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Increased stomach cancer risk following radiotherapy for testicular cancer

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Background: Abdominal radiotherapy for testicular cancer (TC) increases risk for second stomach cancer, although data on the radiation dose–response relationship are sparse.

Methods: In a cohort of 22 269 5-year TC survivors diagnosed during 1959–1987, doses to stomach subsites were estimated for 92 patients who developed stomach cancer and 180 matched controls. Chemotherapy details were recorded. Odds ratios (ORs) were estimated using logistic regression.

Results: Cumulative incidence of second primary stomach cancer was 1.45% at 30 years after TC diagnosis. The TC survivors who received radiotherapy (87 (95%) cases, 151 (84%) controls) had a 5.9-fold (95% confidence interval (CI) 1.7–20.7) increased risk of stomach cancer. Risk increased with increasing stomach dose (P-trend <0.001), with an OR of 20.5 (3.7–114.3) for $\geqslant 50.0$ Gy compared with <10 Gy. Radiation-related risks remained elevated $\geqslant 20$ years after exposure ($P<0.001$). Risk after any chemotherapy was not elevated (OR = 1.1; 95% CI 0.5–2.5; 14 cases and 23 controls).

Conclusions: Radiotherapy for TC involving parts of the stomach increased gastric cancer risk for several decades, with the highest risks after stomach doses of $\geqslant 30$ Gy. Clinicians should be aware of these excesses when previously irradiated TC survivors present with gastrointestinal symptoms and when any radiotherapy is considered in newly diagnosed TC patients.

The incidence of testicular cancer (TC), the most common malignancy affecting males aged 15–34 years in the United States and Europe (McGlynn *et al*, 2003; Garner *et al*, 2005), has continuously increased over the past 30 years (Chia *et al*, 2010). As a result of the introduction of radiotherapy in the 1950s and cisplatin-containing combination chemotherapy in 1978

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(Einhorn and Donohue, 1977), TC is currently among the most curable solid tumours, with 10-year relative survival reaching 95% (Biggs and Schwartz, 2007; Verdecchia *et al*, 2007).

Previous studies of TC survivors have demonstrated increased risks for treatment-related second solid malignancies, beginning 10–15 years after initial diagnosis, with stomach cancer being of particular concern among TC survivors, given reported standardised incidence ratios ranging from 2.0 to 9.2 (Van Leeuwen *et al*, 1993; Travis *et al*, 1997; Kollmannsberger *et al*, 1999; Travis *et al*, 2005; Robinson *et al*, 2007; Van den Belt-Dusebout *et al*, 2007; Horwich *et al*, 2014). Although excess cases have been most often attributed to radiotherapy, the effects of radiation dose to the stomach have not been assessed in large studies. Furthermore, although some investigations among Hodgkin's lymphoma survivors reported especially high risks after combined radiotherapy and chemotherapy (Mauch *et al*, 1996; Birdwell *et al*, 1997; Swerdlow *et al*, 2000; Van Leeuwen et al, 2000; Foss Abrahamsen *et al*, 2002; Morton *et al*, 2013), the effects of specific chemotherapy agents and doses on stomach cancer risk after TC have not been examined. Therefore, in an international cohort of 22 269 5-year survivors of TC, we evaluated treatment-related stomach cancer risk based on estimated radiation dose to the stomach and dose of chemotherapeutic agents for 92 stomach cancer patients and 180 individually matched controls.

MATERIALS AND METHODS

Patient selection. During 2003–2009, we studied 22 269 5-year survivors of histologically confirmed TC as their first primary cancer (except non-melanoma skin cancer), including 19 562 patients identified from population-based cancer registries in Denmark (1943–1999), Finland (1953–2002), Iowa, USA (1973–2001), Ontario, Canada (1964–2003), Sweden (1958–2002) and Norway (1953–2000). We observed 111 cases of second primary stomach cancer diagnosed during 1975–2004. Medical records were obtained for 70 cases (63%). Most TC patients without medical records ($N = 30$, 73.2%) were diagnosed before 1970 (Supplementary Material). We randomly selected two controls per case ($N = 140$) who survived TC without a second cancer at least as long as the corresponding case and individually matched the case by registry, birth date and date of TC diagnosis (both within 2 years that was relaxed, if necessary, to 5 years). Medical records were located for 128 controls (91%). We then sought additional controls to reach a target of 2 controls per case, resulting in a total of 130 controls.

We identified 18 cases and 36 controls from Norway and all had received primary treatment in the Radium Hospital. In 2008–2009, we attempted to expand the original Norwegian study to include an additional 18 cases and 36 controls treated at other hospitals in Norway. However, upon review of the data, we excluded non-Radium Hospital patients because of insufficient information for dose reconstruction in the medical records (33% *vs* 4% among all other cases and controls) and a suggestive bias in ascertainment of exposure information (Supplementary Material).

