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Second Primary Neoplasms in Thyroid Cancer Patients

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To determine risk patterns for second primary neoplasms after the occurrence of thyroid cancer, we conducted a retrospective cohort study of 3321 thyroid cancer patients who were operated and histologically confirmed at the Noguchi Thyroid Clinic and Hospital Foundation between 1946 and 1985. They were followed from the date of operation through the end of 1990 with an observation period from 45 to 5 years. The average observation period of the patients was 13.4 years and the follow-up rate reached 98%. The standardized mortality ratio (SMR) was computed to assess possible risk increase by cancer site. In this computation, the time period less than 5 years after operation was omitted to reduce the influence of deaths related to the original thyroid cancer. A total of 103 deaths from malignant neoplasms other than thyroid cancer were observed during this time period (SMR = 1.6, 95% confidence interval [CI] = 1.3–2.0). Analyses of site-specific cancer mortality revealed significantly elevated risks for the central nervous system (SMR = 16.1, CI = 5.2–37.6) and respiratory organs (SMR = 2.6, CI = 1.5–4.1). Based on a review of available medical records with histological findings, we concluded that the risk increases for these sites were most likely to be attributable to second primary neoplasms. Whether or not the patients had received radiotherapy was not significantly associated with elevated risk. Further investigations are needed to clarify the risk factors responsible for the above findings.

Key words: Second primary neoplasm — Thyroid cancer — Follow-up study — Mortality — Epidemiology

Studies on multiple primary neoplasms provide a clue to the understanding of common etiological factors for cancers at different sites. In this connection, a number of investigations have shown that patients with cancers of specific organs tend subsequently to develop other primary neoplasms (e.g., first primary to second primary; lung–larynx, breast–endometrium, Hodgkin's disease–leukemia).[1–14] Such associations have been linked to the presence of common risk factors that could be either environmental (e.g., smoking, alcohol) or intrinsic (e.g., hormonal dysfunction, genetic predispositions) or to possible adverse effects of treatments for initial cancer (e.g., radiotherapy, chemotherapy).

The etiology of thyroid cancer has not been well understood. The only established cause is ionizing radiation,[15,16] which does not appear to play a major role among general populations. Other factors suspected include previous thyroid disorders,[17,18] hormones,[19–24] diet[25–28] and hereditary factors,[29,30] none of which has been supported by conclusive evidence. In this respect, specific patterns of second primary neoplasms following thyroid cancer are of great interest, since such patterns may suggest underlying common or opposite risk factors. Since thyroid cancer patients have a good prognosis,[31–33] investigators can expect them to develop a considerable number of other primary cancers, which would practically make it easier to clarify the above patterns. Besides, development of second primaries is important for clinicians, who are naturally concerned with the prognosis of thyroid cancer patients.

As is well known, thyroid cancer is uncommon, and long-term follow-up studies on the occurrence of second primary cancers of the thyroid cancer patients are very limited. Elevated risks for the breast, nervous system, urogenital organs and leukemia have been reported.[1,2,5,34–41] However, the results are not conclusive, and further investigations are required. This paper describes a long-term follow-up study of over 3000 patients histologically diagnosed as having thyroid cancer.

SUBJECTS AND METHODS

The study subjects comprised 3321 patients with thyroid cancer who were surgically operated and histologically confirmed between January 1, 1946 and December 31, 1985 at the Noguchi Thyroid Clinic and Hospital Foundation (designated as the Noguchi Hospital), which is located in the north of Kyushu Island, and is one of the largest hospitals for thyroid disorders in Japan. Patients who had been diagnosed with other malignant neoplasms prior to the initial operation were excluded from this study. Information on the permanent registered address

("koseki" in Japanese), which is necessary to determine the vital status and causes of deaths of the patients (see below), as well as dates of birth and surgical operation, histological classification of the thyroid cancers resected and additional treatments before and after operation (radiation and/or use of antineoplastic agents) was extracted from the medical records at the hospital.

The subjects were followed from the date of operation through the date of death or December 31, 1990, whichever occurred first. The patients were urged to have follow-up examinations at the Noguchi Hospital. They also received annual follow-up mailings to assess their vital status and health condition and, if deceased, relevant medical information was sought from the family and attending physicians. The remaining small portion of untraced subjects was checked against the permanent registered address. Copies of death certificates of all deaths were sought through the Bureau of Legal Affairs and underlying causes of death were determined. This was necessary to maintain comparability between observed and expected numbers of deaths, which were computed from the national mortality statistics. The average observation period for the subjects was 13.4 years, with only 62 lost to follow-up. Thus, we determined the vital status for 98% of the subjects, and the cause of death for all the deceased as well. The underlying cause of death on each death certificate was coded according to the 9th revision of International Classification of Disease, Injuries and Causes of Deaths (ICD-9). To enable practical analyses, broader categories for causes of deaths were created as follows (ICD-9 in parentheses): all causes (001–999, E800–E999); malignant neoplasms by site: all sites (140–208), oral cavity (140–149), esophagus (150), stomach (151), small bowel (152), large bowel and rectum (153–154), liver and gall bladder (155–156), pancreas (157), larynx (161), respiratory organs (162), bone (170), breast (174–175), uterus (179–182), ovary (183.0), myelo and lympho-proliferative neoplasm (200–208), thyroid (193), kidney (189), urinary bladder (188), central nervous system (191–192); cerebrovascular diseases (430–438); and heart diseases (393–398, 410–429).

