not be rejected. With 7 years of additional follow-up, Preston and colleagues (*20*) report significant variation in the site-specific standardized ERR estimates but also note that formal statistical tests provide little evidence of variation in the gender effects or temporal patterns of the ERRs for deaths from different types of solid cancer. In this report, we considered temporal patterns and gender effects on radiation-associated excess cancer incidence risks for a large number of organs and groups of organs. Despite the lack of well-developed methods and the limited power to detect significant variation, we offer some comments on variation in excess risk patterns across cancer sites.

Figure 22 summarizes the variation in site-specific ERR estimates by gender, age at exposure, and attained age for sites with an appreciable number of radiation-associated cancers. These comparisons are illustrated by presenting ERR estimates for two values of the factor of interest. The upper panel presents gender-specific standardized ERR estimates (at age 70 after exposure at age 30). The middle panel contrasts the gender-averaged ERR at age 70 for exposure at age 10 with that for exposure at age 40, while the lower panel gives gender-averaged ERR estimates at age 50 and 75 after exposure at age 30. The all-solid-cancer estimates are also included in the figure along with a group of cancers that consists of the 5,936 cancers in sites not otherwise considered. Within each panel, sites are ordered by the magnitude of the ratio of the two values.

The largest gender effects are seen for lung and bladder cancers for which female ERRs are three to five times those for men. It is noteworthy that because smoking is an important risk factor for both of these cancers, baseline rates in women, who have lower smoking rates, are typically about one-third of those for men. Colon cancer is notable because the ERR for men is considerably greater than that for women.

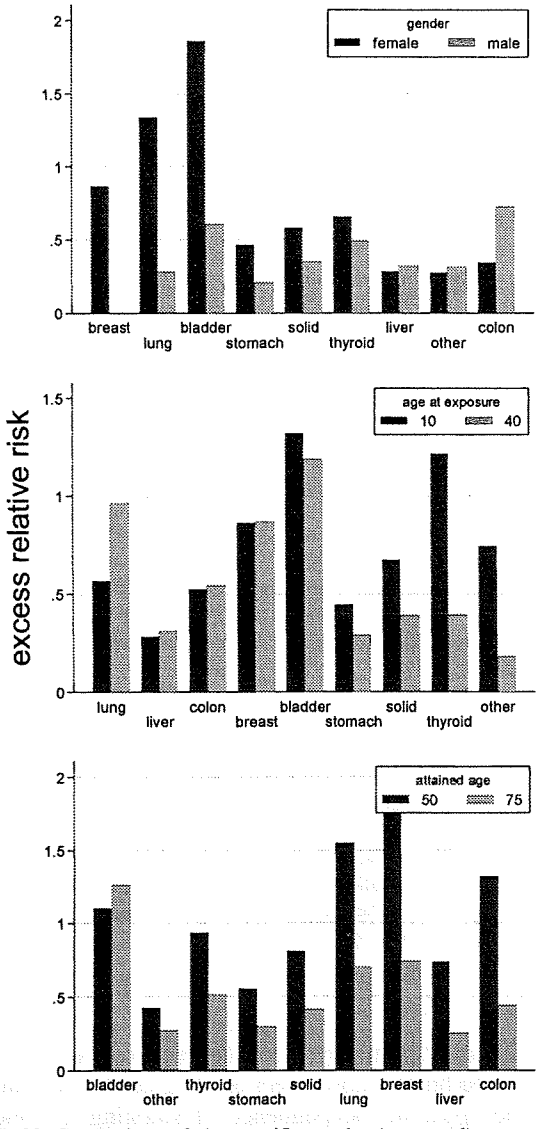

FIG. 22. Comparison of site-specific gender (top panel), age-at-exposure (middle panel), and attained-age (bottom panel) effects on standardized ERR_{1Gy} estimates for selected sites and all solid cancers. The ERR estimates for the *other* category are based on the results of analyses of the 5,396 cancer cases not included in the sites explicitly considered here. The gender-specific estimates correspond to the fitted ERR per Gy at age 70 for a person exposed at age 30. The age-at-exposure specific estimates are gender-averaged ERR estimates at age 70 after exposure at age 10 (left bar) or age 40 (right bar). Attained-age-specific estimates are gender averaged ERR estimates at ages 50 (left bar) and 75 (right bar) after exposure at age 30. Within each panel the sites are ordered based on the magnitude of the ratio of the effect pairs.

With regard to age-at-exposure effects, shown in the middle panel, lung cancer is the only site for which the ERR increased with increasing age at exposure. As noted earlier,

TABLE 46
Tests for Heterogeneity in Site-Specific Excess Relative-Risk Levels and Effect Modification Patterns

Site	Cases	Excess cases	ERR_{1Gy}[b]	ERR effect modification[c]			
				Age at exposure	Attained age	Gender	Global[d]
Oral cavity	277	16	0.5[a]	0.4[a]	0.18[a]	>0.5[a]	>0.5[a]
Esophagus	352	16	>0.5	0.4	0.5	>0.5	0.5
Stomach	4,730	151	**0.01**	>0.5	>0.5	0.4	>0.5
Colon	1,516	78	>0.5	>0.5	0.4	**0.006**	**0.04**
Rectum	838	14	**0.006**	>0.5	0.11	>0.5	0.34
Liver	1,494	54	0.18	>0.5	>0.5	0.3	>0.5
Gallbladder	549	−2	**0.003**	>0.5	>0.5	>0.5	>0.5
Pancreas	512	11	>0.5	0.14	>0.5	0.2	0.2
Lung	1,759	117	**0.06**	**0.02**	0.25	**0.005**	**0.002**
Non-melanoma skin	330	40	**<0.001**	**<0.01**	0.4	>0.5	**<0.001**
Breast	1,073	147	**0.015**	0.25	>0.5	—	0.4
Uterus	1,162	12	**<0.001**	0.36	0.16	—	0.37
Ovary	245	11	0.3	>0.5	>0.5	—	>0.5
Prostate	387	4	>0.5	>0.5	0.5	—	>0.5
Renal cell	167	2	>0.5	0.29	**0.006**	0.37	**0.04**
Bladder	469	35	0.14	0.16	**0.10**	0.4	0.27
CNS	281	19	0.375	0.41	0.44	**0.005**	**0.03**
Thyroid	471	63	0.2	0.4	>0.5	>0.5	>0.5
Other	836	65	**0.04**	>0.5	>0.5	>0.5	>0.5
Total	17,448	853[e]					

[a] Two-sided *P* values for tests of hypotheses that the solid cancer effect estimates apply to specific sites.

[b] The test for level is made by fixing the other effect modifiers at the solid cancer estimates. Information on the direction of the difference is given in the text, Table 11, and Figs. 22 and 23. *P* values of 0.1 or less are printed in bold.

[c] The effect modification tests are made assuming that the level can vary.

[d] The global test is a test that all three (two for gender-specific cancers) parameters have the same value as those for solid cancer.