We also included 22 cases and 50 controls, matched on age and year of TC diagnosis, from a Dutch hospital-based case–control study of second primary stomach cancer among 2707 5-year survivors of TC treated in 1965–1995 and followed through 2002. These patients were included in a previous report (Van den Belt-Dusebout *et al*, 2009). The final analytic population therefore comprised 272 TC patients (diagnosed 1959–1987), including 92 stomach cancer cases (diagnosed 1975–2004) and 180 matched controls.

The study was approved by either the Institutional Review Boards in each study centre or by the Data Inspectorate concerning national data, and exempted from review by the Netherlands Cancer Institute and the National Cancer Institute because only existing de-identified data were used.

Data collection. Details on patient demographics, including height and weight, and TC diagnosis and treatment were abstracted from available records in a standardised manner. Medical and pathology records were reviewed for stomach cancer cases to confirm diagnosis and determine tumour location in the stomach. Chemotherapy data were abstracted for: dates of administration, regimens, number of cycles, drugs, doses (alkylating agents and topoisomerase inhibitors), route of administration and indication (initial or subsequent therapy). Cumulative doses ($mg\,m^{-2}$) were calculated for individual agents.

Abstracted radiotherapy details included dates of administration, indication (initial or subsequent therapy), beam energy, delivered dose, field location and configuration. Patients were generally treated with dog-leg (including para-aortic and ipsilateral iliac nodes) or para-aortic fields. Daily target doses were 1.8–2.0 Gy, resulting in cumulative doses typically ranging from 25 to 50 Gy. Radiation doses to the stomach were similarly estimated for all cases and controls, using a custom-designed dose programme, based on measurements in water and anthropomorphic phantoms constructed of tissue-equivalent material (Stovall *et al*, 2006). Using individual patients treatment parameters, dose was calculated to 464 points in the stomach based on a typical stomach configuration (Supplementary Figure 1) (Leibel and Phillips, 2004), summing all radiotherapy series.

Stomach size, shape and location exhibit intra- and inter-individual variation depending on stomach contents, respiration, abdominal muscle tone and body build (Dowd and Wilson, 1995). Stomach position was unknown for individual patients in the study and likely varied over the course of radiotherapy. Therefore, in addition to the typical J-shaped stomach configuration, we estimated radiation doses to two alternative stomach configurations for sensitivity analyses (Supplementary Figure 1).

Radiation received within 5 years of stomach cancer diagnosis (or equivalent date for controls) were not included in the stomach doses because these were unlikely to have contributed to the stomach cancer. Analyses of radiotherapy risks used the mean dose to the stomach tumour location (same location for matched controls), specified as cardia, fundus, body, lesser curvature, greater curvature, antrum or pylorus. For 2 (2%) cases with unspecified tumour location, analyses used mean dose to the entire stomach.

Statistical analysis. Cumulative incidence of second primary invasive stomach cancer in the population-based cohort was calculated with death and other second cancers as competing risks (Gooley *et al*, 1999). The relative risk of stomach cancer was estimated using odds ratios (ORs) and 95% confidence intervals (CIs) derived from conditional logistic regression (Breslow and Day, 1980), comparing exposure histories among cases to those of matched controls. Radiation dose–response was evaluated by 10 Gy categories. In addition, the excess odds ratio (EOR) per Gy was estimated by the linear dose–response model $OR = EXP(\Sigma_j \alpha_j X_j)[1 + \beta D]$, where D is radiation dose in Gy, β is the EOR/Gy and the X_j are covariates (e.g., chemotherapy) with corresponding log ORs α_j. Departure from linearity was evaluated by a likelihood ratio test of the null hypothesis $\gamma = 0$ in a model including dose as an exponential factor $OR = EXP(\Sigma_j \alpha_j X_j)[1 + \beta D^{*}EXP(\gamma D)]$, where γ indicates downward ($\gamma < 0$) or upward curvature ($\gamma > 0$) in the EOR/Gy. In order to accommodate a local minimum or maximum in the dose–response curve, we also fitted a cubic truncated power spline with knots at tertiles of dose among cases with nonmissing dose (22.1 and 36.1 Gy). Missing radiotherapy dose was handled by including an indicator variable in all analyses.

Odds ratios were assessed by having ever *vs* never received any chemotherapeutic drug reported in the study population adjusting for radiation dose in categories as specified in Table 2. Odds ratios were also calculated by categories of cisplatin dose, the most commonly administered drug, as well as the number of

chemotherapy cycles with alkylating agents, with categories based on approximately equal numbers of cases per category (Table 2).

