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Increased pancreatic cancer risk following radiotherapy for testicular cancer

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Background: Pancreatic cancer risk is elevated among testicular cancer (TC) survivors. However, the roles of specific treatments are unclear.

Methods: Among 23 982 5-year TC survivors diagnosed during 1947–1991, doses from radiotherapy to the pancreas were estimated for 80 pancreatic cancer patients and 145 matched controls. Chemotherapy details were recorded. Logistic regression was used to estimate odds ratios (ORs).

Results: Cumulative incidence of second primary pancreatic cancer was 1.1% at 30 years after TC diagnosis. Radiotherapy (72 (90%) cases and 115 (80%) controls) was associated with a 2.9-fold (95% confidence interval (CI) 1.0–7.8) increased risk. The OR increased linearly by 0.12 per Gy to the pancreas (P-trend <0.001), with an OR of 4.6 (95% CI 1.9–11.0) for $\geqslant 25$ Gy *vs* <25 Gy. Radiation-related risks remained elevated $\geqslant 20$ years after TC diagnosis ($P=0.020$). The risk increased with the number of cycles of chemotherapy with alkylating or platinum agents ($P=0.057$), although only one case was exposed to platinum.

Conclusions: A dose–response relationship exists between radiation to the pancreas and subsequent cancer risk, and persists for over 20 years. These excesses, although small, should be considered when radiotherapy with exposure to the pancreas is considered for newly diagnosed patients. Additional data are needed on the role of chemotherapy.

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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 steadily increased over the past 30 years (Chia *et al*, 2010). As a result of the introduction of radiotherapy in the 1950s and cisplatin-based combination chemotherapy in the 1970s (Einhorn and Donohue, 1977), TC is currently among the most curable solid tumours, with 10-year relative survival reaching 95% (Biggs *et al*, 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. Pancreatic cancer is of particular concern among TC survivors as standardised incidence ratios from registry-based studies have been consistently elevated by two- to four-fold (Van Leeuwen *et al*, 1993; Travis *et al*, 1997; Kollmannsberger *et al*, 1999; Travis *et al*, 2005; Robinson *et al*, 2007; Horwich *et al*, 2014), with patterns of risk consistent with the late effects of radiotherapy. Pancreatic cancer is the fourth most common cause of cancer death in the general US population, with an overall 5-year relative survival of 5.8% (Siegel *et al*, 2015). This high fatality rate and the lack of data on the effect of radiation doses from treatment for prior cancers highlight the importance of assessing pancreatic cancer risk after abdominal radiotherapy (Carr *et al*, 2002; Dores *et al*, 2014). However, no previous study has examined the effects of radiation dose and specific chemotherapy agents on pancreatic cancer risk after TC. Therefore, we performed a case–control study nested in an international cohort of 5-year survivors of TC to evaluate treatment-related pancreatic cancer risk based on estimated radiation doses to the pancreas and cumulative amounts of chemotherapeutic agents.

MATERIALS AND METHODS

Patient selection. We studied 23 982 5-year survivors of histologically confirmed TC as their first primary cancer who were diagnosed between 1947 and 1991 and identified from 6 population-based cancer registries (Sweden, Denmark, Norway, Ontario (Canada), Finland, and Iowa (USA)) or diagnosed at one of the main hospitals in the Netherlands (Van den Belt-Dusebout *et al*, 2009). The TC patients with a prior history of non-melanoma skin cancer were not excluded as such cancers were not consistently recorded in the cancer registries during the study period. We observed 98 cases of second primary invasive pancreatic cancer diagnosed during 1965–2004. Medical records were obtained for 81 cases (83%). Most of the 17 pancreatic cancer patients without medical records were diagnosed before 1970. We randomly selected two controls per case ($N=162$) 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 calendar year of TC diagnosis (both within 5 years). Medical records were located for 135 controls (83%). To reach the target of 2 controls per case, we selected additional controls, relaxing the matching criteria when necessary – with partial success as very old hospital records had often been destroyed. Eventually, we included a total of 145 controls for 80 cases (one additional case was excluded because no matched controls were available) (Table 1).

The study was approved by either the institutional review boards in each centre or by the Data Inspectorate of participating countries, 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 TC diagnosis and treatment as well as patient demographics were abstracted from available records using standardised forms. Medical and pathology records were reviewed for pancreatic cancer cases to confirm the diagnosis and determine tumour location (head, body, tail). Data on TC chemotherapy were abstracted for dates and routes of administration, regimens, number of cycles, drugs, and doses. Cumulative doses (mg m^{-2}) were calculated for individual agents. Because of similarities in mechanisms of action, platinum compounds were combined with alkylating agents into a category of alkylating-like agents, although they form covalent metal DNA adducts instead of alkylating DNA (Brunton *et al*, 2011).