[e] The estimated number of radiation-associated solid cancers from the pooled all-solid-cancer model is 853 (see Table 9).

this pattern is primarily a consequence of the large smoking-related birth cohort effect on lung cancer baseline rates and the apparent independence of smoking and radiation effects on lung cancer risks in the LSS. The large ERR for thyroid cancer among persons exposed to the bombings at a young age is clearly seen in this figure. The lack of an age-at-exposure effect for the breast cancer ERR reflects the fact that temporal variation for this site appears to be captured more effectively by decreases in the ERR with attained age.

With the exception of bladder cancer, the fitted ERRs decrease with increasing attained age. These decreases are most marked for liver, colon and breast cancer, sites for which there is little evidence of variation in the ERR with age at exposure despite fairly marked birth cohort effects (increased risks for later birth cohorts) on the baseline rates.

Figure 22 highlights the considerable inter-site variability in ERR effect modification parameters. As noted earlier in the discussion and indicated by the broad confidence intervals for many of the site-specific risks and effect modification parameters, there is considerable uncertainty in these site-specific results. To provide a rough guide to which sites differ from the level or pattern of the ERR observed for all solid cancers, we formally tested the hypothesis that the level of radiation risk (standardized ERR_{1Gy}) did not differ from that for all solid cancers, and for both ERR and EAR models we considered whether individual effect modification parameters (gender, age-at-exposure, and attained age effects) differed from those for all solid cancers combined.

Table 46 provides information on the results of these tests (*P* values) along with summary information on the total number of cases and estimated number of radiation-associated cases for each site. Tests that provide some suggestion of a difference (*P* values ≤ 0.1) between the site-specific parameter and that for the full model are highlighted.

The site-specific standardized ERR_{1Gy} was significantly lower than that for all solid cancers for stomach, rectum, gallbladder, uterus and non-melanoma skin cancers when using a linear-spline dose–response model. The standardized ERR_{1Gy} estimates for cancers of the lung, breast and other sites were significantly higher than that for all solid cancers. The non-melanoma skin cancer ERR decreased more rapidly with increasing age at exposure than that for

TABLE 47
Tests for Heterogeneity in Site-Specific Excess Absolute Rate Levels and Effect Modification Patterns

Site	EAR effect modification[a]			
	Age at exposure	Attained age	Gender	Global[c]
Oral cavity	0.12[b]	**0.04**[b]	0.40[b]	0.18[b]
Esophagus	0.08	>0.5	0.15	**0.10**
Stomach	0.21	>0.5	>0.5	0.41
Colon	>0.5	0.41	**0.02**	**0.002**
Rectum	>0.5	**0.07**	0.47	0.28
Liver	0.12	0.31	**0.06**	0.15
Gallbladder	>0.5	>0.5	>0.5	>0.5
Pancreas	0.37	>0.5	**0.15**	>0.5
Lung	**<0.001**	**<0.001**	0.20	**<0.001**
Skin	**<0.001**	**<0.001**	>0.5	**<0.001**
Breast	**0.002**	**0.002**	—	**0.003**
Bladder	**0.03**	**0.004**	0.32	**0.03**
Uterus	>0.5	>0.5	—	>0.5
Ovary	>0.5	>0.5	—	>0.5
Prostate	>0.5	>0.5	—	>0.5
Renal cell	0.33	0.17	>0.5	>0.5
CNS	**0.05**	**0.07**	**0.02**	**0.003**
Thyroid	>0.5	**0.004**	0.19	**0.004**
Other	>0.5	>0.5	0.13	0.38

[a] The effect modification tests are made assuming that the level can vary.

[b] Two-sided P values for tests of hypotheses that the solid cancer effect estimates apply to specific sites. P values of 0.1 or less are printed in bold.

[c] The global test is a test that all three (two for gender-specific cancers) parameters have the same value as those for solid cancer.

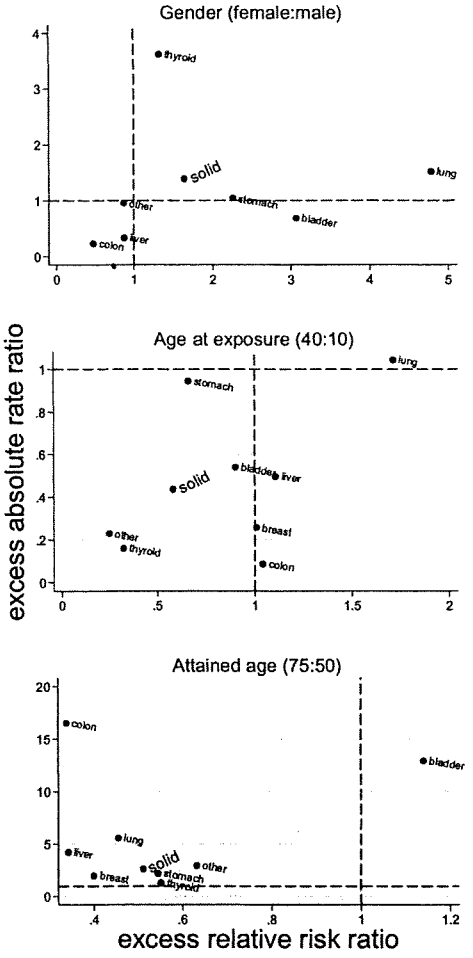

FIG. 23. Summary of site-specific excess relative risk (ERR) and excess absolute rate (EAR) effect modification for gender (top panel), age at exposure (middle panel), and attained age (bottom panel) for selected sites and all solid cancers. Plotting positions are determined by effect ratios in ERR (abscissa) and EAR (ordinate) models. Gender effects are defined as the ratio of the female risks to male risks. Age-at-exposure effects are defined as the ratio of the risk for exposure at age 40 to that for exposure at age 10. Attained-age effects are defined as the ratio of the risk at age 75 to the risk at age 50. The points for the other category are based on the results of analyses of the 5,396 cancer cases not included in the sites explicitly considered here. The dashed grid lines correspond to no variation in the ERR (vertical line) or EAR (horizontal line). Among other things, the plots highlights the extreme gender and age-at-exposure effects for lung and thyroid cancers and the unusual attained-age patterns for bladder and colon cancers.

solid cancer, while the lung cancer ERR appeared to increase more rapidly, with increasing age at exposure There were suggestions that changes in the ERR with attained age for bladder and renal cell cancers may be less rapid than those for all solid cancers. Gender differences in the ERR for cancers of colon, brain and central nervous system, and lung appeared to differ significantly from those seen for all solid cancers. The female:male ERR ratios for colon cancer and tumors of the brain and central nervous system were smaller than those for solid cancers as a group, while the female:male ERR ratio for lung cancer was considerably larger than that for all solid cancers. As noted previously, the large gender effect for lung cancer is primarily a consequence of confounding arising from the gender differences in smoking rates in Japan.

As shown in Table 47, solid cancer EAR effect modification parameters did not adequately describe effects for many sites.

Figure 23 contrasts the site-specific ratios of the ERRs (vertical axes) to the corresponding ratios for EARs for gender, age at exposure, and attained age. In the gender effect (upper) panel, thyroid cancer stands out as having an unusually large female:male EAR ratio, whereas the ERR ratio is similar to that for all solid cancers combined. For lung cancer, the ERR ratio is exceptional, suggesting that the gender difference in baseline rates may not completely explain the gender differences in lung cancer excess rates.