Heterogeneity in risks among patient subgroups under a multiplicative model was evaluated by comparing the goodness of fit of models including separate ORs and EORs for each subgroup and a single estimate, respectively. We performed sensitivity analyses by registry (leaving out each registry one at a time), stomach shape (Supplementary Figure 1) and tightness of matching of controls, and by excluding cases with a prior partial gastrectomy ($N=4$) or controls who did not match the case within 5 years with regard to year of birth ($N=2$), year of TC diagnosis ($N=1$) or follow-up window ($N=3$). SAS (SAS Institute Inc., Cary, NC, USA; version 9.2) and EPICURE (Preston *et al*, 1993) software were used.

RESULTS

Median age at TC diagnosis was 38 years (range, 18–71), 67% of all patients had been treated for a seminoma and almost all had stage I or II disease (92%) at TC diagnosis (Table 1). Treatment for TC included surgery and radiotherapy only (80% cases and 78% controls); surgery, radiotherapy and chemotherapy (14% cases and 6% controls); surgery only (3% cases and 9% controls); and surgery and chemotherapy only (1% cases and 7% controls).

Table 1. Characteristics of testicular cancer survivors who developed stomach cancer and matched controls[a]

	Cases ($N=92$)	Controls ($N=180$)
	N (%)	*N* (%)
Registry[b]		
The Netherlands[c]	22 (23.9)	50 (27.8)
Sweden	20 (21.7)	40 (22.2)
Denmark	20 (21.7)	30 (16.7)
Norway	18 (19.6)	36 (20.0)
Finland	7 (7.6)	14 (7.8)
Ontario	5 (5.4)	10 (5.6)
Year of testicular cancer diagnosis		
1959–1969	28 (30.4)	51 (28.3)
1970–1979	44 (47.8)	87 (48.3)
1980–1987	20 (21.7)	42 (23.3)
Age at testicular cancer diagnosis (years)		
18–29	17 (18.5)	36 (20.0)
30–39	35 (38.0)	70 (38.9)
40–49	23 (25.0)	42 (23.3)
50–59	12 (13.0)	23 (12.8)
60–71	5 (5.4)	9 (5.0)
Testicular cancer histology		
Seminoma	60 (65.2)	121 (67.2)
Non-seminoma	32 (34.8)	58 (32.2)
Other[d]	0 (0)	1 (0.6)
Testicular cancer stage		
I/II[e]	88 (95.7)	172 (95.6)
III/IV	4 (4.3)	6 (3.3)
Unknown	0 (0)	2 (1.1)
Testicular cancer laterality		
Left	37 (40.2)	78 (43.3)
Right	54 (58.7)	100 (55.6)
Synchronous	1 (1.1)	1 (0.6)
Unknown	0 (0)	1 (0.6)
Testicular cancer treatment following orchiectomy		
Radiotherapy only	74 (80.4)	141 (78.3)
Radiotherapy and chemotherapy	13 (14.1)	10 (5.6)
Chemotherapy only	1 (1.1)	13 (7.2)
No chemotherapy, no radiotherapy	3 (3.3)	16 (8.9)
Unknown	1 (1.1)	0 (0)
Radiation treatment fields (for patients who received radiotherapy)		
Dog-leg/inverted Y/spade only	28 (32.2)	70 (46.4)
Dog-leg/inverted Y/spade plus pelvis only	1 (1.1)	3 (2.0)
Dog-leg/inverted Y/spade plus supradiaphragmatic fields (mediastinum, neck/ supraclavicular, other chest) only	10 (11.5)	7 (4.6)
Para-aortic plus pelvis only	22 (25.3)	30 (19.9)
Others	26 (29.9)	41 (27.2)
Interval from testicular cancer to stomach cancer (years)		
7–9	9 (9.8)	
10–14	26 (28.3)	
15–19	23 (25.0)	
20–24	23 (25.0)	
25–39	11 (12.0)	
Year of stomach cancer diagnosis		
1975–1984	20 (21.7)	
1985–1994	39 (42.4)	
1995–2004	33 (35.9)	
Age at stomach cancer diagnosis (years)		
31–49	24 (26.1)	
50–59	31 (33.7)	
60–80	37 (40.2)	
Stomach cancer histology		
Adenocarcinoma	82 (89.1)	
Other/unknown[f]	10 (10.9)	
Stomach cancer site[g]		
Proximal	22 (23.9)	
Body	10 (10.9)	
Lesser curvature	12 (13.0)	
Greater curvature	5 (5.4)	
Distal	41 (44.6)	
Not otherwise specified	2 (2.2)	