Abstracted radiotherapy details included dates of administration, beam energy, delivered dose, field location, and configuration. Patients were generally treated with dog-leg fields (para-aortic and ipsilateral iliac nodes) or para-aortic fields only. Daily target doses were 1.8–2.0 Gy resulting in cumulative doses ranging between 25 and 50 Gy. Dose was calculated to 129 points in the pancreas (divided as 54, 50, and 25 points in the head, body, and tail, respectively) based on a typical pancreas configuration (Perez *et al*, 2008), using a custom-designed dose program, based on measurements in water and anthropomorphic phantoms constructed of tissue-equivalent material (Stovall *et al*, 2006). Analyses of radiotherapy risks used the mean dose to the pancreas tumour location (same location in matched controls), specified as head, body, and tail. For 13 (16%) cases with unknown tumour location, analyses used mean dose to the pancreas head where the majority of pancreatic tumours with known subsite (82%) were located.

Statistical analysis. Cumulative incidence of second primary invasive pancreatic cancer in the population-based cohort (that is, excluding the Netherlands) was calculated with death and other second cancers (except non-melanoma skin cancer) as competing risks (Gooley *et al*, 1999). The relative risk of pancreatic 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 with those of matched controls. Radiotherapy received within 5 years of pancreatic cancer diagnosis (or equivalent date in controls) was not included because it was unlikely to have contributed to the pancreatic cancer. The radiation dose–response relationship was evaluated using dose as a categorical variable. In addition, the excess odds ratio (EOR) per Gy was estimated by the linear additive dose–response model $\mathrm{OR}=\mathrm{EXP}(\Sigma_j\alpha_j X_j)[1+\beta D]$, where D is radiation dose in Gy, β is the EOR per Gy, and the X_j are covariates (for example, 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 $\mathrm{OR}=\mathrm{EXP}(\Sigma_j\alpha_j X_j)[1+\beta D\times\mathrm{EXP}(\gamma D)]$, where γ indicates downward ($\gamma<0$) or upward curvature ($\gamma>0$) in the EOR per Gy. Patients with missing radiotherapy dose were included as a separate category.

The ORs for chemotherapy were assessed by having ever *vs* never received any chemotherapy or any alkylating agent-containing chemotherapy adjusted for radiation dose (0, >0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40.0–44.9, and ⩾45.0 Gy). The ORs were also calculated according to the number of alkylating agent-containing chemotherapy cycles (categorical variable), and trend tests were based on the number of alkylating agent-containing cycles (continuous variable) in an additive model, like for continuous dose as shown above. Heterogeneity in radiation-related 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 with models including a single estimate, respectively. To evaluate the joint effect of radiotherapy (radiation dose <25 *vs* >=25 Gy) and chemotherapy (no *vs* yes), deviances of multiplicative and additive models were compared with those of more general models that included interaction terms. Attributable risks were calculated by averaging the quantities [dose × EOR per Gy]/[1 + (dose × EOR