Looking at the panel for age at exposure (middle), we see that EARs are decreasing with increasing age at exposure (ratios less than 1) for all sites other than stomach and lung cancer, for which the EAR ratios are close to 1. Lung cancer had the highest ERR age-at-exposure effect (most likely, as noted earlier, due to the effect of smoking on lung cancer baseline rates). Thyroid cancer and the groups of

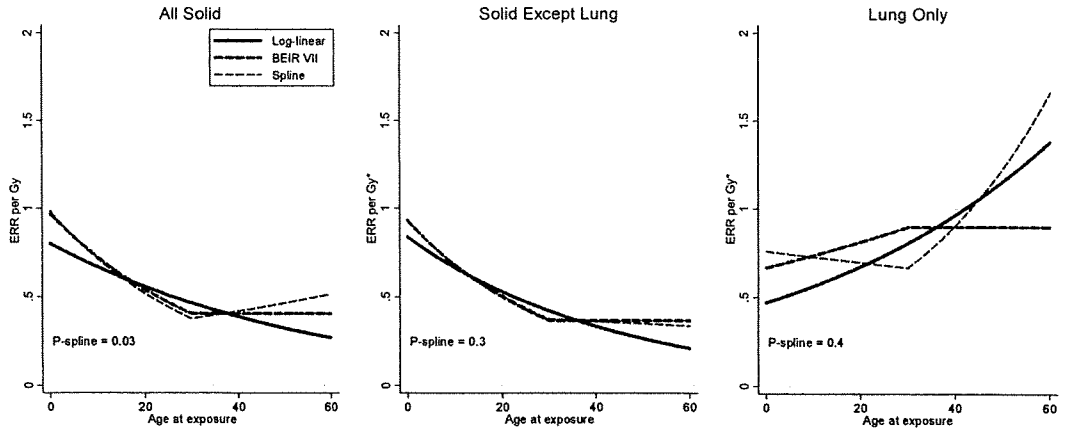

FIG. 24. Alternative age-at-exposure trends for all solid cancers, all solid cancers except lung cancer, and lung cancer. The solid line is the log-linear trend used in the models for this paper. The thick dashed line is a constrained spline with a log-linear trend for exposure ages prior to age 30 and no change after age 30. This is the form used for the BEIR VII risk models. The thin dashed line shows an unconstrained spline with a knot at age 30. The *P* values are based on likelihood ratio tests of the hypothesis that the unconstrained spline fits better than the log-linear trend used for most of the age-at-exposure effect modeling in this paper.

other cancers described above had striking age-at-exposure effects (as reflected by small ratios) for both the ERR and the EAR. EARs were estimated to be increasing with increasing attained age for all sites considered, with particularly large increases for colon and bladder cancers. Bladder cancer was the only site for which the estimated ERR increased with increasing attained age (albeit slightly). The most rapid declines in the ERR with attained age were seen for colon, liver and breast cancers.

The BEIR VII Models

The recently published National Research Council report on the biological effects of radiation, BEIR VII (*35*), made use of site-specific and all-solid-cancer risk models based on the data used for the analyses in this report. The BEIR VII models vary in several respects from those described in this report. In this section, we outline the differences and look at their impact on the nature of the fitted risk models.

The BEIR VII solid cancer models, which did not include the NIC group in the baseline risk modeling, were based on all solid cancers except thyroid and non-melanoma skin cancer. Parametric baseline rate models similar to those used in our ERR and EAR analyses were used in the BEIR VII models; however, the BEIR VII ERR baseline rates were described using a nonparametric model defined by stratification over city, gender, attained-age, and age-at-exposure categories. The use of stratified baseline models and the exclusion of the NIC have almost no impact on the fitted excess risks. The fitted ERRs for solid cancers other than thyroid and skin cancer are somewhat lower than those for all solid cancers, with the largest differences observed for childhood exposures.

The most important difference between the basic excess risk models used in this report and those used in BEIR VII concerns the handling of age-at-exposure effects on the excess risk (ERRs and EARs). In our analyses (see Eq. 1), excess risks were generally assumed to vary log-linearly with exposure age. However, as noted in our presentation of the results for all solid cancer, there were indications that standardized excess risks declined with age at exposure less than 40 years, while standardized risks for all solid cancers as a group increased with age at exposure for exposure late in life. A similar pattern was noted in the BEIR VII modeling, and as a result, in the final BEIR VII models [Tables 12-1 and 12-2 and Annex 12-B in ref. (*35*)] it was assumed that the excess risk varied as a constrained log-linear spline of age at exposure with a log-linear trend for ages 0 to 30 with no further change after age at exposure 30. The left panel in Fig. 24 contrasts the age-at-exposure effects for our log-linear trend model (solid line) with the BEIR VII constrained spline (thick dashed line) and an unconstrained spline with a knot at age 30. For exposures prior to age 20 or after age 40, the fitted ERRs from our standard model are lower than estimates from a BEIR VII-like model, while for those exposed between about 20 and 40 years of age, our model predicts slightly higher risks. The unconstrained spline model fits the all solid-cancer data significantly better than the simple log-linear trend ($P = 0.03$). A formal significance test to compare the BEIR VII constrained spline and the simple log-linear model is not possible, but the deviance reduction of 3.9 associated with the introduction of the constrained spline corresponds to a P value of 0.05 for a 1 *df* test.

As was noted above, the lung cancer ERR appears to increase with increasing age at exposure. Our analysis of the lung cancer data indicates that the unconstrained spline does not describe the lung cancer risks significantly better than the simple log-linear trend ($P = 0.4$) while the BEIR VII constrained spline fits slightly worse than the simple log-linear trend. These patterns can be seen in the rightmost

panel of Fig. 24. Analysis of the age-at-exposure trends for all solid cancers except lung cancer, as seen in the middle panel of Fig. 24, indicates that while the unconstrained spline shows a flattening for exposures after age 30, this does not offer a significant improvement over the simple trend ($P = 0.3$).

The suggestion that a more complex pattern provides a somewhat better fit to the data for all solid cancers as a group reflects to some extent the rather anomalous result for lung cancer. However, there are other sites, most notably stomach and liver, for which the data suggest that risks for those exposed late in life may be somewhat larger than predicted by the simple log-linear trend. In our opinion a simple log-linear trend provides an adequate, simple description of the age-at-exposure effects for most cancer sites, but in future analyses more attention should be given to alternative descriptions of age-at-exposure effects on both the ERR and EAR.

Main Conclusions and New Findings

More than 50 years after the atomic bombs were dropped on Hiroshima and Nagasaki, the updated solid cancer incidence data demonstrated that the shape of the dose response is well described by a linear no-threshold model. With the introduction of DS02, the risk estimates were generally reduced by about 10%, but the patterns of risk generally remained the same. The solid cancer EAR increased throughout life for all ages. The ERR decreased with increasing attained age; however, an elevated risk was still observed at the end of follow-up. The age-at-exposure effect is somewhat smaller in the current follow-up than in previous reports. Overall, women had higher excess relative and absolute risks than men, although when gender-specific cancers were excluded from the analyses the gender-specific excess absolute rates were essentially equal.