[a]Patients were ineligible as cases or controls after the occurrence of a second non-stomach cancer (except metachronous testicular cancer that occurred in 3 cases and 3 controls and non-melanoma skin cancer), because it was logistically not feasible to collect detailed treatment information on multiple cancers.
[b]Cases and controls were selected from a cohort of 22 269 testicular cancer (TC) survivors including 6858 patients from Denmark, 1346 from Finland, 1300 from Iowa, 3440 from Ontario, 4732 from Sweden, 1886 from Norway and 2707 from The Netherlands.
[c]Patients from a previous report (Van den Belt-Dusebout *et al*, 2009) were included in the current study.
[d]First primary non-germ cell tumour of the testis.
[e]In this group, 12 cases and 12 controls were coded as localised, 3 controls were coded as regional and 1 case and 7 controls were coded as localised/regional.
[f]Includes 5 carcinoma not otherwise specified, 1 neuroendocrine carcinoma, 1 other specified and 3 unknown.
[g]Proximal includes cardia ($n=17$ cases), stump cancer (4) and gastro-oesophageal junction (1); body includes body (8), fundus/body (1), body/antrum (1); distal includes antrum (25), pylorus (15) and antrum/pylorus (1).

In the population-based cohort, the cumulative incidence of second primary invasive stomach cancer was 0.30% (95% CI 0.20–0.39%) at 15 years and 1.45% (95% CI 1.15–1.74%) at 30 years after TC diagnosis. Of all stomach cancers (median age at diagnosis, 58 years; range, 31–80), 37% occurred $\geqslant$20 years after TC diagnosis (median, 17; range, 7–39).

Three types of fields delivered the highest radiation doses to the stomach: dog-leg (58% of patients), para-aortic (32%) and other abdominal (9%) (Figure 1). Mean radiation doses from these fields were highest to the antrum and pylorus (37, 32 and 24 Gy, respectively) and the lesser curvature (34, 28 and 17 Gy, respectively); mean doses to other specific parts of the stomach were $<$15 Gy. For all other radiation fields (including

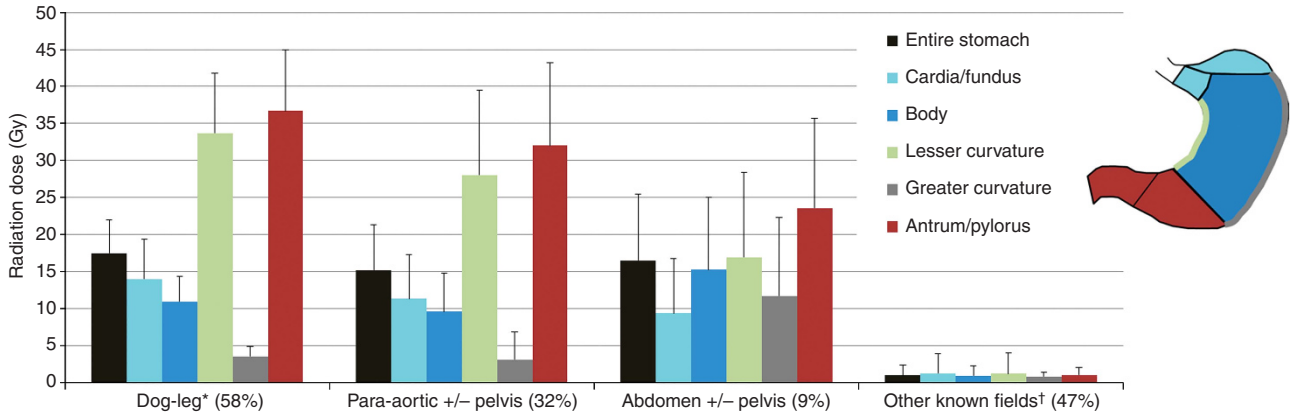

Figure 1. Mean radiation dose of cases and controls to the stomach, by stomach region, for specific testicular cancer radiotherapy fields. Note that percentages add to >100 as most patients were treated using more than one field type (parallel and opposing fields are combined for this purpose). *Includes inverted Y and spade. †Other known fields include those to the mediastinum, neck or supraclavicular area, testes, spine, chest other than para-aortic and head.

