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Second Malignancies in Thyroid Cancer Patients: a Population-based Survey of 3658 Cases from Norway

Lars A. Akslen and Eystein Glattre

In a population-based survey of 3658 thyroid cancer patients diagnosed in Norway during 1955–85, a total of 200 cases of second malignancies were observed (30 414 person-years, mean follow-up 8.4 years). Male patients had a significantly increased incidence of urogenital cancer [standardised incidence ratio (SIR) = 1.96, 95% confidence interval (CI) 1.4–2.7], including cancer of the testis (SIR = 11.8, 95% CI 3.2–30.1) and urinary bladder (SIR = 3.0, 95% CI 1.5–5.2). The occurrence of malignant melanoma was also increased among males (SIR = 4.2, 95% CI 1.4–9.7). This apparent association with urogenital cancers among males at the present time cannot be explained, although increased surveillance as well as specific aetiological factors should be considered.
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INTRODUCTION

THE AETIOLOGY of thyroid cancer is not completely understood. However, some factors are thought to be of pathogenetic significance in humans, such as radiation exposure [1–3], dietary habits [4–6] and genetic determinants [7–8]. Hormonal influences may also be involved [5, 9, 10]. In the present study, primary malignant tumours developing subsequent to thyroid cancer were examined among 3658 patients reported to the Cancer Registry of Norway during 1955–1985, with special reference to the possibility of common aetiological factors.

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PATIENTS AND METHODS

Since 1953 the Cancer Registry of Norway has received information on almost all cancer patients in the entire population, based on clinical reports, histology and cytology reports, and autopsy records. A total of 3944 thyroid cancer patients were reported to the Registry during 1955–1985. Of these, cases not histologically verified and those diagnosed at autopsy or by death certificate alone were excluded (n = 286), giving a total of 3658 cases for further analyses. Sex, age at thyroid cancer diagnosis and time of diagnosis (month and year) were recorded, and the time between thyroid cancer and subsequent malignancies was calculated. Histological type of thyroid cancer according to the WHO classification [11] was included for patients reported during 1970–1985. Detailed information on treatment with radioactive iodine and external radiation as well as radiation treatment during childhood has not been available.

Second cancers diagnosed within 2 months after the thyroid

Table 1. Multiple cancers among 3658 patients with thyroid cancer reported in Norway 1955–1985

Tumour sequence	Females		Males	
	n	%	*n*	%
Thyroid cancer first	133	61.6	67	63.8
Other cancer first	66	30.5	23	21.9
Synchronous cancers*	17	7.9	15	14.3
Total	216	100.0	105	100.0
No. of patients	2737		921	

*Synchronous cancers occurring within 2 months after the diagnosis of thyroid cancer.

primary (n = 32) were regarded as synchronous tumours and excluded in the final analyses [12]. Calculation of expected numbers was based on the sex-, age- and calendar-specific incidence rates multiplied by the observed number of person-years at risk. A Poisson distribution was assumed valid for the observed numbers when presenting confidence intervals (95% CI) for the standardised incidence ratio (SIR) between observed and expected numbers. The end of the follow-up was determined by death, emigration or the end of the study period by 31 December 1987.

RESULTS

Table 1 shows that 321 cases of other malignant tumours were recorded amongst 3658 patients with thyroid cancer (8.8%), and 62.3% of these were subsequent malignancies. In the last group, 7 cases of third tumours were also included. No more cases of second cancers than expected occurred among females (Table 2). Among males, the incidence tended to be increased (SIR = 1.21; 95% CI 0.94–1.53, P = 0.07), especially among those below 35 years of age (SIR = 3.60, 95% CI 1.17–8.39) (Table 3). No significant associations to specific histological groups of thyroid cancer were found (not shown).

Second cancers of the larynx and pharynx tended to occur slightly more often than expected (SIR = 2.48; 95% CI 0.44–4.13, P = 0.08), but only 4 such cases were observed. No significant relationships to cancers in the gastrointestinal organs or lungs were found, in neither females nor males. Furthermore, there were no significant associations to subsequent cancers of the female breast and genital organs.