The large number of additional cancers in the current follow-up provided more precise estimates of risk and allowed us to conduct more detailed analyses of the effects of gender, age and time. Thus we found that the elevated radiation-associated relative and absolute risks of esophageal cancer now reached statistical significance and that the ERR for cancer of the uterine corpus among women exposed during the bombings before age 20 years was increased, although the point estimate was of borderline statistical significance.

Another new finding is the significant dose response observed for each of the five main histological groupings (adenocarinomas, squamous cell carcinomas, other and unclassified epithelial cancers, sarcomas, and other non-epithelial cancers). Sarcomas, as a group, were of particular interest because information on radiation exposure and the risk of sarcomas is sparse and previous reported associations usually were observed after high-dose radiotherapy (*127*).

The additional years of follow-up allowed a more precise evaluation of radiation-related cancer risks for those cancers that generally develop late in life. Thus the large ERR noted for bladder cancer in this report emphasizes the radiosensitivity of the bladder at all ages at exposure and demonstrates, for the first time, an elevated ERR among persons exposed to the bombings before age 20. Additional follow-up should help clarify the link between radiation exposure and cancers occurring among the elderly, such as gallbladder, pancreas and prostate cancers, for which associations have not been seen to date.

Finally, we described the large relative increases in the risk of occurrence of adolescent and young adult malignancies associated with childhood radiation exposure. Subset analyses based solely on cases diagnosed prior to ages 20, 25 and 30 suggest that the ERR for solid cancers diagnosed before age 13, i.e. prior to the beginning of this follow-up, would have been extremely large. Since baseline cancer rates are very low at young ages, the excess absolute rates (and number of excess cases) would not be large.

Predictions for the Future

While a great deal has already been learned about radiation risks from the LSS, important questions about age and temporal patterns remain. We expect that over the next 15 to 20 years, a large proportion of the radiation-associated excess solid cancers will be diagnosed. Based on a linear dose–response model that allows for changes in the ERR with attained age and age at exposure, it is predicted that the peak number of cancers per year will be reached in about 2015. The accumulating data should therefore offer important new insights into lifetime risks, risk patterns for survivors who were less than 20 years old at the time of the bombings, and gender differences in risks. Since children continue to be exposed to radiation from medical diagnostic X-ray examinations, interventional radiology, and radiotherapy, further follow-up of the LSS is essential to understanding the lifetime cancer risks associated with exposure to radiation in childhood or adolescence. Indeed, the LSS is the single largest cohort of generally healthy individuals exposed to radiation as children. Ongoing site-specific incidence studies of cancers of the thyroid, lung and ovary as well as lymphoma, which include detailed pathological reviews of tumor tissue, should advance our knowledge regarding radiation effects for specific histological types of cancer. Future studies focusing on uterine cancers (corpus vs. cervix) and sarcomas of different organs and tissues may also provide new information on the radiation effects. With close collaboration among epidemiologists, statisticians, radiobiologists and pathologists, we should be able to improve our understanding of radiation risks and their implications for radiation protection.

APPENDIX

This appendix contains tables that give information on the distribution of cases and crude rates stratified by age at exposure (birth cohort), dose and gender for each of the sites considered in the main text of this report. For relatively less common cancer types, three age-at-exposure groups are used (0–19, 20–39 and 40+) while for sites with more cases, there are six age-at-exposure groups (0–9, 10–19, 20–29, 30–39, 40–49 and 50+). Although these tables provide useful simple summaries of the data, it should be kept in mind that birth cohort and age at exposure are perfectly correlated in this cohort and that lifetime follow-up is far from complete for those who were under age 40 at the time of exposure (i.e. born after 1905). Thus the increased risks in older age-at-exposure (earlier year of birth) cohorts reflect differences in the range of follow-up ages and cannot readily be interpreted as reflecting birth cohort effects on the baseline rates.

The detailed person-year table used for these analyses is available through the RERF home page (www.rerf.jp).

TABLE A1
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancers of the Oral Cavity and Pharynx by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	1.0	1.2	0.9	3.1	0.4	0.4	1.0	1.8
	Cases	37	27	2	7	16	9	3	5
20–39	Crude rate	2.2	2.1	2.2	2.0	0.7	0.6	0.6	1.8
	Cases	30	15	2	2	29	14	2	4
40+	Crude rate	2.4	2.5	2.7	1.4	0.9	1.3	0.8	—
	Cases	25	15	2	1	15	14	1	—

[a] Weighted skin dose (shielded kerma) in Gy.

TABLE A2
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancer of the Esophagus by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	1.3	1.1	1.8	4.1	0.1	0.1	—	0.7
	Cases	47	27	3	6	5	3	—	1
20–39	Crude rate	3.2	3.4	5.6	1.8	0.5	0.5	—	—
	Cases	45	26	4	1	18	13	—	—
40+	Crude rate	7.0	7.1	3.6	10.6	0.8	1.0	2.4	5.0
	Cases	72	47	2	4	13	11	2	2

[a] Weighted stomach dose in Gy.

TABLE A3
Crude Stomach Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	5.0	5.6	4.3	17.1	2.6	2.7	6.2	8.7
	Cases	91	74	3	10	52	39	5	5
10–19	Crude rate	13.2	15.1	18.2	17.3	5.5	5.9	8.9	11.7
	Cases	236	161	18	15	134	80	14	11
20–29	Crude rate	30.1	25.6	43.7	35.0	9.9	12.3	12.3	25.7
	Cases	180	85	13	9	211	162	15	18
30–39	Crude rate	43.2	42.8	45.6	54.2	18.1	20.2	17.6	31.7
	Cases	343	190	19	16	322	252	13	17
40–19	Crude rate	59.9	52.5	63.7	83.2	22.8	24.0	21.2	34.8
	Cases	424	231	24	22	260	189	13	11
50+	Crude rate	63.9	78.5	63.9	96.1	35.3	42.8	46.8	80.0
	Cases	207	172	11	11	175	150	10	7

[a] Weighted stomach dose in Gy.

TABLE A4
Crude Colon Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	3.2	2.3	1.4	10.3	1.5	1.6	3.7	5.2
	Cases	58	31	1	6	29	23	3	3
10–19	Crude rate	6.8	7.9	14.2	19.7	3.9	2.8	3.2	4.3
	Cases	122	84	14	17	94	38	5	4
20–29	Crude rate	10.2	10.9	9.9	7.9	5.9	6.1	5.7	14.3
	Cases	61	36	3	2	125	80	7	10
30–39	Crude rate	7.3	12.4	4.8	27.5	6.6	7.4	4.1	5.6
	Cases	58	55	2	8	117	92	3	3
40–49	Crude rate	7.2	8.6	16.0	7.6	6.9	6.0	4.8	9.7
	Cases	51	38	6	2	79	47	3	3
50+	Crude rate	6.2	7.3	11.4	0.0	6.3	5.7	18.7	0.0
	Cases	20	16	2	0	31	20	4	0

[a] Weighted colon dose in Gy.