Table 2. Treatment-related risks for stomach cancer among patients with testicular cancer and matched controls

	Number of cases	Number of controls	Odds ratio	95% Confidence intervals
Any radiotherapy[a]				
No	4	29	1	Ref
Yes	87	151	5.9	1.7–20.7
Unknown	1	0	Inf	0.9–Inf
Radiation dose (Gy)[a]				
0–9.9	15	49	1	Ref
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[b]	8	6	20.5	3.7–114.3
Unknown[c]	6	6	4.5	1.0–21.5
P-trend[d]EOR per Gy = 0.27 (95% CI 0.054–1.44)			<0.001	
Any chemotherapy[e,f]				
No	77	157	1	Ref
Yes	14	23	1.1	0.5–2.5
Unknown	1	0		
Cisplatin[e,g,h]				
None	84	170	1	Ref
$<500\,mg\,m^{-2}$	4	6	1.4	0.3–5.6
$\geqslant 500\,mg\,m^{-2}$	3	4	1.3	0.2–8.2
Unknown	1	0		
P-trend[i]			0.692	
Number of chemotherapy cycles including alkylating agents[e]				
0	80	161	1	Ref
1–4	5	10	0.9	0.3–3.0
⩾5	5	9	1.1	0.3–3.8
Unknown	2	1		
P-trend[j]			0.245	

Abbreviations: CI = confidence interval; EOR = excess odds ratio; Gy = gray; Inf = infinity; Ref = reference.
[a]Not adjusted for chemotherapy.
[b]Range: 50–59.1 Gy, median: 50.8 Gy.
[c]For 11 of 12 patients with unknown dose, it was established that they had received radiotherapy. All 12 patients were included in the analysis via a missing dose indicator variable as described in the Materials and Methods section.
[d]Based on continuous (linear) dose.
[e]Adjusted for radiation dose in seven categories specified in the table.
[f]In all, 7 cases and 10 controls received cisplatin, including 1 case and 4 controls who also received etoposide and 1 control who also received doxorubicin; 1 case received ifosfamide, cisplatin and etoposide; 4 cases and 4 controls received cyclophosphamide, including 1 control who also received doxorubicin; 5 controls received exclusively chlorambucil; 3 cases and 4 controls received only antitumour antibiotics other than doxorubicin, epirubicin or mitoxantrone, including 1 case who also received a vinca alkaloid (specific drug not coded).
[g]In all, 6 of the 7 cases and 3 of the 10 controls exposed to cisplatin also received radiotherapy, respectively.
[h]One cycle of chemotherapy often includes $100\,mg\,m^{-2}$ cisplatin.
[i]Based on continuous (loglinear) dose.
[j]Based on continuous (loglinear) number of cycles.

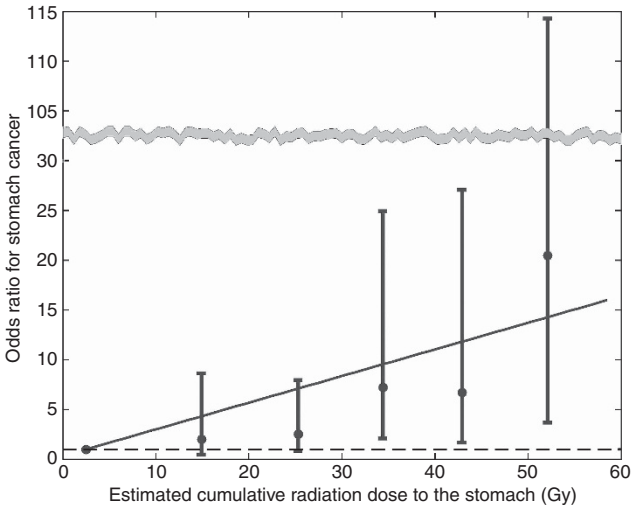

Figure 2. Radiation dose–response relationship for stomach cancer following testicular cancer based on 92 cases and 180 controls. Filled circles and error bars indicate odds ratios and 95% confidence intervals for categories of dose to the stomach tumour location in cases and a corresponding location in controls (as shown in Table 2) plotted at the mean dose per category. The solid line indicates the linear EOR per Gy (0.27, 95% CI 0.054–1.44) forced to pass through unity (dashed line) at the mean of the reference category (2.5 Gy). The ordinate is broken at the horizontal zigzag lines in order to display the upper confidence bound of the highest dose category.

mediastinum, neck or supraclavicular area, testes, spine, chest other than mediastinum and head), the stomach received on average <3 Gy to any part. The dose to particular parts of the stomach varied considerably between patients even within the same field type.

Patients who received radiotherapy had a 5.9-fold (95% CI 1.7–20.7) increased risk of stomach cancer compared with patients who did not receive radiotherapy (Table 2). Risk increased with increasing dose to the stomach tumour site (P-trend <0.001), reaching 20.5 (95% CI 3.7–114.3) at $\geqslant 50.0$ Gy compared with doses <10 Gy. The EOR per Gy was 0.27 (95% CI 0.054–1.44) and consistent with linearity ($P=0.567$) (Figure 2). A cubic spline did not fit the data better than linearity ($P=0.456$). Among patients treated with radiotherapy, the estimated proportion of stomach cancers attributable to radiotherapy was 83% (95% CI 41–95), and this increased to 87% (95% CI 55–96) for patients who received $\geqslant 30$ Gy to the stomach. Radiation-related risks remained increased $\geqslant 20$ years after exposure, based on a significantly elevated EOR per Gy for that period (Table 3).