Subsequent cancers of the testis were few (n = 4), but they showed a highly significant SIR of 11.8 (95% CI 3.2–30.1). None of these cases were found at autopsy. The mean age of these patients was 37.3 years at the time of first diagnosis, with a mean time lapse of 91 months until the second cancer was diagnosed. Two cases of seminoma, one embryonal carcinoma and one poorly differentiated malignant tumour occurred. No significant relationship to specific histological types of thyroid cancer was present. Second cancers of the prostate tended to occur more often than expected (SIR = 1.40; 95% CI 0.81–2.23), although not statistically significant.

Table 2. Second malignancies among 3626 patients with thyroid cancer reported in Norway 1955–1985

	*n**	Person-years	Mean follow-up	O	SIR	95% CI
Females	2720	23957	8.8	133	0.94	0.79–1.11
Males	906	6457	7.1	67	1.21	0.94–1.53
Total	3626	30414	8.4	200	1.01	0.88–1.16

*Synchronous cancers were excluded (n = 32).
(O = observed, SIR = standardised incidence ratio, CI = confidence interval).

Table 3. Second malignancies among 3626 patients with thyroid cancer reported in Norway 1955–1985, specified for various age groups

Age at first diagnosis (years)	Females			Males		
	O	SIR	95% CI	O	SIR	95% CI
0–34	10	1.08	0.52–1.99	5	3.60	1.17–8.39
35–54	51	1.01	0.75–1.33	13	1.07	0.57–1.83
55–74	62	0.90	0.69–1.15	41	1.19	0.85–1.61
75+	10	0.76	0.36–1.40	8	1.10	0.47–2.14
Total	133	0.94	0.79–1.11	67	1.21	0.94–1.53

(O = observed, SIR = standardised incidence ratio, CI = confidence interval)

Regarding the urinary bladder, a strong association was found to be present among males (SIR = 2.99, 95% CI 1.55–5.23), with 10 secondary cancers occurring among patients diagnosed during the last part of the period (1970–1985) (SIR = 3.91, 95% CI 1.87–7.18). None of the 12 cases were diagnosed at autopsy, and the association did not depend on the histological type of thyroid cancer. All cases occurred in the two middle age groups (35–54 years and 55–74 years), giving an age-specific SIR of 4.74. The patients had a mean age of 62.6 years at the time of first diagnosis, and the average time lapse between the two cancers was 43 months. These patients were thus clearly older than those with subsequent development of testicular malignancies. In females, no significant relationship was observed. According to available clinical data, none of the male patients had received any kind of radiation treatment for the thyroid malignancy. In comparison, 2 of the 3 females were treated with external irradiation. The occurrence of kidney cancers was not significantly increased. In total, 36 cases of second malignancies occurred in the urogenital organs among males, compared with 18.4 expected cases (SIR = 1.96, 95% CI 1.4–2.7).

Among males, 5 cases of malignant melanoma occurred (SIR = 4.17, 95% CI 1.35–9.72). None of these cases were found at autopsy. The mean age at the time of thyroid cancer diagnosis was 44.6 years. Three nodular malignant melanomas and two of the superficial spreading type occurred with an average time lapse of 107 months, none of them being synchronous tumours.

Among females, 6 cases of second tumours in the central nervous system occurred (SIR = 1.75, 95% CI 0.64–3.81), with a mean time lapse of 65 months (two anaplastic astrocytomas, one glioma, two meningeomas, 1 case without histological diagnosis). However, this association was not statistically significant. No cases of second CNS tumours occurred among males (95% CI 0–3.42).

The occurrence of subsequent leukaemia, malignant lymphoma and myelomatosis was not significantly increased. 5 cases of leukaemia were observed (SIR = 1.19, 95% CI 0.39–2.78). 6 cases of malignant lymphoma were observed in females (SIR = 1.58, 95% CI 0.58–3.44), compared with only one case among male patients (SIR = 0.65, 95% CI 0.02–3.62). 5 cases of myelomatosis occurred (Table 4).

Table 4. Second malignancies among 3626 females and males with thyroid cancer reported in Norway 1955–1985, specified for major organ sites

