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Radiation Dose Reconstruction.

Detailed information on dates of administration, indication for treatment, beam energy, dose delivered, and field location and configuration was abstracted from patient records. Daily target doses were generally in the range 1.5-2.0 Gy for all three first cancers. The objective of the radiation dose reconstruction was to estimate the mean dose to the stomach tumor location specified as cardia, fundus, body, lesser curvature, greater curvature, antrum, or pylorus, and to a comparable location for the matched controls. Using a custom-designed dose program, based on measurements in water and anthropomorphic phantoms constructed of tissue-equivalent material, dose was calculated to 464 points in the stomach *(1).* Doses to stomach tumor locations (cardia, fundus, etc.) were calculated by averaging subsets of the 464 points of calculation.

Radiotherapy that included abdominal fields resulted in the largest doses to the stomach tumor location (Supplementary Table 1). Testicular cancer (TC) radiotherapy nearly always included abdominal fields, and thus these patients typically received high radiation doses to the stomach. By contrast, most cervical cancer (CX) patients who received radiation were treated with pelvic fields, with very few treated with abdominal fields. Therefore, CX survivors received much lower radiation doses to the stomach (usually <4 Gy). Radiotherapy for Hodgkin lymphoma (HL) usually included supradiaphragmatic fields with or without subdiaphragmatic fields; the subdiaphragmatic fields, received by about half of HL survivors, resulted in radiation doses to the stomach that were generally comparable to those received by TC patients. There has been a general trend toward the use of smaller radiation fields and a reduction in the use of subdiaphragmatic fields for Hodgkin lymphoma. However, these changes were not widely implemented until the 1990's so that stomach tumor doses did not decline greatly over the period of our study.

A typical J-shaped stomach configuration was used for these calculations *(2)*. Because of inter-individual variability in stomach size, shape and location *(3-4),* doses were also calculated to two alternative stomach configurations (Figure 1 in main paper) for use in sensitivity analyses. According to available literature on stomach morphology *(4),* the J-shaped stomach configuration represents a typical shape for an adult of normal weight and no stomach pathology *(2).* The first alternative stomach configuration is located higher in the body than the J-shaped stomach and has been found to occur more frequently in persons with massive body build and higher weight. By contrast, the second alternative stomach configuration is located lower within the body, is longer than the J-shaped stomach, and has been found to occur more frequently in persons with thinner body build and lower weight *(5-6).* The correlation coefficients between doses based on different stomach configurations were high (>0.94).

Comparison with Results from Original Papers.

Supplementary Table 2 shows the results of radiation dose-response analyses as presented in papers in the individual first cancers *(7-9*).* Although the cut points used for the categorical analyses are different, the statistical methods used in these papers are otherwise similar to those used in the pooled analyses. For TC *(8)*, the methods are identical. For CX *(9)*, analyses were either adjusted for brachytherapy dose or were based on the total dose (sum of dose from external beam therapy and brachytherapy). Because our pooled analyses focused on external beam therapy and because there was no evidence that the relatively small doses from brachytherapy increased risks, we based our analyses on external beam dose alone. As discussed in the statistical methods section, our HL analyses effectively excluded subjects treated with high dose procarbazine because of an identified interaction with high dose radiation, and this led to a lower estimated EOR/Gy than in analyses where the dose-response was based on all

subjects as in *(7)* and in Supplementary Table 2; these latter analyses were adjusted for the number of cycles of treatment with alkylating-agent containing chemotherapy. Procarbazine was one of the main alkylating agents used to treat HL patients in our study.

Evaluating Effects of Age at Exposure and Time Since Exposure

An objective of this paper was to assess how time since exposure and age at exposure modify the radiation dose-response. Although many second cancer analyses have used the date of first cancer diagnosis to define these variables, using the actual dates of exposure allows a more precise assessment. For most patients treated with radiotherapy and included in our analyses, the first course of radiotherapy was initiated less than one year following diagnosis of the first cancer (median interval between diagnosis and treatment was 22 days). However, one HL case and two TC controls did not begin radiotherapy until more than 5 years after their first cancer diagnoses. In addition to these 3 patients, 17 cases and 18 controls received additional course(s) of radiotherapy a year or more after completing the first course, usually with radiation fields that were different from those received with initial treatment. Overall, 4 HL cases, 4 HL controls, 2 TC controls, and one CX control received ≥25 Gy to the stomach tumor location between one and 11 years after the first cancer diagnosis, with an additional HL case and TC control receiving doses of 5-25 Gy in this period. Typically, HL survivors in this group were initially treated with supradiaphragmatic fields and were later treated with abdominal fields.