Chemotherapy did not significantly increase subsequent stomach cancer risk (OR = 1.1, 95% CI 0.5–2.5, adjusted for radiation dose; Table 2). This was also the case for patients who received alkylating agents (11 cases and 19 controls, OR = 1.0, 95% CI 0.4–2.5), and those who received cisplatin (7 cases and 10 controls, OR = 1.4, 95% CI 0.4–4.2). No association was observed with cisplatin dose or the number of cycles containing alkylating agents. Based on small numbers of exposed patients, nonsignificant ORs for other individual classes of chemotherapeutic agents ranged from 0.8 for topoisomerase II inhibitors to 1.9 for vinca alkaloids (data not shown). Carboplatin use was not reported for any patient.

Chemotherapy did not influence radiation-related risk estimates that were within 10% of the crude radiation risks when adjusted for any chemotherapy, any cisplatin, any alkylating agents or categorical cisplatin dose. In addition, there was no evidence indicating that radiation-related risks were modified by chemotherapy or vice versa based on nonsignificant interaction terms between binary indicators of chemotherapy and radiotherapy ($P=0.132$), or radiation dose above or below 25 Gy ($P>0.5$) or continuous radiation dose ($P=0.392$), added to a multiplicative model for the joint effect. Therefore, the final models on radiation dose were not adjusted for chemotherapy.

We observed larger relative risks for cancers in the distal stomach (infinite EOR per Gy) and body (EOR per Gy = 1.48) *vs* those in the proximal stomach (EOR per Gy = 0.012, P-homogeneity = 0.012). We observed some evidence for larger relative risks at younger age at TC diagnosis, although age-dependent risks did not differ significantly. Risks did not vary substantially by year of diagnosis and interval from TC to stomach cancer (Table 3).

We performed sensitivity analyses to evaluate the robustness of our findings. Results were similar when each registry was left out one at a time (range EOR per Gy 0.19–0.48) and when we assigned three different stomach shapes based on BMI (Supplementary Material). All major results were only minimally affected when we excluded cases with a prior partial gastrectomy or controls who did not strictly match the case within 5 years for year of birth, year of TC diagnosis or follow-up window.

DISCUSSION

In an international nested case–control study within a cohort of 22 269 5-year survivors of TC, patients who received radiotherapy were at increased risk of developing stomach cancer, particularly those who received $\geqslant 30$ Gy to the stomach. These data are unique for the high proportion of patients who received high-dose radiotherapy to the abdomen in the absence of chemotherapy, thus providing strong evidence for a dose-dependent role of ionising radiation in stomach carcinogenesis. No increased risk was observed after chemotherapy only, although numbers were small.

Previous investigations of stomach cancer risk based on quantitative radiation dose estimates in the absence of chemotherapy are generally consistent with our results, although our study covered a substantially wider range of radiation doses. For example, significantly increased stomach cancer risks were observed in a nested case–control study of stomach cancer after cervical cancer (EOR per Gy = 0.11, mean stomach dose = 2.6 Gy; Kleinerman *et al*, 2013) and in a study of patients exposed to radiation for peptic ulcer (excess relative risk (ERR) per Gy = 0.16, mean stomach dose = 14.8 Gy; Carr *et al*, 2002) but not for ankylosing spondylitis (Weiss *et al*, 1994; ERR per Gy = -0.004, mean stomach dose = 3.2 Gy).

The EOR per Gy of 0.27 (95% CI 0.054–1.44) observed in our study was similar in magnitude to the ERR per Gy of 0.21 (90% CI 0.10–0.34) among male atomic bomb survivors at age 70 years following radiation exposure at age 30 years, both consistent with a linear dose–response (Preston *et al*, 2007). This is in contrast with lower risks per Gy observed in studies of fractionated, high-dose radiation exposure and second cancer risk (National Council on Radiation Protection and Measurements Scientific Committee 1-17, 2011; Travis *et al*, 2012; Berrington de Gonzalez *et al*, 2013). However, comparisons with atomic bomb survivors are uncertain because of the differences in background cancer rates between Japanese and Western populations. Nonetheless, clarifying the magnitude of the risk is essential to refine the development of second solid cancer risk projection models for modern radiotherapy modalities, including intensity-modulated radiotherapy (National Council on Radiation Protection and Measurements Scientific Committee 1-17, 2011; Travis *et al*, 2012).