	Females			Males			Total		
	O*	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
All sites	133	0.94	0.79–1.11	67	1.21	0.94–1.53	200	1.01	0.88–1.16
Lip	0			0					
Oral cavity	0			0					
Salivary glands	0			1					
Pharynx	1			2	5.71	0.69–20.64	3	4.00	0.82–11.69
Oesophagus	0			0					
Stomach	9	0.99	0.45–1.88	3	0.60	0.12–1.74	12	0.85	0.44–1.48
Small bowel	2	4.44	0.54–16.05	0			2	3.23	0.39–11.65
Large bowel	16	1.12	0.64–1.82	6	1.34	0.49–2.92	22	1.17	0.73–1.77
Rectum	4	0.60	0.16–1.53	2	0.66	0.08–2.38	6	0.62	0.23–1.35
Liver	0			1					
Gall bladder	1			0					
Pancreas	3	0.63	0.13–1.83	2	0.95	0.11–3.42	5	0.72	0.24–1.69
Larynx	1			0					
Lung	8	1.52	0.66–3.00	3	0.44	0.09–1.28	11	0.91	0.45–1.62
Breast	33	1.03	0.71–1.44	—					
Cervix uteri	4	0.54	0.15–1.39	—					
Corpus uteri	9	1.19	0.55–2.27	—					
Ovaries	9	1.03	0.47–1.95	—					
Prostate	—			17	1.40	0.81–2.23			
Testis	—			4	11.76	3.21–30.12			
Kidney	4	1.18	0.32–3.01	3	1.60	0.25–3.49	7	1.33	0.53–2.74
Urinary bladder	3	0.79	0.16–2.30	12	2.99	1.55–5.23	15	1.92	1.07–3.16
Malignant melanoma	3	0.62	0.13–1.81	5	4.17	1.35–9.72	8	1.32	0.57–2.61
Nervous system	6	1.75	0.64–3.81	0			6	1.33	0.49–2.90
Endocrine organs	0			0					
Bones	1			0					
Soft tissues	0			0					
Leukaemia	2	0.70	0.08–2.53	3	2.24	0.46–6.54	5	1.19	0.39–2.78
Lymphoma	6	1.58	0.58–3.44	1			7	1.31	0.53–2.70
Myelomatosis	4	1.77	0.48–4.53	1			5	1.53	0.50–3.58
No. of patients†	2720			906			3626		

*SIR and 95% CI are given where observed >1.
†Synchronous cancers were excluded (n = 32).
(O = observed, SIR = standardised incidence ratio, CI = confidence interval).

DISCUSSION

In the present series of thyroid cancer patients, about 5.5% developed a second malignancy during the follow-up. Although this occurrence of second cancers was not significantly increased in total, an association to certain tumour types was present among males. Other studies have indicated that some tumours may occur more often than expected in thyroid cancer patients [13–18], but the results so far have not been conclusive. In general, several factors may influence the frequency of multiple cancers. The diagnostic opportunities are considered to be important, and close surveillance of cancer patients probably increases the detection of other tumours [12, 19].

In our study, thyroid cancers not histologically verified as well as cases with synchronous tumours were excluded to avoid biased associations, for example due to the misinterpretation of thyroid metastases as primary tumours. The study has focused on cancers subsequent to the thyroid primary, as the opposite may be unreliable as a measure of specific associations. It is known that thyroid malignancies are frequently found among cancer patients [12, 19].

Second cancers in the testis occurred significantly more often than expected, on average 7.5 years after the diagnosis of thyroid cancer. The reason for this association is not clear. Common aetiological factors may be involved, such as some sort of hormonal dysfunction [20], but a carcinogenic influence of radioactive iodine should also be considered as possible and studied further [21].

In males, a significant association to second cancers of the urinary bladder was found, and these cases occurred on average almost 4 years after the thyroid primary. Increased occurrence of subsequent cancers in other urinary tract organs has been reported previously [16, 17, 22]. In addition, malignant tumours of the kidney, bladder, testis and prostate have also been found to be associated, [23–25], although no common aetiological factors are known. The carcinogenic influence of therapeutic iodine-131 has been suggested by others [26, 27], but in the present material, no radiation treatment had been given to any of the male patients, and the average time lapse from the first to the second cancer was only about 4 years.

Nitrosamines are suspected to have a carcinogenic effect on

bladder epithelium [28, 29], and they have been found to increase the incidence of experimental thyroid tumours as well [30, 31]. In addition, iodine should be mentioned as a possible aetiological factor [4, 27]. The importance of dietary habits may thus be suggested, for instance related to the consumption of fish products [5, 32, 33]. Interestingly, the incidence of bladder cancer was found to be increased in fishing communities (personal observation), and the same has been described for thyroid cancer [33]. However, other factors are probably necessary to explain the sex difference observed in this study, for example smoking habits and occupational hazards.

