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Risk Factors for the Development of Oesophageal Cancer as a Second Primary Tumour

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Exposure to irradiation or chemotherapy as well as prolonged exposure to risk factors, such as alcohol and tobacco, may induce a second primary carcinoma of the oesophagus. To estimate the potential risk of previous treatment regimens, we performed a case–control study. In the Tumour Registry of The Netherlands Cancer Institute, from 1955, 27 cases of squamous cell carcinoma of the oesophagus were identified following treatment for malignant lymphoma (n = 11), breast cancer (n = 8) and lung cancer (n = 8). The median interval was 6.6 years (range 1–16). Preferably 3 controls from the same tumour registry were matched to each case on the basis of sex, age, primary tumour, location of primary treatment (academic or general hospital), calendar year at diagnosis of primary tumour and duration of follow-up. Clinical data and details of treatment were obtained from the medical records. In patients who had smoked for more than 5 years, there was a 3.2-fold increased risk of oesophageal carcinoma (P = 0.04); for those with a regular alcohol intake the relative risk was 3.3 (P = 0.01). There was no significant relationship between irradiation of the mediastinum and subsequent risk for oesophageal cancer. The number of chemotherapy-treated patients was too small to calculate the relative risk associated with cytostatic drugs. In conclusion, oesophageal cancer as second primary cancer is extremely rare. Risk factors include the well known abuse of alcohol and tobacco. No significant relationship with previous mediastinal irradiation could be demonstrated.

Key words: oesophageal cancer, aetiology, radiotherapy, case–control
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INTRODUCTION

IN RECENT years, we have been confronted more and more with secondary tumours following successful treatment of the initial primary cancer [1, 2]. Irradiation as well as chemotherapy may play an important role in the induction of a second malignancy. Patients who are being irradiated on the internal mammary chain or the mediastinal lymph nodes often temporarily experience dysphagia or retrosternal burning [3–6]. Many authors stress the carcinogenic potential of irradiation in such cases, and a radiation-induced carcinoma of the oesophagus is a widely accepted concept [6–11].

Information on incidence is lacking, but it is probably a rare condition. Recently, we described the clinical outcome in 16 cases of radiation-induced oesophageal carcinoma seen in a 15 year period in The Netherlands Cancer Institute [12]. So far, evidence for an increased risk of oesophageal cancer after radiotherapy has been limited to an increased incidence of squamous cell carcinomas of the oesophagus among nuclear bomb survivors and among patients irradiated for ankylosing spondylitis [13, 14]. In mice, squamous cell carcinomas of the oesophagus have been induced by means of continuous irradiation with a $Cobalt^{60}$-source [15].

To determine the risk of developing a malignancy in the oesophagus following cancer treatment, a case–control study was performed. The primary tumours included were Hodgkin's disease, non-Hodgkin's lymphoma, breast cancer and lung cancer.

PATIENTS AND METHODS

Collection of cases and controls

Cases and controls were identified from the Tumour Registry of The Netherlands Cancer Institute. This registry contains records of all patients who have been treated in The Netherlands Cancer Institute from 1955 until the present. Only patients with a squamous cell carcinoma of the oesophagus who had been treated previously for breast cancer, malignant lymphoma or lung cancer were entered as cases (n = 27).

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The controls were defined as patients treated for the same primary tumour in whom oesophageal cancer has not been diagnosed. For each case, 3 controls were sought. They were individually matched to the case on the basis of sex, date of birth (±3 years), date of diagnosis of primary tumour (±2 years), location where treatment of the primary had taken place (university or general hospital), pathology and duration of follow-up (at least as long as the interval between the diagnosis of the primary tumour and diagnosis of oesophageal cancer). When more than 3 controls per case met the above criteria, we selected those whose year of diagnosis of primary tumour and then date of birth were closest to the corresponding case. 3 controls were found for 18 cases, 2 controls were found for 7 cases, and for 2 cases only one control could be found.

Data collection

For each case and the corresponding matched control, the full medical record was reviewed for detailed data abstraction. Information was collected on: smoking habits (never or stopped smoking more than 5 years ago; yes, or stopped less than 5 years ago); drinking habits (never or sporadically 1 unit per day; 2–3 units per day; >3 units per day); a history of coeliac disease, tylosis or lye ingestion; anaemia due to iron deficiency; previous chemotherapy (no further specified); previous radiotherapy (irradiation covering the midline between the cricoid cartilage and the 12th thoracic vertebra versus all other regimens or no radiotherapy). The radiotherapy charts of all cases and controls were available for consultation.