Several studies have investigated stomach cancer risk with quantitative radiation dose estimates among patient populations also commonly exposed to chemotherapy. An EOR per Gy of 0.84

Table 3. Risk of stomach cancer associated with radiation dose by characteristics at testicular cancer diagnosis and other variables[a,b]

	RT dose <25 Gy (Ref)		RT dose ⩾25 Gy						
	Cases	Controls	Cases	Controls	OR	95% CI	*P* hom[c]	EOR (*P*)	*P* hom[d]
All patients	30	83	56	91	3.5	1.5–8.6	NA	0.27 (<0.001)	NA
Age at testicular cancer diagnosis (years)									
18–29	6	21	11	12	Inf	3.5–Inf		0.56 (0.005)	
30–39	12	28	21	41	1.8	0.4–7.4		0.47 (0.010)	
40–71	12	34	24	38	3.3	0.9–11.4	0.100	0.086 (0.062)	>0.5
Year of testicular cancer diagnosis									
1959–1969	11	26	13	21	2.3	0.6–9.4		0.17 (0.084)	
1970–1979	10	33	32	53	7.1	1.4–37.6		0.50 (<0.001)	
1980–1987	9	24	11	17	2.8	0.5–15.0	>0.5	0.10 (0.234)	>0.5
Testicular cancer histology									
Non-seminoma	11	33	19	23	6.2	1.6–23.6		1.15 (<0.001)	
Seminoma	19	49	37	68	2.8	1.1–7.6	0.268	0.16 (0.013)	0.210
Age at stomach cancer diagnosis (years)									
31–49	9	29	15	18	Inf	4.4–Inf		0.22 (0.014)	
50–59	10	21	19	34	2.4	0.5–12.9		Inf (0.033)	
60–80	11	33	22	39	2.4	0.7–7.7	0.076	0.24 (0.013)	>0.5
Year of stomach cancer diagnosis									
1975–1984	7	21	11	13	8.3	1.0–69.9		0.072 (0.081)	
1985–1994	8	25	25	44	5.2	0.9–29.6		Inf (0.001)	
1995–2004	15	37	20	34	2.0	0.6–6.7	0.417	0.54 (0.007)	0.136
Stomach cancer site									
Proximal	7	20	14	20	2.2	0.6–7.9		0.012 (>0.5)	
Body[e]	19	32	7	15	0.5	0.03–8.0		1.48 (0.003)	
Distal	3	28	35	56	Inf	7.1–Inf	0.012	Inf (<0.001)	0.014
Interval from testicular cancer to stomach cancer (years)									
7–14	12	33	21	35	2.8	0.8–9.8		0.096 (0.042)	
15–19	6	21	15	22	Inf	3.0–Inf		0.11 (0.115)	
20–39	12	29	20	34	2.3	0.6–8.9	0.144	Inf (<0.001)	0.090

Abbreviations: CI = confidence interval; EOR = excess odds ratio; Gy = gray; hom = homogeneity; Inf = infinity; NA = not applicable; OR = odds ratio; Ref = reference; RT = radiotherapy.

[a]For each characteristic of cancer diagnosis, analyses were limited to patients with nonmissing values for this variable. Missing radiation dose was accounted for by an indicator variable. Numbers of missing values are specified in Tables 1 and 2.

[b]For specified matching variables, controls were assigned according to the value for the corresponding case. For example, if the case was 30 years of age at testicular cancer diagnosis and the controls were 29 and 32 years, all the controls would be included in the 30–39-year category in order to keep each full case–control set in the same category.

[c]*P*-value for test of homogeneity of ORs across categories. Additional analyses of interaction between binary radiation dose (<25 Gy *vs* ⩾25 Gy) and continuous mean-centred age at or year of diagnosis revealed that the radiation dose effect decreased by 2.4% per year for age at testicular cancer diagnosis ($P = 0.49$), by 0% per year for year of testicular cancer diagnosis ($P > 0.5$), by 5.6% per year for age at stomach cancer diagnosis ($P = 0.201$), by 5.7% per year for year of stomach cancer diagnosis ($P = 0.353$) and by 7.8% per year for latency ($P = 0.236$).

[d]*P*-value for test of homogeneity of EORs across categories.

[e]Body includes lesser and greater curvature.

(95% CI, 0.12–15.6) and a significant association with procarbazine (Van den Belt-Dusebout *et al*, 2009) was observed among survivors of either Hodgkin's lymphoma (HL) or TC. However, procarbazine is not used for TC treatment. A larger international nested case–control study of stomach cancer after HL (Morton *et al*, 2013), which also included HL patients from the study of Van den Belt-Dusebout *et al* (2009), revealed significant dose–response relationships for radiation (EOR per Gy = 0.09, 95% CI 0.04–0.21) as well as for alkylating agents (*P*-trend for number of cycles = 0.02) with markedly elevated 78-fold risks for patients who received radiotherapy with stomach doses exceeding 25 Gy and high-dose procarbazine-containing chemotherapy (*P*-interaction < 0.001).