TABLE A5
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancer of the Rectum by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	2.7	2.3	4.1	3.4	1.4	1.4	1.3	3.3
	Cases	98	54	7	5	60	40	3	5
20–39	Crude rate	5.4	6.1	2.8	5.5	2.7	3.4	4.1	4.9
	Cases	75	47	2	3	105	87	8	6
40+	Crude rate	6.6	7.9	9.1	5.3	3.4	3.8	6.0	5.1
	Cases	68	52	5	2	56	43	5	2

[a] Weighted bladder dose in Gy.

TABLE A6
Crude Liver Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	2.7	2.6	1.4	8.5	0.4	0.3	0.0	1.7
	Cases	50	34	1	5	7	4	0	1
10–19	Crude rate	9.8	12.8	16.2	16.2	2.9	2.7	3.2	6.4
	Cases	176	137	16	14	71	37	5	6
20–29	Crude rate	10.4	10.6	33.3	18.8	3.9	3.7	3.3	4.3
	Cases	62	35	10	5	83	49	4	3
30–39	Crude rate	11.8	10.4	5.0	15.9	5.5	4.7	2.8	3.6
	Cases	94	46	2	5	98	58	2	2
40–49	Crude rate	11.4	11.1	10.7	0.0	5.5	6.6	14.5	3.2
	Cases	81	49	4	0	63	52	9	1
50+	Crude rate	12.0	10.5	28.7	17.2	5.0	4.3	14.0	11.2
	Cases	39	23	5	2	25	15	3	1

[a] Weighted liver dose in Gy.

TABLE A7
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancer of the Gallbladder and Extrahepatic Bile Ducts by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	2.7	2.3	4.1	3.4	1.4	1.4	1.3	3.3
	Cases	98	54	7	5	60	40	3	5
20–39	Crude rate	5.4	6.1	2.8	5.5	2.7	3.4	4.1	4.9
	Cases	75	47	2	3	105	87	8	6
40+	Crude rate	6.6	7.9	9.1	5.3	3.4	3.8	6.0	5.1
	Cases	68	52	5	2	56	43	5	2

[a] Weighted pancreas dose in Gy.

TABLE A8
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancer of the Pancreas by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	1.0	0.7	0.6	0.7	0.3	0.4	1.7	2.0
	Cases	35	17	1	1	14	12	4	3
20–39	Crude rate	2.4	3.7	8.1	0.0	2.2	1.8	3.6	4.1
	Cases	34	29	6	0	88	47	7	5
40+	Crude rate	5.3	5.6	5.4	13.5	3.5	4.2	4.7	0.0
	Cases	55	37	3	5	57	48	4	0

[a] Weighted pancreas dose in Gy.

TABLE A9
Crude Lung Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	1.4	1.2	0.0	3.4	0.7	0.6	2.5	1.7
	Cases	26	16	0	2	13	9	2	1
10–19	Crude rate	5.2	6.3	8.3	7.9	1.8	1.3	2.7	5.8
	Cases	93	67	7	8	44	18	4	6
20–29	Crude rate	12.7	9.4	11.8	12.4	3.7	4.6	5.4	13.7
	Cases	76	31	3	4	80	60	6	11
30–39	Crude rate	20.0	17.4	7.9	34.3	5.3	7.4	10.9	15.9
	Cases	159	77	3	12	95	92	7	10
40–49	Crude rate	25.4	24.5	41.8	27.9	7.4	8.9	9.9	28.3
	Cases	180	108	15	8	84	70	5	12
50+	Crude rate	23.5	23.8	49.6	52.7	8.9	11.7	24.9	18.4
	Cases	8	6	1	0	23	22	1	1

[a] Weighted lung dose in Gy.

TABLE A10
Crude Non-melanoma Skin Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.0	0.3	0.0	3.8	0.1	0.0	0.7	6.7
	Cases	0	4	0	3	1	0	1	6
10–19	Crude rate	0.7	1.0	0.0	6.2	0.2	0.2	0.6	2.0
	Cases	12	10	0	9	5	3	1	4
20–29	Crude rate	1.0	1.3	0.0	9.5	0.7	0.7	1.2	3.9
	Cases	6	4	0	4	16	9	2	5
30–39	Crude rate	2.1	1.5	2.0	0.0	1.9	2.6	1.5	4.2
	Cases	17	6	1	0	33	30	2	4
40–49	Crude rate	2.1	3.2	4.4	3.7	3.0	2.4	3.6	5.2
	Cases	15	13	2	2	34	17	3	4
50+	Crude rate	2.2	3.5	3.6	0.0	3.4	2.2	4.9	5.7
	Cases	7	7	1	0	17	7	2	1

[a] Weighted skin dose (shielded kerma) in Gy.

TABLE A11
Crude Female Breast Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Weighted breast dose (Gy)			
		<0.005	−0.5	−1	1–4
0–9	Crude rate	4.3	5.1	8.8	20.9
	Cases	85	72	5	17
10–19	Crude rate	6.1	7.2	13.6	25.9
	Cases	149	95	17	40
20–29	Crude rate	6.1	7.6	11.5	16.6
	Cases	130	97	14	18
30–39	Crude rate	5.5	5.6	8.7	22.6
	Cases	98	67	10	16
40–49	Crude rate	5.4	4.9	5.9	8.4
	Cases	62	37	5	4
50+	Crude rate	4.4	2.7	7.0	14.8
	Cases	22	9	2	2

TABLE A12
Crude Uterine Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Weighted uterine dose (Gy)			
		<0.005	−0.5	−1	1–4
0–9	Crude rate	4.1	4.0	3.8	7.3
	Cases	180	110	9	11
10–19	Crude rate	7.6	8.1	7.0	7.5
	Cases	298	207	14	9
20–29	Crude rate	11.0	11.7	8.4	10.2
	Cases	180	133	7	4
30–39	Crude rate	4.1	4.0	3.8	7.3
	Cases	180	110	9	11
40–49	Crude rate	7.6	8.1	7.0	7.5
	Cases	298	207	14	9
50+	Crude rate	11.0	11.7	8.4	10.2
	Cases	180	133	7	4

TABLE A13
Crude Ovarian Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Weighted ovarian dose (Gy)			
		<0.005	−0.5	−1	1–4
0–9	Crude rate	1.0	0.8	1.3	3.3
	Cases	43	21	2	6
10–19	Crude rate	1.6	1.5	1.5	2.5
	Cases	61	38	4	3
20–29	Crude rate	2.3	2.1	3.5	5.2
	Cases	38	22	4	3
30–39	Crude rate	1.0	0.8	1.3	3.3
	Cases	43	21	2	6
40–49	Crude rate	1.6	1.5	1.5	2.5
	Cases	61	38	4	3
50+	Crude rate	2.3	2.1	3.5	5.2
	Cases	38	22	4	3

TABLE A14
Crude Prostate Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Weighted bladder dose (Gy)			
		<0.005	−0.5	−1	1–4
0–9	Crude rate	0.8	0.6	0.6	2.1
	Cases	28	14	1	3
10–19	Crude rate	6.7	6.3	9.7	5.5
	Cases	94	49	7	3
20–29	Crude rate	10.6	10.8	9.1	7.9
	Cases	109	71	5	3
30–39	Crude rate	0.8	0.6	0.6	2.1
	Cases	28	14	1	3
40–49	Crude rate	6.7	6.3	9.7	5.5
	Cases	94	49	7	3
50+	Crude rate	10.6	10.8	9.1	7.9
	Cases	109	71	5	3

TABLE A15
Crude Incidence Rates (Cases per 10,000 Person Years) for Renal Cell Cancer by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.4	0.4	0.0	2.1	0.3	0.3	0.4	1.3
	Cases	16	9	0	3	12	8	1	2
20–39	Crude rate	0.9	1.3	0.0	0.0	0.4	0.5	1.0	0.8
	Cases	13	10	0	0	15	14	2	1
40+	Crude rate	2.7	1.8	0.0	0.0	0.8	0.7	0.0	0.0
	Cases	28	12	0	0	13	8	0	0

[a] Weighted bladder dose in Gy.