Statistical analysis

The relative risk of oesophageal cancer was estimated for several factors by comparing the cases' treatment history with that of their matched controls, using conditional logistic regression methods. Relative risk estimates, two-sided P-values and 95% confidence intervals were calculated with the microcomputer programme EGRET [16]; comparisons between exposure categories were based on likelihood-ratio tests. The treatment of the cases was considered only for the period between the diagnosis of the primary tumour and the diagnosis of oesophageal cancer. For each control, therapy was considered for an equivalent interval, starting with the date that the primary tumour was diagnosed. Multivariate analyses were conducted to evaluate the potentially confounding effects of radiotherapy and chemotherapy, as well as smoking and drinking habits.

RESULTS

The study population consisted of 27 cases and 70 controls, previously treated for malignant lymphoma, breast cancer or lung carcinoma (Table 1). The median interval between primary tumour diagnosis and the detection of oesophageal carcinoma was 6.6 years (range 1–16 years).

The distribution of possible risk factors (Table 2) showed that more cases than controls had recently smoked (59% versus 39%). The relative risk of developing oesophageal cancer as a second primary tumour was 3.2 times greater for smokers (95% confidence interval 1.0–10.3; $P = 0.04$). Also alcohol consumption was more prevalent in the cases (48%) than in the controls (21%) and the relative risk for oesophageal carcinoma was 3.3 times greater for subjects who drank more than 3 units per day (95% confidence interval 1.3–8.4; $P = 0.01$). Since smokers were usually drinkers too, it was difficult to examine interaction between the two factors, in the sense of a synergistic effect on oesophageal cancer risk.

The oesophagus was located, at least partly, in the radiation field in 52% of the cases, similar to the 64% in the controls. The relative risk of developing oesophageal cancer following irradiation was not significantly increased (0.6, 95% confidence interval 0.2–1.5; $P = 0.24$). Stratified analysis by type of primary tumour was based on too small numbers to be additive, but a tendency towards an increased risk associated with irradiation was not found. For instance, in breast cancer the relative risk of developing oesophageal cancer following irradiation was 0.9 (range 0.2–4.1; $P = 0.86$); in lymphoma patients the relative risk was 1.1 (range 0.2–5.4; $P = 0.98$) and in lung cancer patients' exposure variation between cases and controls did not allow a separate calculation. In smokers, there was also no increased risk associated with radiotherapy (0.3; 95% confidence interval 0.2–2.5; $P = 0.27$), nor was there evidence of radiation-related risk in drinkers (0.3; 95% confidence interval 0.2–2.3; $P = 0.25$). Since a relationship with radiotherapy would be less likely for cases with a short interval between the two primary tumours, we excluded the lung cancer patients, most of whom were characterised by a short interval. The results were no different: the relative risk for oesophageal cancer was 2.4 (confidence interval 0.3–3.0) and was not significantly ($P = 0.98$) increased following irradiation. The relative risk of alcohol and smoking in this group without lung cancer patients remained increased: 2.4 (range 0.7–7.8; $P = 0.32$) and 1.9 (range 0.5–6.7; $P = 0.32$), respectively.

Only 19% of the cases and 34% of the controls had previously received chemotherapy. There was no significantly increased risk of developing oesophageal cancer, but numbers were too small to allow calculations. In addition, too few patients were exposed to other possible risk factors for oesophageal cancer (e.g. lye ingestion) to be able to study their effects in the statistical analysis.

DISCUSSION

Major advances in the treatment of several tumours over the past decade have resulted in increased cure rates and long-term survival. Several studies have reported an increased risk of developing a second malignancy. For instance, patients with testicular cancer who had undergone irradiation of the paraaortal lymph nodes have been found to have an increased risk of developing gastric cancer; this risk being particularly present with increasing length of follow-up [1]. Studies of patients treated for Hodgkin's disease have revealed a relationship between radiotherapy and the development of solid tumours of the lung, stomach and breast, as well as melanomas [2, 17–21]. These studies did not show a higher incidence of squamous cell carcinoma of the oesophagus following exposure to therapeutic irradiation, despite the fact that duration of follow-up was fairly long.