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

	Cases (*N* = 80) *N* (%)	Controls (*N* = 145) *N* (%)
Registry[b]		
Sweden	20 (25.0)	40 (27.6)
Denmark	20 (25.0)	25 (17.2)
Norway	13 (16.3)	26 (17.9)
Netherlands	9 (11.3)	18 (12.4)
Ontario	7 (8.8)	14 (9.7)
Finland	6 (7.5)	12 (8.3)
Iowa	5 (6.3)	10 (6.9)
Calendar year of testicular cancer diagnosis		
1947–1959	3 (3.8)	4 (2.8)
1960–1969	31 (38.8)	55 (37.9)
1970–1979	35 (43.8)	69 (47.6)
1980–1991	11 (13.8)	17 (11.7)
Age at testicular cancer diagnosis (years)		
19–29	14 (17.5)	25 (17.2)
30–39	23 (28.8)	46 (31.7)
40–49	33 (41.3)	55 (37.9)
50–59	5 (6.3)	13 (9.0)
60–73	5 (6.3)	6 (4.1)
Testicular cancer histology		
Seminoma	55 (68.8)	99 (68.3)
Non-seminoma	23 (28.8)	42 (29.0)
Other[c]	2 (2.5)	4 (2.8)
Testicular cancer stage		
I/II[d]	74 (92.5)	138 (95.2)
III/IV	6 (7.5)	7 (4.8)
Testicular cancer laterality		
Left	34 (42.5)	67 (46.2)
Right	46 (57.5)	77 (53.1)
Extragonadal seminoma	0 (0.0)	1 (0.7)
Testicular cancer treatment after orchiectomy		
Radiotherapy only	65 (81.3)	107 (73.8)
Radiotherapy and chemotherapy	6 (7.5)	8 (5.5)
Chemotherapy only	3 (3.8)	8 (5.5)
Surgery only	5 (6.3)	22 (15.2)
Radiotherapy, chemotherapy unknown	1 (1.3)	0 (0.0)
Interval from testicular cancer to pancreatic cancer (years)		
6–9	6 (7.5)	
10–14	12 (15.0)	
15–19	23 (28.8)	
20–24	18 (22.5)	
25–29	14 (17.5)	
30–34	6 (7.5)	
35–38	1 (1.3)	
Calendar year of pancreatic cancer diagnosis		
1965–1974	4 (5.0)	
1975–1984	8 (10.0)	
1985–1994	36 (45.0)	
1995–2004	32 (40.0)	
Age at pancreatic cancer diagnosis (years)		
41–49	13 (16.3)	
50–59	23 (28.8)	
60–69	33 (41.3)	
70–79	8 (10.0)	
80–81	3 (3.8)	
Pancreatic cancer histology		
Adenocarcinoma	69 (86.3)	
Other[e]	5 (6.3)	
Without histologic confirmation	6 (7.5)	
Pancreatic cancer site		
Head	55 (68.8)	
Body	9 (11.3)	
Tail	3 (3.8)	
Unknown	13 (16.3)	

[a]Patients were ineligible as cases or controls after the occurrence of a second non-pancreatic cancer (except metachronous testicular cancer that occurred in 3 cases and 1 control and non-melanoma skin cancer), because treatment for an intervening cancer could confound risk estimates for the subsequent pancreatic cancer.
[b]Cases and controls were selected from a cohort of 23 982 TC survivors including 6858 patients from Denmark (1947–1991), 1346 from Finland (1960–1977), 1300 from Iowa (1974–1986), 3440 from Ontario (1964–1980), 4732 from Sweden (1958–1983), 3599 from Norway (1960–1987), and 2707 from The Netherlands (1968–1988).
[c]Four non-germ cell tumours (1 case and 3 controls), 1 germ cell tumour, not otherwise specified (control), and 1 testis cancer, not otherwise specified (case).
[d]In this group, 51 cases and 112 controls were coded as localised, 18 controls and 19 cases were coded as regional, and 5 cases and 7 controls were coded as localised/regional.
[e]Includes 2 carcinoma, not otherwise specified; 1 large cell carcinoma; 1 adenosquamous carcinoma; and 1 malignant neoplasm, not otherwise specified.

per Gy)] over cases with known dose. The SAS (version 9.2; SAS Institute, Cary, NC, USA) and EPICURE (Preston *et al*, 1993) software were used.

RESULTS

The cumulative incidence of second primary invasive pancreatic cancer in the population-based cohort was 0.14% (95% CI 0.07–0.20%) and 1.08% (95% CI 0.83–1.34%), respectively, at 15 and 30 years after TC diagnosis. Of all pancreatic cancers (median age at diagnosis, 61 years; range, 41–81 years), 48% occurred ⩾20 years after TC diagnosis (median, 20 years; range, 6–38 years), and the majority were located in the head of the pancreas (69%). The median age at diagnosis is lower than that reported in the US population (73 years) during 1973–2002 (Lau *et al*, 2010) or peak occurrence reported in Denmark (70–74 years) during 1978–2003 among males and females (Teiblum *et al*, 2009). In both the United States and Denmark, tumours of the pancreatic head predominated in the general population (Teiblum *et al*, 2009; Lau *et al*, 2010).

Among pancreas cancer cases and controls, median age at TC diagnosis was 40 years (range, 19–73 years), 68% had been treated for seminoma, and 94% had stage I or II disease (Table 1). The TC treatment included surgery and radiotherapy (81% cases, 74% controls); surgery, radiotherapy, and chemotherapy (8% cases, 6% controls); surgery only (6% cases, 15% controls); or surgery and chemotherapy (4% cases, 6% controls).