TABLE A16
Crude Bladder Cancer Incidence Rates (Cases per 10,000 Person Years) by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.8	0.9	0.0	1.7	0.1	0.2	0.0	0.0
	Cases	15	12	0	1	2	3	0	0
10–19	Crude rate	2.0	1.8	2.0	5.8	0.3	0.4	0.6	0.0
	Cases	35	19	2	5	7	5	1	0
20–29	Crude rate	3.8	3.6	6.7	15.6	0.7	1.6	2.5	1.4
	Cases	23	12	2	4	16	21	3	1
30–39	Crude rate	4.8	3.4	0.0	0.0	0.7	1.5	1.3	3.8
	Cases	38	15	0	0	12	19	1	2
40–49	Crude rate	5.2	6.8	16.0	11.3	1.5	2.0	1.6	6.5
	Cases	37	30	6	3	17	16	1	2
50+	Crude rate	9.9	8.7	5.7	8.8	2.6	3.1	13.8	11.8
	Cases	32	19	1	1	13	11	3	1

[a] Weighted bladder dose in Gy.

TABLE A17
Crude Incidence Rates (Cases per 10,000 Person Years) for Tumors of the Brain and Central Nervous System by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.7	0.7	1.5	4.9	0.9	0.7	1.1	1.0
	Cases	25	16	2	9	39	19	2	2
20–39	Crude rate	1.0	0.5	3.6	1.2	0.8	1.3	2.1	2.2
	Cases	14	4	2	1	32	34	3	4
40+	Crude rate	0.9	1.2	9.3	0.0	1.5	2.2	2.8	0.0
	Cases	9	8	4	0	25	25	2	0

[a] Weighted brain dose in Gy.

TABLE A18
Crude Incidence Rates (Cases per 10,000 Person Years) for Thyroid Cancer by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.4	0.6	0.7	3.9	1.3	2.0	5.4	8.8
	Cases	13	14	1	7	57	55	10	18
20–39	Crude rate	0.7	0.5	5.8	1.2	1.4	2.6	4.0	3.8
	Cases	10	4	3	1	54	66	6	7
40+	Crude rate	1.8	2.6	2.1	0.0	3.2	4.1	4.2	9.8
	Cases	19	17	1	0	53	46	3	6

[a] Weighted thyroid dose in Gy.

TABLE A19
Crude Incidence Rates (Cases per 10,000 Person Years) for Cancers not Considered in Other Analyses by Age-at-Exposure and Dose Categories (in Gy)

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Crude rate	0.7	1.1	1.4	6.8	0.3	0.5	2.5	5.2
	Cases	12	15	1	4	5	7	2	3
10–19	Crude rate	2.4	2.3	4.0	5.8	0.9	1.2	2.6	3.2
	Cases	43	25	4	5	22	16	4	3
20–29	Crude rate	3.8	4.8	9.9	4.0	2.2	2.2	2.5	7.1
	Cases	23	16	3	1	46	29	3	5
30–39	Crude rate	6.2	7.2	16.6	17.2	3.4	3.9	6.8	3.7
	Cases	49	32	7	5	60	48	5	2
40–49	Crude rate	7.9	8.6	5.3	7.6	4.3	6.1	6.4	13.0
	Cases	56	38	2	2	49	48	4	4
50+	Crude rate	11.4	11.0	5.7	26.5	6.1	5.1	4.7	23.2
	Cases	37	24	1	3	30	18	1	2

[a] Weighted colon dose in Gy.

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Tumor Induction by Monoenergetic Neutrons in B6C3F1 mice

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Monoenergetic neutrons/Tumor induction/Mouse.

This study was undertaken to investigate induction of tumors by monoenergetic neutrons in B6C3F1 mice. Individual groups of 6 week-old animals of both sexes (about 30 mice/group) were exposed to 0.5 Gy of various monoenergetic neutrons (dose rate 0.5 cGy/min) and then observed for 13 months. The incidences of tumors (mainly liver neoplasms) in non-irradiated male and female controls were 11% and 0%, respectively. In the irradiated animals, the incidences were 53%, 50%, 60% and 43% in males, and 75%, 81%, 71%, and 85% in females, after 0.18, 0.32, 0.6 and 1.0 MeV neutron exposure, respectively. There were no significant differences in the tumor induction rate among the different energy groups.

INTRODUCTION

The biological effects of monoenergetic neutrons are of clear interest to basic science and radiation protection, as evidenced by a number of reports of *in vitro* studies.[1–11] To our knowledge, however, there has been relatively little work on the genetic effects of monoenergetic neutrons at various energy levels *in vivo*. In order to study the radiobiological effects of neutrons, the Hiroshima University Radiobiological Research Accelerator (HIRRAC) can be operated under conditions of high proton beam currents of 1mA and acceleration voltages up to 3 MeV. Neutron irradiation is possible in the energy range from 0.07 to 1.13 MeV using a lithium target.[12,13]

Specifications for biological irradiation cover monoenergetic beam conditions, dose rates and deposited energy spectra. High dose rates of monoenergetic neutron fields are useful for studying the neutron energy dependence of biological effects, and also the basic mechanisms of action of neutrons. Monoenergetic neutrons which have a narrow neutron spectrum are particularly useful in this regard. Therefore the present study was undertaken to investigate their long-term biological effects in mice, with the focus on tumor development.

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MATERIALS AND METHODS

Animals

Crj:B6C3F1 mice of both sexes were purchased from Charles River Japan Inc. (Hino, Japan) and housed about five per autoclaved cage on sterilized wood chips, in a room with controlled temperature (24 ± 2°C) and humidity (55 ± 10%) under a regular 12-h light, 12-h dark cycle. The animals were maintained according to the 'Guide for Care and Use of Laboratory Animals' established by Hiroshima University. All mice received a normal diet MF (Oriental Yeast Co. Ltd., Tokyo) and tap water *ad libitum*. The experimental protocol was reviewed and approved by the Animal Use Committee at Hiroshima University.