Earlier, we described the treatment results of radiation-associated oesophageal cancer in 16 cases [12]. Compared with the 37 patients described in the literature, this appeared to be a large group. Therefore, we performed the present study to determine the effect of previous treatment on the development of oesophageal cancer. Based on the relative low incidence of this secondary oesophageal tumour, we chose to perform a case–control analysis within the Tumour Registry of our cancer centre. Because cases and controls were matched for cancer type andfceveral other important, possibly confounding factors, the effect of these variables (e.g. age and sex) could not be studied

Table 1. Characteristics of cases with oesophageal carcinoma as a second tumour and their matched controls

Characteristics	Cases (n = 27) n	(%)	Controls (n = 70) n	(%)
Sex				
Male	11	41	26	37
Female	16	59	44	63
Primary tumour				
Hodgkin's disease	3	11	6	9
NHL	8	30	19	27
Breast cancer	8	30	24	34
Lung cancer	8	30	21	30
Age at diagnosis of primary tumour (yr)				
≤55	12	44	25	36
>55	15	56	45	64
Interval between primary tumour and oesophageal cancer (yr)				
≤ 6 yr				
NHL	1	8	2	9
Breast cancer	5	38	6	27
Lung cancer	7	54	14	64
>6 yr				
Hodgkin's disease	3	21	6	13
NHL	7	50	17	35
Breast cancer	3	21	18	38
Lung cancer	1	7	7	15
Treatment				
Radiotherapy	15	56	50	71
Chemotherapy	5	19	24	34
Surgery alone	7	26	—	—

NHL, non-Hodgkin's lymphoma.

Table 2. Distribution of possible risk factors among cases with oesophageal cancer as a second tumour and their matched cancer controls in a univariate analysis

	Cases n	(%)	Controls n	(%)	RR	95% CI	P-value
Smoking							
Yes	16	59	27	39	3.2	1.0–10.3	0.04
No	8	30	34	49			
Unknown	3	11	9	13			
Alcohol							
Yes	13	48	15	21	3.3	1.3–8.7	0.01
No	10	37	35	50			
Unknown	4	15	20	29			
Radiotherapy							
Including the oesophagus	14	52	45	64	0.6	0.2–1.5	0.24
Irradiation elsewhere or no irradiation	13	48	25	36			
Chemotherapy							
Yes	5	19	24	34	0.44	0.1–1.4	0.13
No	22	81	46	66			

RR, relative risk; CI, confidence interval; NS, not significant.

in the analysis. Within the group of cases, there was a predominance of males.

The risk of developing oesophageal cancer appeared not to be increased by radiotherapy. This unexpected negative finding may be related to a relatively short interval (6.6 years) compared with that of 10 years reported in the literature [12]. The relatively small numbers in our study did not allow stratification for the length of the interval. For this purpose, a large multicentre study would be needed. There was, however, a striking difference in the length of interval among the various primary tumours: following treatment for lung cancer the interval was relatively short (<6 years). Whether this is treatment-related or, more likely, due to a joint aetiological factor, such as smoking, remains speculative. However, exclusion of the lung cancer patients from the analysis still failed to reveal a significant increase in the risk of oesophageal cancer.

The present study confirmed the well-known increased risk of oesophageal cancer in relation to smoking and drinking [22–24]. Unexpectedly, this was less strong in case of previous exposure of the oesophagus to irradiation. A biological explanation is difficult to find. In general, high dose radiotherapy will lead to cell kill, whereas a submaximal dose might cause sublethal cell changes, which are thought to be related to dysplasia and tumour induction. In malignant lymphoma and breast cancer, the radiation dosage applied was usually submaximal (40 Gy in 4 weeks). In lung cancer, however, the total dose was often as high as 55–60 Gy in 5–6 weeks, which may possibly not increase the risk of oesophageal cancer. In addition, in this subgroup of patients, the mutual risk factor, smoking, is more often present, which may be responsible for an increased risk of oesophageal cancer. These opposite influences may explain why there is no overt increased risk following radiotherapy, even in the presence of smoking. Exposure to irradiation in the group of lung cancer patients might hypothetically have led to elimination of areas of dysplasia or carcinoma *in situ*, and in fact only led to delay of cancer development in the oesophagus. Whenever there is a second primary in the oesophagus following lung cancer, the interval is relatively short, probably due to joint aetiology.

The percentage of patients treated with chemotherapy was larger in the controls than in the cases. Because absolute numbers were small and no data had been collected on type of chemotherapy administered, this finding is inconclusive. Overall, the risk of oesophageal cancer was not increased.