Two common fields resulted in average radiation doses of ~30 Gy to the head and body of the pancreas: dog-leg (40% of patients who received radiotherapy) and para-aortic fields (35%) (Table 2). Abdominal (13%) and non-central para-aortic fields (11%) resulted in average doses to the head and body of the pancreas of 15–20 Gy. For all other radiation fields (including mediastinum, pelvis, mantle, testes, neck, or supraclavicular area), the pancreas received on average <2 Gy to any pancreas subsite.

Patients who received radiotherapy had a 2.9-fold (95% CI 1.0–7.8) increased risk of pancreatic cancer compared with patients who did not receive radiotherapy (Table 3). Risk increased with increasing dose to the pancreatic tumour site (P-trend < 0.001), with ORs of 0.9 (95% CI 0.2–3.2), 2.5 (95% CI 0.6–11.4), 4.5 (95% CI 1.3–15.6), 8.1 (95% CI 1.8–35.5), 2.3 (95% CI 0.6–9.7), and 7.1 (95% CI 1.5–33.2) for >0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40.0–44.9, and ⩾45.0 Gy, respectively, compared with no radiotherapy. The EOR per Gy was 0.12 (95% CI 0.03–0.42) and consistent with linearity (test of nonlinearity, $P = 0.127$), although power to detect nonlinearity is limited (Figure 1). Among patients treated with radiotherapy, the estimated percentage of pancreatic cancers attributable to radiotherapy was 70% (95% CI 44–83%)

Table 2. Average radiation doses to subsites of pancreas by radiation therapy fields among 187 testicular cancer patients treated with radiotherapy

	Patients[a] *N* (%)		Average radiation dose (Gy)			
Field name	**Seminoma**	**Non-seminoma**	**Entire pancreas**	**Pancreas head**	**Pancreas body**	**Pancreas tail**
Dog-leg[b]	59 (42)	15 (35)	28.7	34.4	33.3	6.8
Para-aortic[b]	47 (33)	17 (40)	26.1	31.2	29.9	7.4
Abdomen[c]	16 (11)	7 (16)	16.3	19.1	15.3	12.3
Non-central para-aortic[d]	13 (9)	6 (14)	14.2	16.8	15.8	5.7
Mediastinum	7 (5)	2 (5)	1.2	0.7	1.7	1.2
Pelvis	63 (44)	23 (53)	0.8	1.1	0.7	0.6
Mantle[e]	9 (6)	0 (0)	0.6	0.4	0.6	0.8
Testes	3 (2)	2 (5)	0.1	0.1	0.1	0.1
Neck or supraclavicular area	4 (3)	0 (0)	<0.1	<0.1	<0.1	<0.1
Other or unknown fields	16 (11)	7 (16)	NA	NA	NA	NA

Abbreviation: NA = unable to calculate dose.
[a]Numbers of patients do not sum to 187 as some patients received radiotherapy to more than one field. Percentages represent the fraction of patients who received a certain field relative to all 187 patients who received radiotherapy and therefore do not sum to 100% (for example, 74 patients received radiotherapy to the dog-leg field, that is 40% of all patients who received radiotherapy).
[b]Without spleen or unknown. The dog-leg category also includes 11 patients with inverted Y or spade fields as the para-aortic abdominal component of these fields is the same as the dog-leg field. The difference between the three fields is in the pelvic component: dog-leg treats one side of the pelvis, inverted Y treats both sides with a central block, and spade treats a large central portion of the pelvis.
[c]With or without spleen.
[d]Non-central para-aortic fields include lateral, oblique, or rotational para-aortic fields (R and/or L) as well as anterior and/or posterior fields with the central axis to the right or left of the midline.
[e]Mantle or T-fields treat the supraclavicular region and mediastinum only with the lower border at the diaphragm.

that increased to 81% (95% CI 52–94%) for patients who received ⩾25 Gy to the pancreas.

Radiation-related risk estimates were similar or increased slightly when adjusted for the number of alkylating agent-containing chemotherapy cycles, with an EOR per Gy of 0.20 (95% CI 0.05–0.88) (Supplementary Table 1). In addition, there was no evidence that radiation-related risks were modified by chemotherapy or vice versa. Interaction terms between both binary and continuous indicators of chemotherapy and radiotherapy were nonsignificant ($P>0.5$; Tables 3 and 4).