Second cancer analyses, including those in analyses of data from the individual studies *(6-8)* , have typically used the date of first cancer diagnosis to define time since exposure and age at exposure under the assumption that most radiation dose is received close to this date. However, as noted above, several survivors received radiotherapy a few years following the first cancer diagnosis and some of these doses exceeded 5 Gy. In our analyses of time since exposure and age at exposure, we made use of data on the date that radiation treatments were actually given. Using information on annual doses, we calculated dose for each 5-year category of age at exposure and time since exposure, and estimated EORs/Gy for each of several 5-year categories as shown in Table 3. For the purpose of evaluating trends with age at exposure and time since exposure, we used the year of the first annual dose that exceeded 5

Gy or the date of the first dose, for patients who never received an annual dose of 5 Gy or more. Four HL cases, 4 HL controls, and one CX control received an annual dose exceeding 5 Gy in a year that was at least 2 years later than the year of their first dose; none of the earlier doses for these subjects exceeded 2 Gy.

Analyses Including data from the Life Span Study cohort of Japanese atomic-bomb survivors.

To obtain parameter estimates for comparison with those based on the Japanese atomic-bomb survivor Life Span Study (LSS) cohort, we excluded cancer survivors followed for less than 12 years because LSS cancer incidence data were not available for this period. Poisson regression was used to analyze the publicly available LSS cohort data using baseline rate models developed by Preston et al *(9)*. For comparability with our case-control data, LSS analyses excluded persons exposed at less than15 years of age and person-years beyond 40 years of follow-up. The EORs for both the LSS and pooled stomach cancer studies were initially expressed as βz, (z is dose in Gy) with no modifiers of the dose-response. To evaluate trends with time since exposure and age at exposure, we fitted models with $EOR = \beta z \exp(\gamma_1 w_1 + \gamma_2 w_2)$ where w_1 denotes time since exposure and w_2 denotes age at exposure. Estimates and confidence intervals for both LSS and pooled stomach parameters were likelihood ratio based. To test whether parameter estimates based on our data differed from those based on the LSS cohort, we estimated the standard error of the difference in the two estimates by taking the square root of the sum of the two variances.

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Supplementary Table 1. Numbers of cases and controls receiving radiotherapy 5 or more years prior to stomach cancer diagnosis (or comparable date in controls) and mean tumor doses by first cancer and type of radiotherapy fields.

First cancer	Hodgkin lymphoma (HL)		Testicular cancer (TC)		Cervical cancer (CX)	
	Cases/Controls	Mean tumor dose (Gy) Cases/Controls	Cases/Controls	Mean tumor Dose (Gy) Cases/Controls	Cases/Controls	Mean tumor Dose (Gy) Cases/Controls
Total [a]	46/128	20.6/14.5	82/145	29.8/27.5	165/300	2.70/2.09
Treatment including subdiaphragmatic fields that exposed the abdomen.[b]	29/61	32.1/29.2	82/141	29.8/28.3	5/3	27.6/24.7
Treatment including supradiaphragmatic fields[c] but without abdominal field	17/67	0.9/1.2	0/1	--/0.66	0/0	--/--
Treatment including pelvic fields[c,d] but without abdominal or supradiaphragmatic fields	0/0	--/--	0/3	--/0.89	160/297	1.95/1.89

[a] Excludes survivors who were not treated with radiotherapy, were treated with radiotherapy only in the 5-year period preceding stomach cancer diagnosis, or whose radiation doses could not be estimated.

[b] For HL, the most common fields that exposed the abdomen were mantle extending into the abdomen, para-aortic with or without spleen, inverted Y/spade/dogleg with or without spleen. For TC, the most common fields that exposed the abdomen were para-aortic without spleen, inverted Y/spade/dogleg without spleen, and other abdominal fields.

[c] The supradiaphragmatic fields received by HL patients included the mantle with the lower border at the diaphragm, mediastinum, supraclavicular, axilla, head and/or neck, and other neck and chest.

[d] Radiotherapy for about 94% of CX patients who received external beam therapy included parallel-opposed anterior/posterior pelvic fields, either alone or in combination with other fields such as perineal or lateral pelvis. An additional 4% of CX patients were treated with pelvic rotational fields.