Monoenergetic neutron irradiation

Various energy neutrons were produced in the Hiroshima University Radiobiological Research Accelerator (HIRRAC) with the $^{7}Li(p,n)^{7}Be$ reaction. Doses of neutrons and gamma rays were measured at room temperature using paired ionization chambers, IC-17 ATW (FWT Inc. Goleta, CA, USA) or IC-17G (model GM539, FWT Inc. Goleta, CA, USA). The incident neutron energy was calculated by incident proton energy with quantum theory. The incident proton energies were 2.05, 2.2, 2.5 and 2.9 MeV, respectively, then primary energy of produced neutron toward to 30 degrees were 0.254, 0.418, 727 and 1.127 MeV, respectively. According to Lee's theory,[14] the produced neutron energy distribution with thick lithium target can be calculated. Fig. 1 shows the theoretical neutron energy distributions used in following experiments.

Contamination with gamma-rays was less than 3% in the neutron spectrum when using 10 μm-thick ^{7}Li targets. Indi-

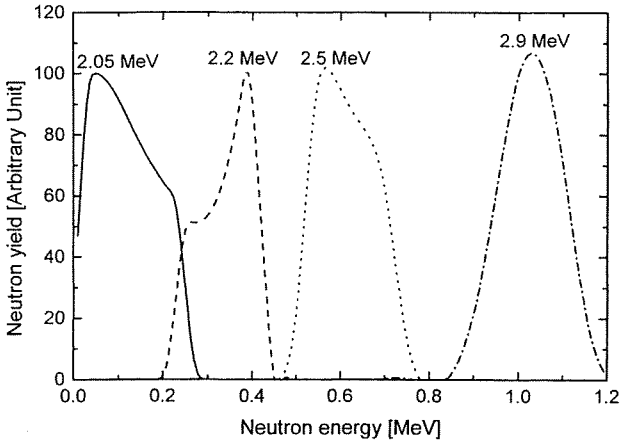

Fig. 1. The neutron energy distribution toward to 30 degrees respect to incident proton beam direction. The distributions are normalized at maximum yield. The energy levels shown on the top of each curve indicate incidence photon energies.

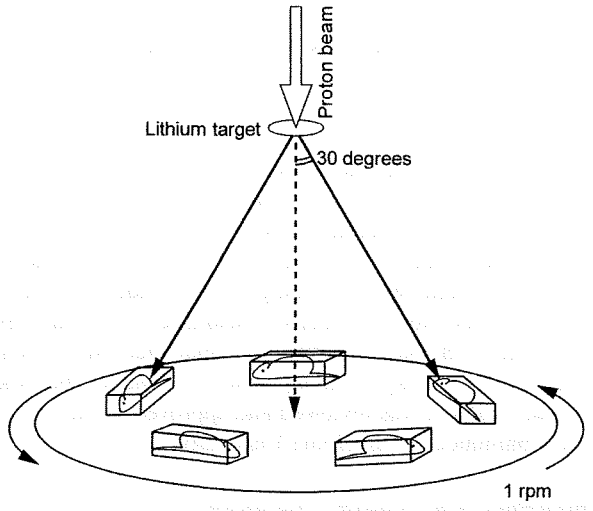

Fig. 2. Experimental setup for neutron irradiation. Five mice were located 20 cm from the neutron producing source at an angle of 30 degrees. In order to provide uniform individual neutron doses, the mice were rotated at a speed of 1 rpm.

vidual mice were placed in individual boxes (3cm × 3cm × 5cm) and groups of 5 mice were located 20 cm from the neutron source at an angle of 30 degrees (Fig. 2) and exposed to monoernergetic neutrons at energy levels of 0.18, 0.32, 0.6 or 1.0 MeV (dose 50cGy, dose rate 0.5cGy/min) without anesthesia. In order to provide uniform individual neutron doses, mice were rotated at a speed of 1 rpm.

Pathology

All animals were regularly observed on a daily basis and weighed once a month. At the time of necropsy, full autopsies were carried out after over ether anesthesia, and body and liver, kidney, adrenal, spleen, testis (male), ovary (female) and uterus (female) weights were determined. The numbers and sizes of liver tumor nodules were also determined and samples of liver and other organs with neoplastic changes were taken and routinely processed for histological examination.

Statistical analysis

The significance of differences in numerical data was determined using 2 × 7 contingency table analysis and the Dunnett's method for multiple comparisons using logarithmic transformation.

RESULTS

Males

Three animals (293, 367 and 362 days after irradiation) died before scheduled autopsy in the 0.18 MeV group, one (365 days) in the 0.32 MeV group, one (319 days) in the 0.6 MeV group and one (403 days) in the 1.0 MeV group. Mean survival period did not significantly differ among the groups. Body weights in the 0.32 MeV group were significantly decreased as compared to control and 1.0 MeV groups. Liver weights with 0.18 MeV were significantly increased as compared with those in control and 0.6 MeV group values, and relative liver weights in the 0.18 MeV group and kidney weights in 0.32 MeV group were elevated (data not shown). There were no other differences in kidney, testis, adrenal and spleen weights among the groups.

Tumor bearing animals accounted for 43% to 60% of the total animals, and the numbers of tumors per animal varied from 0.43 to 0.70. Liver tumors predominated at incidences of 17 to 33%. The number and sizes of liver tumors in the 0.60 MeV group were significantly increased as compared with those in non-irradiated controls but a tendency for decrease was noted with the 1.0 MeV group (see Table 1). There were no significant differences among the irradiated groups. Tumors in sites other than the liver were significantly more frequent in the 0.60 MeV and 1.0 MeV groups than in the controls. Histological findings are summarized in Table 2. Most tumors were rather low in malignancy. However, one osteosarcoma each appeared in the 0.18 MeV and 0.32 MeV groups, one hepatocarcinoma at 0.18 MeV, and 1, 2, and 2 lung adenocarcinomas at 0.18 MeV, 0.32 MeV and 0.6 MeV, respectively. Numbers of hepatomas did not significantly differ among the irradiated groups (Table 2).

Females

Four animals (289, 342, 366 and 388 days after irradiation) died before scheduled autopsy in the 0.18 MeV group, four (219, 276, 366 and 388 days) in the group 0.32 MeV group, three (337, 391 and 419 days) in the 0.6 MeV group, and five (165, 341, 380, 384 and 402 days) in the 1.0 MeV group. There were no differences in the mean survival and

Table 1. Mean survival and tumor induction in male mice

Group	Effective animal	Mean survival (Days)	Tumor bearing animals (%)	No of tumor /mouse	Liver			Lung (%)	Other (%)
					Incidence (%)	No / mouse	Size (mm)		
0.18 MeV	30	407 ± 25	16(53)*	0.53 ± 0.50**	10(33)*	0.43 ± 0.73	3.33±6.56	4(13)	2(7)
0.32 MeV	26	412 ± 10	13(50)*	0.54 ± 0.58**	8(31)*	0.38 ± 0.64	3.21±3.52	3(12)	3(12)
0.60 MeV	30	410 ± 6	18(60)*	0.70 ± 0.75**	12(40)*	0.57 ± 0.82**[a]	4.07±7.28*	2(7)	8(27)*
1.0 Mev	30	414 ± 6	13(43)*	0.43 ± 0.50*	5(17)*	0.20 ± 0.48[a]	0.95±2.93	2(7)	6(20)*
Control	36	413 ± 2	4(11)	0.11 ± 0.32	4(11)	0.11 ± 0.32	0.81±2.64	0	0