The OR for pancreas cancer among TC patients given chemotherapy (Supplementary Table 2), adjusted for radiation dose, was 1.4 (95% CI 0.5–3.7; Table 3). For patients treated with alkylating-agent containing chemotherapy, the OR was 2.2 (95% CI 0.7–6.9), based on 8 cases and 11 controls. Risk reached 3.5-fold for ⩾5 cycles (2 cases, 4 controls, 95% CI 0.4–32.4), with a borderline significant trend (P-trend = 0.057). Six of 154 seminoma patients (4%, chemotherapy unknown for one seminoma patient) and 18 of 65 non-seminoma patients (28%) received chemotherapy. For alkylating agent-containing chemotherapy, corresponding numbers were 4% and 18%, respectively. For the number of alkylating agent-containing chemotherapy cycles, the association was pronounced among non-seminoma patients, where ORs increased up to 10.9 (95% CI 1.0–117.6) for ⩾5 cycles (P-trend = 0.034), whereas there was no apparent association for patients with other histology (P-trend = 0.298) (data not shown).

We observed no evidence of heterogeneity of radiation-related risks for cancers in the head of the pancreas (EOR per Gy = 0.10) *vs* those in the body or tail (EOR per Gy = 0.02, P-homogeneity = 0.330; Table 4). Power was limited as only 11 pancreatic cancers were located in the body or tail. Furthermore, risks appeared homogeneous by age at and year of diagnosis of TC or pancreatic cancer and by TC histology. There was a significant radiation dose–response among patients who did not receive chemotherapy (EOR per Gy = 0.15, $P<0.001$), the largest treatment group (89% of cases, 89% of controls). Risks remained significantly increased ⩾20 years after exposure (EOR per Gy = 0.07, $P=0.020$).

We performed sensitivity analyses to evaluate the robustness of our findings. Results were similar when each registry was excluded one at a time (range EOR per Gy, 0.08–0.21). All major results were only minimally affected when we excluded controls who did not strictly match the case within 5 years for date of birth ($N=2$), year of TC diagnosis ($N=1$), or follow-up period ($N=3$). We also evaluated obesity, a pancreatic cancer risk factor (Ryan *et al*, 2014; Maisonneuve and Lowenfels, 2015), among patients with recorded body mass index (BMI; 44 cases and 60 controls). The unadjusted EOR per Gy (0.10) was similar after adjustment for continuous or categorical BMI ($kg\,m^{-2}$) at TC diagnosis (0.10 and 0.11, respectively).

DISCUSSION

In an international nested case–control study within a cohort of 23 982 5-year survivors of TC treated between 1947 and 1991, we observed a significant dose–response relationship between cumulative radiation dose to the pancreas and risk of pancreatic cancer. Elevated radiation-associated risk persisted for more than two decades. The TC survivor population is of interest for the high proportion of patients who received abdominal radiotherapy in the absence of chemotherapy, thus permitting an unconfounded evaluation of the role of high-dose ionising radiation in pancreatic carcinogenesis.

Our study is among the first to establish a radiation dose–response relationship for second primary pancreatic cancer among cancer patients not treated with alkylating agent-containing chemotherapy, with an EOR per Gy of 0.15 (95% CI 0.03–0.66). In an earlier report of pancreatic cancer among Hodgkin's lymphoma survivors (Dores *et al*, 2014), the number of patients treated with radiation in the absence of alkylating agent-containing chemotherapy was too small (10 cases and 33 controls) to establish a dose–response in this group alone. The overall EOR per Gy of 0.10 (95% CI 0.02–0.42) was similar between studies. Our current results add to the evidence for a causal association between radiation and pancreatic cancer.

Table 3. Treatment-related risks for pancreatic cancer among patients with testicular cancer and matched controls