Supplementary Table 2. Risk of stomach cancer by radiation dose to the specific stomach tumor location as shown in the original studies *(3-5).*

Stomach tumor dose category (Gy)	Cases/Controls	OR (95% CI)
Hodgkin lymphoma *(reference 3, Table 2)*[a,b]		
0	9/10	1.0 (referent)
0.1-0.9	13/15	1.3 (0.4, 4.1)
1.0-4.9	13/15	1.0 (0.3, 3.5)
5.0-24.9	4/4	0.5 (0.1, 2.7)
25.0-34.9	12/13	4.6 (1.2, 20.5)
35.0-39.9	24/27	8.2 (2.6, 29.7)
≥40.0	12/13	4.2 (1.2, 15.5)
Missing dose	1/7	Not available
p-trend[c]		<0.001
EOR/Gy (95% CI)		0.09 (0.04, 0.21)
Testicular cancer *(reference 4, Table 2)*[a,d]		
0-9.9	15/49	1.0 (referent)
10.0-19.9	7/16	2.0 (0.5, 8.7)
20.0-29.9	17/43	2.5 (0.8, 7.9)
30.0-39.9	28/39	7.2(2.1, 24.9)
40.0-49.9	11/21	6.7 (1.7, 27.1)
≥ 50.0	8/6	20.5 (3.7, 114.3)
Missing dose	6/6	4.5 (1.0, 21.5)
p-trend[c]		<0.001
EOR/Gy (95% CI)		0.27 (0.054, 1.44)
Cervical cancer *(reference 5, Table 3)*[d]		
No radiotherapy	9/28	1.0 (referent)
Dose from external beam therapy		
>0-0.49	7/14	1.45 (0.35, 5.89)
0.50-0.99	37/59	1.57 (0.75, 3.37)
1.0-1.99	66/124	1.23 (0.63, 2.43)
2.0-2.99	28/66	0.92 (0.43, 1.99)
3.0-3.99	11/22	1.24 (0.46, 3.26)
4.0-4.99	6/8	1.77 (0.45, 6.87)
5.0-45.8	12/11	3.61 (1.18, 12.12)
Missing external dose	8/9	2.65 (0.78, 9.21)
p-trend[c]		0.052
EOR/Gy (95% CI)		0.106(-0.0005, 0.48)
Dose from brachytherapy		
>0-0.49	67/120	1.15 (0.49, 2.77)
0.50-0.99	94/168	1.19 (0.52, 2.83)
1.0-2.00	24/51	1.03 (0.36, 3.02)
Missing brachytherapy dose	3/5	0.92 (0.15, 4.84)
p-trend[c]		>0.5
EOR/Gy (95% CI)		Not presented

Abbreviations: CI, confidence interval; OR, odds ratio; EOR, excess odds ratio; Gy, Gray; HL, Hodgkin lymphoma; OR, odds ratio.
[a]All dose is from external beam therapy.
[b]Analyses adjusted for number of cycles of alkylating agent-containing chemotherapy included as a log-linear variable.
[c]Based on continuous radiation dose included as a linear variable.
[d]Analyses unadjusted for chemotherapy as there was no evidence that chemotherapy increased stomach cancer risk.

Supplementary Table 3. Excess odds ratio per Gray by windows of dose defined by latency or age at exposure for each first cancer.

First cancer	HL		TC		CX	
	Cases/ Controls[a]	EOR/Gy (95% CI)	Cases/ Controls[a]	EOR/Gy (95% CI)	Cases/ Controls[a]	EOR/Gy (95% CI)
Latency window (years)						
5-9.99	11/18	0.047 (-.012, 0.44)	7/15	0.041 (-0.015, 3.0)	44/71	-0.029 (<0, 0.57)
10-14.99	12/35	-0.001 (-0.020, 0.12)	25/42	0.075 (-0.004, 0.60)	32/48	0.43 (-0.022, 2.77)
15-19.99	14/38	0.035 (-0.011, 0.21)	21/39	0.50 (0.041, 8.2)	27/58	0.088 (-0.012, 0.59)
20-24.99	6/22	0.044 (-0.018, 1.7)	19/31	4.5 (0.29, 400)	26/44	1.10 (-0.072, 7.6)
25-29.99	6/14	0.96 (0.070, 34)	9/17	1.4 (0.030, 125)	20/43	0.22 (-0.078, 1.30)
30-41.83	4/10		4/5		20/42	0.060 (<0, >1)
p-trend[b]		0.069		0.039		0.46
p-trend adjusted for age at exposure[b]		0.26		0.048		0.46
Latency window (years)						
<20	33/88	0.026 (-0.007, 0.12)	50/95	0.14 (0.021, 0.85)	101/174	0.088 (-0.006, 0.51)
≥20	14/43	0.32 (0.035, 6.1)	32/50	1.5 (0.16, 43)	65/127	0.15 (-0.062, 0.75)
p-difference		.044		.038		>.5
Age at exposure window (years)						
10-24.99	13/50	0.14 (0.016, 0.82)	5/8	0.62 (0.10, 5.0)	0/0	
25-34.99	10/33	0.089 (<0, 0.54)	22/26		5/12	0.21 (-0.014, 2.9)
35-44.99	6/20	0.031 (-0.014, 0.24)	34/70	0.077 (-0.002, 0.66)	28/61	-0.008 (<0, 0.40)
45-54.99	9/14	0.096 (-0.012, 1.1)	15/29	0.10 (-0.006, 3.4)	47/81	0.11 (-0.021, 0.93)
55-64.99	4/12	-0.00 (<0, 0.11)	5/12	1.3 (-0.002, ∞)	52/92	0.12 (-0.019, 1.1)
65-83.67	8/4		3/2		33/55	0.40 (<0, 2.8)
p-trend[b]		0.15		>0.5		>0.5
p-trend adjusted for latency[b]		>0.5		>0.5		>0.5