Few studies have evaluated time since radiation exposure and stomach cancer risk. Although elevated risks were observed ⩾15 years after treatment (Kleinerman *et al*, 2013; Morton *et al*, 2013), our study is the first to our knowledge providing evidence of increased radiation-related risks ⩾20 years after exposure, based on a significantly elevated EOR per Gy for that period. As observed previously (Kleinerman *et al*, 2013), distal stomach cancers were associated with the highest risks per Gy, and those were closest to the radiation therapy fields and received the highest doses. No other interactions were observed, perhaps because of the small numbers.

Compelling evidence exists that increasing cumulative dose of cisplatin is associated with significantly elevated risks of second leukaemia (*P*-trend for dose <0.001) in patients with either TC (Travis *et al*, 2000) or ovarian cancer (Travis *et al*, 1999). We observed a nonsignificant 1.4-fold increased risk of stomach cancer among the 7 cases and 10 controls who received cisplatin, representing the largest evaluation of platinum-related stomach cancer risk to date. Among 6000 non-seminoma patients treated with chemotherapy in the modern era of cisplatin-based chemotherapy (although no information on individual cytotoxic drugs was available), without radiotherapy, a nonsignificant 1.9-fold increased stomach cancer risk was observed, based on 3 cases and <10 years average follow-up (Fung *et al*, 2013). The Childhood Cancer Survivor Study, based on 45 cases of second gastrointestinal cancers, found increased risks with abdominal radiation (hazard ratio = 5.4, 95% CI 2.6–11.2) and with platinum agents (hazard ratio = 7.6, 95% CI 2.3–25.5) (Henderson *et al*, 2012). Results for stomach cancer (6 cases) were not presented separately. In the same study population, a suggestive association between cisplatin exposure and renal carcinoma was observed (RR = 3.5, 95% CI 1.0–11.2) (Wilson *et al*, 2013). Therefore, further research is warranted to determine whether platinum agents have a role in solid tumour carcinogenesis.

A major strength of our study is the case–control design nested in an international cohort of 22 269 TC patients followed for many decades that enabled us to gather an extensive amount of clinical and demographic information for participating patients and to perform individual dosimetry in order to estimate the radiation dose to the tumour location. Despite the large study base, the size of our study remains relatively small for the evaluation of cisplatin-based chemotherapy (Einhorn and Donohue, 1977). Failure to obtain medical records was more common for patients diagnosed before 1970 and therefore a larger number of cases could not be included from registries that started earlier. However, this is not likely to introduce bias because controls were matched to cases on year of TC diagnosis, registry and birth date. Another challenge is the uncertainty in radiation dose estimation to specific parts of the stomach because of variations in shape, size and location of the stomach. Using a slightly different approach, Van den Belt-Dusebout *et al* (2009) estimated the average dose to the entire stomach. These differences, together with the small study size, may explain the higher EOR per Gy of 0.84 that they observed compared with 0.27 in this study. Furthermore, we were unable to adjust our analyses for established stomach cancer risk factors such as *H. pylori* infection, family history and smoking (Nomura 1996; International Agency for Research on Cancer, 2004; Forman and Burley, 2006; Brenner *et al*, 2009), as information was not available for most patients in our study. However, it is unlikely that there is substantial confounding of the treatment-related risks by established risk factors as a strong association between treatment and a risk factor would be required. We are not aware of evidence suggesting that stomach cancer risk factors influence TC treatment or radiation doses.

In this large international study, we observed that patients treated with radiotherapy for TC between 1960 and 1990 are at increased risk of developing stomach cancer, particularly those who received $\geqslant 30$ Gy to the stomach, and that the elevated radiation-associated risk persists for more than two decades. The median age at stomach cancer diagnosis among our cases was relatively young (i.e., 58 years) compared with 69 years in the US general population (Howlader *et al*, 2013). Although the proportion of TC patients receiving radiotherapy has decreased substantially during recent decades, presently up to one-third of seminoma patients may receive radiotherapy, although with smaller fields and lower doses than those in this study (Jones *et al*, 2005; Hoffman *et al*, 2008; Schmoll *et al*, 2009; Yu *et al*, 2009; Arvold *et al*, 2012; National Comprehensive Cancer Network (NCCN), 2013). Our findings add to the knowledge of potential adverse sequelae associated with radiotherapy in TC survivors. When radiation therapy (including a boost to the upper abdomen) is considered in TC treatment plans with curative intent, clinicians and patients should be aware of radiation-related stomach cancer risk that persists for more than 20 years, and carefully consider the short- and long-term risks and benefits of therapy in their decision making.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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