	Number of cases (%)	Number of controls (%)	Odds ratio	95% CI
Any radiotherapy[a]				
No	8 (10.0)	30 (20.7)	1.0	Ref
Yes	72 (90.0)	115 (79.3)	2.9	1.0–7.8
Radiation dose (Gy)[a]				
<25	16 (20.0)	60 (41.4)	1.0	Ref
⩾25	55 (68.8)	70 (48.3)	4.6	1.9–11.0
Unknown[b]	9 (11.3)	15 (10.3)	2.0	0.7–5.4
Radiation dose to pancreas (Gy)[a]				
0	8 (10.0)	30 (20.7)	1.0	Ref
>0–24.9	8 (10.0)	30 (20.7)	0.9	0.2–3.2
25.0–29.9	9 (11.3)	17 (11.7)	2.5	0.6–11.4
30.0–34.9	18 (22.5)	22 (15.2)	4.5	1.3–15.6
35.0–39.9	10 (12.5)	7 (4.8)	8.1	1.8–35.5
40.0–44.9	8 (10.0)	17 (11.7)	2.3	0.6–9.7
⩾45.0[c]	10 (12.5)	7 (4.8)	7.1	1.5–33.2
Unknown[b]	9 (11.3)	15 (10.3)	1.8	0.5–6.6
P-trend[d]			<0.001	
EOR per Gy = 0.12 (95% CI 0.03–0.42)				
Any chemotherapy[e,f,g]				
No	70 (88.6)	127 (88.8)	1.0	Ref
Yes	9 (11.4)	16 (11.2)	1.4	0.5–3.7
Any alkylating agent-containing chemotherapy[e,g,h]				
No	71 (89.9)	132 (92.3)	1.0	Ref
Yes	8 (10.1)	11 (7.7)	2.2	0.7–6.9
Number of alkylating agent-containing chemotherapy cycles[e,g,h]				
0	71 (89.9)	132 (92.3)	1.0	Ref
1–4	6 (7.6)	7 (4.9)	1.9	0.5–6.8
⩾5	2 (2.5)	4 (2.8)	3.5	0.4–32.4
P-trend[i]			0.057	
Radiation dose (Gy) and chemotherapy (yes/no)[g,j]				
<25 Gy, No	13 (18.3)	51 (39.2)	1.0	Ref
⩾25 Gy, No	49 (69.0)	64 (49.2)	4.6	1.8–12.1
<25 Gy, Yes	3 (4.2)	9 (6.9)	1.4	0.3–7.3
⩾25 Gy, Yes	6 (8.5)	6 (4.6)	6.2	1.5–25.5
P-value multiplicative joint effect			>0.5	
P-value additive joint effect			>0.5	

Abbreviations: CI = confidence interval; EOR = excess odds ratio; Ref = reference.
[a]Not adjusted for chemotherapy.
[b]All 24 patients with unknown dose had received radiotherapy. They were included in the analysis with a missing dose indicator variable as described in the Materials and Methods section. Missing radiation dose occurred in 22 risk sets and resulted in 15 of them (including 15 cases and 23 controls) being non-informative, whereas the other 7 risk sets remained informative as radiation dose was missing for only one of two controls.
[c]Range: 45.1–72.4 Gy, median: 48.3 Gy.
[d]Based on continuous dose in an additive model.
[e]Adjusted for continuous radiation dose as a linear term.
[f]See Supplementary Table 1 for frequency of specific chemotherapy agents.
[g]One patient with unknown chemotherapy status (and his two associated control patients) were excluded from analysis.
[h]Alkylating agents include cisplatin (1 case, 7 controls), chlorambucil (3 cases), cyclophosphamide (4 cases, 4 controls), procarbazine (1 control). One control received cyclophosphamide and procarbazine.
[i]Based on continuous number of cycles in an additive model.
[j]Median doses (range) per group in Gy were 7.6 (0–24.8) (<25 Gy, No), 32.5 (25.0–72.4) (⩾25 Gy, No), 0 (0–23.8) (<25 Gy, Yes), 41.1 (27.6–56.1) (⩾25 Gy, Yes), unknowns excluded.

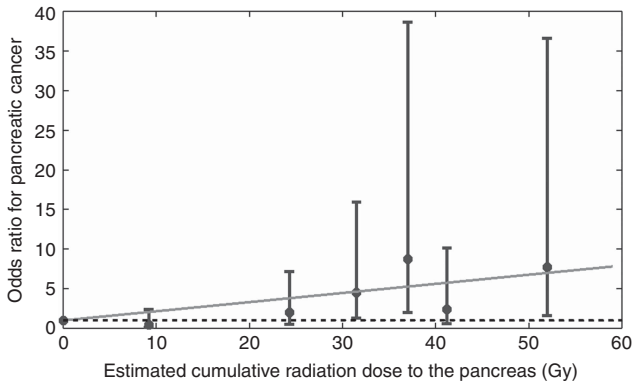

Figure 1. Radiation dose–response relationship for pancreatic cancer following testicular cancer based on 80 cases and 145 controls. Filled circles and error bars indicate odds ratios and 95% confidence intervals for categories of dose to the pancreatic tumour location in cases and a corresponding location in controls (as shown in Table 3) plotted at the mean dose per category. The slope of the solid line is the linear excess odds ratio (EOR) per Gy (0.12, 95% CI 0.03–0.42).