Abbreviations: CI, confidence interval; CX, cervical cancer; EOR, excess odds ratio; Gy, Gray; HL, Hodgkin lymphoma; TC, testicular cancer.

[a]Numbers of cases and controls with radiation dose in the specified window. Patients could have radiation dose included in more than one window. Thirty four cases and 104 controls did not have a radiation dose in any window, and of these, 28 cases and 78 controls were CX patients.

[b]Adjusted for study.

Supplementary Table 4. Excess odds ratio per Gy by stomach cancer site, first cancer, and combined first cancers.[a,b]

Stomach cancer site	Cases/ Controls	Mean Dose (Gy)	EOR/Gy (95% CI)	Cases/ Controls	Mean Dose (Gy)	EOR/Gy (95% CI)	Cases/ Controls	Mean Dose (Gy)	EOR/Gy (95% CI)
First cancer									
	Hodgkin lymphoma (HL)			**Testicular cancer (TC)**			**Cervical cancer (CX)**		
Proximal	12/27	14.6	0.10 (0.001, 0.77)	21/40	24.7	0.012 (-0.018, 0.26)	29/56	1.64	-0.025 (<0, 0.071)
Body	20/55	11.5	0.028 (-0.022, 0.18)	26/47	15.1	1.47 (0.11, 46)	62/119	1.34	0.16 (-0.13, 1.36)
Distal	14/50	21.1	0.042 (-0.003, 0.21)	38/84	30.8	∞ (0.18, ∞)	66/129	2.70	0.24 (0.028, 0.84)
p-homogeneity across stomach cancer sites			>0.5			0.014			0.061
Combined first cancers									
	HL, TC, CX			**HL, TC**					
Proximal	62/123	11.9	0.035 (-0.005, 0.16)	33/67	20.7	0.062 (0.001, 0.31)			
Body	108/221	6.71	0.095 (0.006, 0.37)	46/102	13.3	0.092 (0.004, 0.40)			
Distal	118/263	14.8	0.17 (0.057, 0.45)	52/134	27.4	0.14 (0.039, 0.52)			
p-homogeneity across stomach cancer sites			0.25			>0.5			

Abbreviations: CI, confidence interval; CX, cervical cancer; EOR, excess odds ratio; Gy, Gray; HL, Hodgkin lymphoma; TC, testicular cancer.

[a]Excludes 39 cases and 71 controls where the stomach cancer site was unknown (2 cases and 3 controls for HL, 1 case and 3 controls for TC, and 36 cases and 65 controls for CX).

[b]The adjustment for missing dose was stomach cancer site-specific for TC, the only first cancer for which the stomach cancer site-specific adjustment was needed.

Supplementary Table 5. EOR/Gy and latency p-value after excluding first cancers and registries one at a time.

Data omitted	Cases/ Controls included[a]	EOR/Gy (95% CI)	P-value for latency trend[b]
None	327/678	0.090 (0.036, 0.20)	0.0038
HL study	279/543	0.16 (0.050, 0.42)	0.049
TC study	242/504	0.059 (0.014, 0.16)	0.045
CX study	134/309	0.090 (0.032, 0.22)	0.0043
Denmark	257/567	0.10 (0.040, 0.23)	0.0012
Finland	272/563	0.074 (0.025, 0.17)	0.0030
Iowa	324/667	0.091(0.035, 0.20)	0.0020
Ontario	291/602	0.12 (0.045, 0.28)	0.068
Sweden	216/450	0.089 (0.039, 0.23)	0.053
Norway	304/632	0.094 (0.036, 0.21)	0.0060
Netherlands	301/590	0.08 (0.029, 0.20)	0.0069

Abbreviations: CI, confidence interval; CX, cervical cancer; EOR, excess odds ratio; Gy, Gray; HL, Hodgkin lymphoma; TC, testicular cancer.
[a]Excludes patients with missing radiation doses and HL patients who received high cumulative doses of procarbazine.
[b]Conducted as in Table 3.