Mean ± SD
*: Significantly different from Control value ($P < 0.05$)
**: Significantly different from Control value ($P < 0.01$)
[a] :Significantly different between 0.6 MeV and 1.0 MeV($P < 0.05$)

Table 2. Numbers of histological typing tumors of male mice

Group (Mev)	Liver		Lung		Other	
	Hepatoma	Hepatocelluar - carcinoma	Adenoma	Adeno - carcinoma	No	Tumor type
0.18	12	1	3	1	2	Harderian gland adenoma 1
						Bone osteosarcoma 1
0.32	10	0	1	2	3	Harderian gland adenoma 1
						Bone osteosarcoma 1
						Skin papilloma 1
0.6	17	0	0	2	8	Harderian gland adenoma 2
						Pituitary adenocarcinoma 2
						Leukemia 1
						Muscle sarcoma 2
						Adrenal cortical adenoma 1
1.0	6	0	2	0	6	Harderian gland adenoma 3
						Pituitary adenoma1
						Skin papilloma 2
Control	5	0	0	0	0	

body weights among the female groups. Uterus weights in all irradiated groups were significantly decreased as compared to the control values, whereas adrenal weights increased in 0.18 MeV group (relative to both control and 1.0 MeV groups). Relative liver weights at 0.32 and 0.6 MeV and kidney weights at 0.32 MeV were significantly higher than control values while weights of adrenals at 1.0 MeV and spleen at 0.6 Mev were significantly decreased as compared to the 0.18 MeV values (data not shown).

Tumors were found in 71% to 85% of animals in the irradiated groups, with mean incidences of 1.27 to 1.56 tumors per animal (see Table 3). The highest incidences were noted for tumors of the ovary (41–54%), followed by the Harderian glands. There were no significant differences among the radiation groups. From histopathological findings, radiation-induced tumors were rather low in malignancy (Table 4). However, 3, 3, 1, and 6 malignant granulosa cell tumors in the ovary were observed at 0.18, 0.32, 0.6 and 1.0 MeV, respectively, and three had metastasized to the lungs in the 1.0 MeV group.

Table 3. Mean survival and tumor induction in female mice

	Effective No	Mean survival (Days)	Total (%)	No of tumor / mouse	Ovary (%)	Lung (%)	Liver (%)	Harderian Gland (%)	Lymphoma (%)	Others (%)
0.18 MeV	28	412 ± 35	22(79)*	1.32 ± 0.47*	19(68)*	1(4)	4(14)	2(7)	2(7)	2(7)
0.32 MeV	27	410 ± 49	22(81)*	1.27 ± 0.55*	18(67)*	2(7)	1(4)	3(11)	1(4)	4(15)
0.6 MeV	28	421 ± 17	23(82)*	1.38 ± 0.57*	15(54)*	3(11)	4(14)	7(25)*	0	6(21)*
1.0 MeV	27	408 ± 52	25(93)*	1.56 ± 0.83*	15(56)*	1(4)	7(26)	6(22)*	2(7)	2(7)
Control	36	427 ± 1	0	0	0	0	0	0	0	0

Mean ± SD
*: Significantly different from Control value ($P < 0.05$)

Table 4. Number of histological typing tumors in male mice

Group	Ovary			Lung		Liver		Harderian gland		Others	
(MeV)	Tubulostomal adenoma	Benign granulosa cell tumor	Malignat granulosa cell tumor	Adenoma	Adeno-carcinoma	Hepatoma	Hepatocellular-carcinoma	Adenoma	Adeno-carcinoma	No	
0.18	13	3	3	0	1	3	0	2	0	2	Adrenal cortical adenoma 1
											Lymphoma 1
0.32	10	5	3	0	1	2	1	2	1	4	Muscle sarcoma 1
											Pituitary adenoma 3
0.6	9	5	1	1	0	3	1	5	2	6	Pituitary adenoma 1
											Uterus endometrial tumor 1
											Muscle sarcoma 1
											Skin papilloma 1
											Adrenal cortical adenoma 2
1.0	6	6	6	1	0	4	3	5	1	2	Skin squamous cell carcinoma 1
											Mammary adenocarcinoma 1
Control	0	0	0	0	0	0	0	0	0	0	

DISCUSSION

In the present study, there were no consistent differences in tumor incidence among the groups with various energies of neutron irradiation. In males, the incidence, number and size of liver tumors were significantly increased in irradiated animals as compared with non-irradiated controls, but without significantly differences among the irradiated groups. In females, some tumors in the irradiated groups were significantly more common than in their non-irradiated counterparts but again there was no significant variation with the dose applied. Induced tumor incidences in males were 43%–60% and in females were 79%–93%. Takahashi *et al*[15] reported an incidence of 46.7% (hepatic tumors 43.3%) in B6C3F1 male mice and 23.3% in females receiving 50 cGy of ^{252}Cf neutrons, while we[16] reported tumor incidences of 30% in both sexes of mice receiving 42.5 cGy of 290 MeV/u carbon-iron irradiation. In males, the tumor incidence seems to be the same between ^{252}Cf neutrons and monoenergetic neutrons but the incidence of tumors after heavy-iron irradiation was less than that after neutrons in the present experiment. In females, the tumor incidence in the present experiment was higher than with ^{252}Cf neutrons.

Inverse dose-rate dependence of fission-spectrum neutron induction on somatic *hprt* mutations in mouse leukemia L5178Y cells has been reported by Nakamura and Sawada[10], Hill *et al* observed that reduction of the dose rate of fission neutrons increased their effectiveness for transformation of C3H 10T1/2 cells.[17,18] Brenner and Hall published a model of an inverse dose-rate effect for neoplastic transformation *in vitro* following high LET irradiation.[19] Harrison and Bakcer-Kubiczek *et al*, however, found modification of fission neutron dose-response curves by dose rate

to be negligible or absent.[20, 21] Watanabe *et al* reported that a single ^{252}Cf neutron dose resulted in higher incidences of ovarian and Harderian gland tumors than the same total dose given at a low dose rate with B6C3F1 mouse whole body irradiation.[22] Clearly there may be differences in dose-rate effect between the *in vitro* and *in vivo*. It is considered that cells with large chromosomal aberrations or other abnormalities might be able to survive *in vitro*, but *in vivo* they might not, so smaller non-lethal chromosomal changes such as point mutations, frame shifts, as small insertions or deletions could be essential for tumor induction *in vivo*. The source of irradiation, strain, sex, and age are all clearly the factors, which need to be taken into account when determining radiation sensitivity. The reason why tumor incidences in mice were not influenced by the various neutron energies is not understood; however, Sasaki *et al*[23] recently reported that induction of chromosome aberrations is not largely dependent on neutron energy. Further studies on different biologic endpoints are required to address this issue.

In conclusion, there were no consistent differences in tumor incidence among the various energies of neutron irradiation applied.

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