In conclusion, smoking and drinking did increase the risk of developing oesophageal cancer as a second primary malignancy. Previous exposure of the oesophagus to irradiation does not appear to lead to a higher risk of oesophageal cancer in the first 10 years following radiotherapy. In order to examine whether radiotherapy definitely does not increase the long-term risk of oesophageal cancer, a multicentre analysis is needed using a sufficient number of patients who developed oesophageal cancer a long time after initial treatment.

1. van Leeuwen FE, Stiggelbout AM, van den Belt-Dusebout AW, *et al.* Second cancer risk following testicular cancer: a follow-up of 1,990 patients. *J Clin Oncol* 1993, **11**, 415–424.
2. van Leeuwen FE, Klokman WJ, Hagenbeek A, *et al.* Second cancer risk following Hodgkin's disease: a 20 year follow-up study. *J Clin Oncol* 1994, **12**, 312–325.
3. Sherill DJ, Grishkin BA, Galal FS, Zajtchuk R, Graeber GM. Radiation-associated malignancies of the oesophagus. *Cancer* 1984, **54**, 726–728.
4. Ogino T, Kato H, Tsukiyama I, *et al.* Radiation-associated carcinoma of the oesophagus. *Acta Oncol* 1992, **31**, 475–479.
5. Davidson NGP, Roy UK, Khanna S. Oesophageal carcinoma following internal mammary chain irradiation for carcinoma of the breast—a report of six cases. *Acta Oncol* 1990, **29**, 1059–1060.
6. Chudecki B. Radiation cancer of the thoracic oesophagus. *Br J Radiol* 1972, **45**, 303–304.
7. Vanagunas A, Jacob P, Olinger E. Radiation-induced oesophageal injury: a spectrum from oesophagitis to cancer. *Am J Gastroenterol* 1990, **7**, 808–812.
8. Goffman TE, McKeen EA, Curtis RE, Schein PhS. Oesophageal carcinoma following irradiation for breast cancer. *Cancer* 1983, **52**, 1808–1809.
9. Marchese MJ, Liskow A, Chang CH. Radiation therapy-associated cancer of the oesophagus. *N Y State J Med* 1986, **86**, 152–153.
10. O'Connell EW, Seaman WB, Ghahremani GG. Radiation-induced oesophageal carcinoma. *Gastrointest Radiol* 1984, **9**, 287–291.
11. Black WC, Ackerman W. Carcinoma of the large intestine as a late complication of pelvic radiotherapy. *Clin Radiol* 1965, **16**, 278–281.
12. Taal BG, Aleman BMP, Lebesque JV, Steinmetz R. The management of radiation-associated oesophageal carcinoma: a report of 16 cases. *Eur J Cancer* 1993, **29A**, 1114–1119.
13. Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. Chapter 7. Mortality, 1950–1978. Part I. Cancer mortality. *Radiat Res* 1982, **25**, 25–52.
14. Doll R. Radiation hazards: 25 years of collaborative research. *Br J Radiol* 1981, **54**, 179–186.
15. Gates O, Warren S. Radiation-induced experimental cancer of the oesophagus. *Am J Pathol* 1968, **53**, 667–679.
16. Statistics and Epidemiology Research Corporation: EGRET Statistical Software. Seattle, Washington, Serc Inc., 1990.
17. Henry-Amar M, Hayat M, Meerwoldt JH, *et al.* Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1155–1157.
18. Tucker MA, Coleman CN, Cox RS, *et al.* Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med* 1988, **318**, 76–83.
19. Boivin JF, O'Brien K. Solid cancer risk after treatment of Hodgkin's disease. *Cancer* 1988, **66**, 2541–2546.
20. Cimino G, Papa G, Tura S, *et al.* Second primary cancer following Hodgkin's disease: updated results of an Italian multicentric study. *J Clin Oncol* 1991, **9**, 432–437.
21. Kaldor JM, Day NE, Band P, *et al.* Second malignancies following testicular cancer, ovarian cancer and Hodgkin's disease: an international collaborative study among cancer registries. *Int J Cancer* 1987, **39**, 571–585.
22. Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the etiology of cancers of the digestive tract. *Int J Cancer* 1991, **49**, 381–386.
23. Jarebinski M, Adanja B, Vlajinac H, Pekmezovic T, Sipetic S. Evaluation of the association of cancer of the oesophagus, stomach and colon with habits of patients. *Vojnosanit Pregl* 1992, **49**, 19–24.
24. Kato I, Nomura AM, Stemmermann GN, Chyou PH. Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. *Cancer Causes Control* 1992, **3**, 145–151.