Significant radiation dose-response relationships for pancreatic cancer have been observed among patients exposed to medical radiation for indications other than cancer treatment (Weiss *et al*, 1994; Ryan *et al*, 2014; Maisonneuve and Lowenfels, 2015) with doses to the pancreas varying widely but typically less than ~15 Gy. Among atomic bomb survivors, who received doses generally under 4 Gy, a nonsignificant positive association (EOR per Gy = 0.26, 90% CI −0.07–0.68) was observed in the most recent analysis of those data (Travis *et al*, 2003).

Although numbers were quite small, we observed a suggestive association between alkylating agent-containing chemotherapy and subsequent pancreatic cancer, particularly among non-seminoma patients who were more likely to receive chemotherapy. Radiation-related risks did not appear to differ according to the receipt of alkylating agents. However, these findings should be interpreted cautiously as numbers were too small to compare patients with substantial exposure to radiation and alkylating agents with patients with neither treatment. In the only other study of second primary pancreatic cancer with detailed information on antecedent radiation and chemotherapy, Dores *et al* (2014) observed especially high risks (18-fold) of pancreatic cancer among Hodgkin's lymphoma survivors who received both subdiaphragmatic radiotherapy and ⩾6 cycles of alkylating agent-containing chemotherapy.

Although the proportion of TC patients receiving radiotherapy has decreased substantially during recent decades, our results apply to the large number of TC survivors who have been effectively treated with radiotherapy in the past and remain alive. In view of the increasing incidence of TC in the past decades (Chia *et al*, 2010) and the availability of curative therapy, TC survivors currently comprise ~4% of all male US cancer survivors (DeSantis *et al*, 2010) and ~5% of all male cancer survivors in the Nordic countries (Engholm *et al*, 2010). In addition, currently up to one-third of seminoma patients may receive radiotherapy (DeSantis *et al*, 2010; Vossen *et al*, 2012; Kohut *et al*, 2014). The cumulative radiotherapy target volume dose decreased from 40 to 30 Gy after 1980 and further to 20 Gy since ~1990 (Jones *et al*, 2005; Hoffman *et al*, 2008; Yu *et al*, 2009; Schmoll *et al*, 2009; Arvold *et al*, 2012; National Comprehensive Cancer Network (NCCN), 2013; Comprehensive Cancer Center Netherlands, 2014). Among non-seminoma patients, cumulative radiation doses were 45–50 Gy before 1980, whereas radiotherapy was rarely used after 1980, when cisplatin became available (Einhorn and Donohue, 1977). Alkylating agent-containing chemotherapy may also increase pancreatic cancer risk, as observed in our study and one other series (Dores *et al*, 2014), although results here are based on small numbers.

A major strength of our study is the case–control design nested in an international cohort of 23 982 TC patients, most of them

Table 4. Risk of pancreatic cancer associated with radiation dose to the pancreas by patient characteristics 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	16	60	55	70	4.6	1.9–11.0	NA	0.12 (<0.001)	NA
Age at testicular cancer diagnosis (years)									
19–29	1	12	11	12	5.0	1.0–26.0		0.08 (0.035)	
30–39	5	18	16	19	4.6	0.9–22.5		0.18 (0.011)	
40–73	10	30	28	39	4.3	1.3–14.8	0.989	0.12 (0.008)	0.823
Year of testicular cancer diagnosis									
1947–1969	6	25	20	20	5.5	1.5–20.8		0.14 (0.006)	
1970–1979	8	20	26	44	1.8	0.5–5.9		0.03 (0.252)	
1980–1991	2	15	9	6	Inf[e]	4.1–Inf	0.058	Inf (0.002)	0.131
Testicular cancer histology									
Non-seminoma	7	21	13	17	3.0	0.9–9.9		0.08 (0.015)	
Seminoma	9	35	41	53	5.4	1.8–16.7	0.404	0.14 (0.005)	0.559
Age at pancreatic cancer diagnosis (years)									
41–49	3	15	10	10	9.6	1.1–81.8		0.23 (0.008)	
50–59	5	13	15	22	1.5	0.4–6.7		0.04 (0.249)	
60–81	8	32	30	38	5.9	1.7–19.8	0.262	0.11 (0.005)	0.636
Year of pancreatic cancer diagnosis									
1965–1984	3	12	5	5	4.5	0.4–48.3		0.20 (0.038)	
1985–1994	5	25	27	33	5.1	1.6–16.7		0.18 (0.002)	
1995–2004	8	23	23	32	3.8	1.0–15.1	0.948	0.07 (0.036)	0.604
Pancreatic cancer site									
Head	9	35	41	54	3.4	1.3–8.8		0.10 (0.002)	
Body/tail	5	12	6	9	3.9	0.3–23.1	0.840	0.02 (0.529)	0.330
Interval from testicular cancer to pancreatic cancer (years)									
6–14	4	20	14	14	Inf[e]	4.3-Inf		Inf (<0.001)	
15–19	5	16	13	20	1.8	0.4–8.4		0.05 (0.191)	
20–38	7	24	28	36	3.9	1.3–12.3	0.085	0.07 (0.020)	0.083
Any chemotherapy[f]									
No	13	49	49	64	4.6	1.8–12.1		0.15 (<0.001)	
Yes	3	9	6	6	4.3	0.7–27.7	0.944	0.07 (0.124)	0.610
Any alkylating agent-containing chemotherapy[f]									
No	13	51	50	67	4.6	1.8–12.0		0.15 (<0.001)	
Yes	3	7	5	3	5.3	0.7–43.0	0.902	0.09 (0.132)	0.720