The occurrence of malignant melanoma among males with thyroid cancer was significantly increased. This was not due to the attention of synchronous tumours, as the cutaneous melanomas were detected on average 9 years after the thyroid primary. Common aetiological factors may be operating, although little is known. Both malignant melanoma and experimental thyroid tumours are thought to be promoted by androgen hormones [34–36]. A shared relationship to alcohol consumption has also been suggested [37].

Hormonal factors probably influence the development of thyroid cancer, as indicated by a marked female predominance [38] and the suggested relationship to reproductive factors [5, 9, 10]. However, no significant associations to cancer of hormonally affected organs such as the female breast, uterine body and ovaries were found in this study. An association to breast cancer has earlier been discussed [17, 39], but no significant relationship was found, in line with others [12, 22].

In summary, subsequent development of cancer in the testis and urinary bladder as well as of malignant melanoma was significantly increased among males. Close surveillance of cancer patients may be one explanation, but the findings must be further examined, especially with respect to the importance of aetiological factors.

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Dietary Factors in Lung Cancer Prognosis

Marc T. Goodman, Laurence N. Kolonel, Lynne R. Wilkens, Carl N. Yoshizawa, Loic Le Marchand and Jean H. Hankin

A hypothesis-generating analysis of the role of diet on survival was conducted among a sample of 463 men and 212 women with histologically-confirmed lung cancer. Interview information was obtained from two population-based case-control studies of lung cancer conducted on the Island of Oahu, Hawaii, between 1979 and 1985. The interview consisted of a quantitative dietary history to assess the usual intake of foods 1 year prior to diagnosis, a complete tobacco history, and other demographic and lifestyle information. Records from the Hawaii Tumor Registry were reviewed for data on stage, histology, and follow-up status of these patients. A food group analysis showed a significant reduction in the risk of death with increasing consumption of all vegetables combined among women (*P* for trend = 0.03), but not among men. The covariate-adjusted median survival times for women from the highest to the lowest quartiles of vegetable intake were 33, 21, 15, and 18 months, respectively. The results also suggested an association of fruit intake and survival among women (*P* for trend = 0.02), although a similar effect was not found among men. Increased consumption of certain foods, such as tomatoes and oranges among men, and broccoli and, perhaps, tomatoes among women, appeared to improve survival. This exploratory analysis provides mixed indications that certain components of vegetables and fruits may prolong survival in lung cancer patients.
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INTRODUCTION

A NUMBER of studies have suggested that dietary factors are important in the pathogenesis of human cancer, and that the carcinogenic process can be blocked both *in vitro* and *in vivo* by dietary supplementation [1]. Studies in human populations have shown that the dietary intake of micronutrients, such as vitamin A and beta-carotene, as well as the consumption of certain vegetables and fruits, reduce the risk of lung cancer [2]. Two recent studies of the effects of etretinate (a synthetic vitamin A derivative), folate, and vitamin B_{12}, on the regression of bronchial metaplasia among tobacco smokers, provide preliminary evidence that vitamin supplementation can reduce the risk for potentially premalignant lesions of the lung [3, 4]. However, the role of dietary intervention or vitamin supplementation to enhance the prognosis in lung cancer patients is largely unexplored. This is unfortunate, since factors that block tumour promotion may be similar to those that reduce cancer recurrence.

The current study is an outgrowth of several previous investigations of the influence of diet on the risk for lung cancer in Hawaii [5–7]. Two case-control studies showed a negative association between dietary vitamin A, beta-carotene [5, 7], and vegetable consumption [7], and the risk for this disease. The objective of the present analysis is to merge this interview data with information from a population-based cancer registry to examine the potential for certain dietary micronutrients, vegetables, and fruits to prolong survival in lung cancer patients. This exploratory analysis might generate hypotheses to be used in future clinical research of dietary intervention in lung cancer patients.

PATIENTS AND METHODS

Two case-control studies of risk factors for lung cancer incidence were conducted among residents of Oahu, Hawaii, between 1 September 1979 and 14 March 1983 [5] and between 1 March 1983 and 30 September 1985 [7]. These studies had similar designs and questionnaires, which made it possible to merge the data for this analysis. Patients with primary lung cancer were identified through the pathology logs and admission records in each of the seven major civilian hospitals on the island. Hawaii Tumor Registry data indicate that more than 84% of lung cancer cases on Oahu were admitted to one of these hospitals during the study period. Cases were restricted to

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