Abbreviations: CI = confidence interval; EOR = excess odds ratio; 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 non-missing values for this variable. Missing radiation dose was accounted for by an indicator variable. Numbers of missing values are specified in Tables 1 and 3.

[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 (TC) diagnosis and the controls were 29 and 32 years, all the controls would be included in the 30–39 years 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 1.4% per year for age at testicular cancer diagnosis ($P = 0.703$), by 3.4% per year for age at pancreatic cancer diagnosis ($P = 0.383$), by 3.6% per year for year of pancreatic cancer diagnosis ($P = 0.600$), and by 3.9% per year for latency ($P = 0.485$), and increased by 2.3% per year for year of testicular cancer diagnosis ($P = 0.384$).

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

[e]Infinite OR estimates occur because all subjects in some of the cells are dropped from the conditional logistic regression analysis because of the fact that their risk sets are non-informative, that is, cases and matched controls have the same exposure level.

[f]One case with unknown chemotherapy status and its two associated controls were excluded from analysis.

followed for more than three decades, with collection of detailed clinical and demographic data. We performed individual dosimetry and estimated the radiation dose to the tumour subsite that likely led to accurate dose estimates, although uncertainties remain because of, among others, computed tomography-based plans for radiotherapy. Our study has several limitations. Despite the large study base, the small number of patients treated with platinum-based chemotherapy (1 case and 7 controls) did not permit adequate statistical power to evaluate this modality. Furthermore, the inability to obtain medical records was more common for patients diagnosed before 1970, and thus a larger number of cases from registries that were established in earlier years could not be included. However, differential ascertainment of medical records is unlikely to introduce bias as controls were matched to cases on year of TC diagnosis, registry, and birth date. Adjustment for BMI at TC diagnosis among patients with available data did not substantially change radiation risk estimates. As information on other established pancreatic cancer risk factors such as smoking, *Helicobacter pylori* infection, blood group, diabetes mellitus, and chronic pancreatitis (International Agency for Research on Cancer, 2004; Ryan *et al*, 2014; Maisonneuve and Lowenfels, 2015) was not available in this retrospective study, we were unable to adjust our analyses accordingly. It is unlikely, however, that confounding of therapy-related risks by the aforementioned factors exists, as to our knowledge they do not influence clinical decisions with regard to TC treatments. The effect of increased BMI as an intermediate factor in increased pancreas cancer risk caused by therapy for TC could not be evaluated because of the lack of post-treatment BMI data.

Our findings add to the knowledge of potential adverse sequelae associated with TC treatment. Although second pancreatic cancer is a rare complication of TC therapy, it is highly fatal. In our study, median survival was 4 months among the 77 pancreatic cancer cases who were known to have died. The results may also be

applicable to patients with cancers at other sites in whom similar abdominal regions may be irradiated today (Halperin *et al*, 2013; Teepen *et al*, 2016). Consideration of administering radiotherapy with curative intent should include an evaluation of the radiation-related pancreatic cancer risk that may persist for >20 years, although the small magnitude of any excess risk must be weighed against the potential benefits of radiotherapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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