The standardized mortality ratio (SMR) by cause was estimated by dividing the observed number of deaths (Obs) by the expected number of deaths derived by multiplying age (5-year group)-, sex-, calender year (5-year interval)- and cause-specific mortality rates for Japan[42] by the corresponding person-years at risk. To reduce the bias caused by inclusion of metastatic thyroid cancers which were possibly misdiagnosed as second primary cancers, the SMR was estimated for the time period five or more years after operation by excluding both the observed and expected numbers of deaths within 5 years after operation. The statistical significance and confidence intervals (CIs) of the SMR were computed assuming that the observed number of deaths follows the Poisson distribution. In addition, we assessed a possible effect of radiotherapy on site-specific cancer mortality by modeling the data through the Cox proportional hazard regression.[43] In the model, the occurrence of death due to a specific cause of interest was included as a dependent variable, an indicator for the presence or absence of radiotherapy as a main exposure variable, and a continuous variable for age and a dichotomous variable for sex as covariates. The adjusted rate ratios and their 95% CIs were obtained through the model by using the PHGLM procedure of the SAS statistical software package.[44]

RESULTS

The sex and age distributions of the study subjects at the time of operation are shown in Table I. Females accounted for 89% of the subjects. The age at operation ranged widely from 6 to 88 years, with an average of 44.3 years. The histological types of thyroid cancer were classified into six categories: papillary adenocarcinoma (2774, 83.5%), follicular adenocarcinoma (355, 10.7%), anaplastic carcinoma (50, 1.5%), medullary carcinoma (38, 1.1%), complication of papillary and follicular adenocarcinoma (9, 0.3%), and other types (95, 2.9%). Thus, a great majority of the subjects had papillary adenocarcinoma. Radiation treatment was prescribed to 2820 patients (84.9%), while only the patients with anaplastic carcinoma underwent chemotherapy. At the closing date of the study, 2677 were alive, 582 were dead, and 62 were lost to follow-up. The total observation period after elimination of the time period within 5 years after operation was 28,456 person-years. Two hundred and thirty-five patients, including all cases of anaplastic carcinoma, had died within 5 years after operation, and these cases were excluded from the analysis as described above.

Table I. Distribution of Study Subjects by Sex and Age at Operation

Age group (years)	Male	Female	Both sexes (%)
0–9	1	1	2 (0.1)
10–19	9	73	82 (2.5)
20–29	46	427	473 (14.2)
30–39	88	672	760 (22.9)
40–49	77	765	842 (25.4)
50–59	66	601	667 (20.1)
60–69	59	313	372 (11.2)
70–79	19	94	113 (3.4)
80+	5	5	10 (0.3)
Total	370	2951	3321 (100.0)

Table II. Observed Number of Deaths (Obs) and Standardized Mortality Ratio (SMR) with 95% Confidence Interval (95% CI) for Major Causes of Deaths

Cause of death	Male			Female			Total		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	55	1.7	1.2–2.1	292	1.4	1.3–1.6	347	1.5	1.3–1.6
Cerebrovascular diseases	4	0.7	0.2–1.7	39	1.2	0.8–1.6	43	1.1	0.8–1.5
Heart diseases	4	0.7	0.2–1.8	36	1.0	0.7–1.4	40	1.0	0.7–1.3
Malignant neoplasms	35	3.6	2.5–5.0	168	3.1	2.7–3.6	203	3.2	2.8–3.7
Malignant neoplasms except thyroid cancer	13	1.3	0.7–2.3	90	1.7	1.4–2.1	103	1.6	1.3–2.0

Table III. Observed Number of Deaths (Obs) and Standardized Mortality Ratio (SMR) with 95% Confidence Interval (95% CI) according to Cancer Site

Cancer site	Male			Female			Total		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All sites	35	3.6	2.5–5.0	168	3.1	2.7–3.6	203	3.2	2.8–3.7
Digestive tract	2	0.5	0.1–1.6	27	1.3	0.8–1.8	29	1.1	0.8–1.6
Oral cavity	0	0.0	0.0–28.0	1	2.3	0.1–12.6	1	1.7	0.0–9.7
Esophagus	0	0.0	0.0–6.9	2	2.3	0.3–8.4	2	1.4	0.2–5.2
Stomach	1	0.4	0.0–2.0	19	1.4	0.8–2.1	20	1.2	0.7–1.8
Small bowel	0	0.0	0.0–187.3	0	0.0	0.0–31.6	0	0.0	0.0–27.1
Large bowel	1	1.2	0.0–6.4	5	0.8	0.3–1.9	6	0.9	0.3–1.9
Liver and gall bladder	2	1.3	0.2–4.7	9	1.2	0.6–2.3	11	1.2	0.6–2.2
Pancreas	1	1.9	0.0–10.8	4	1.3	0.4–3.3	5	1.4	0.4–3.2
Larynx	0	0.0	0.0–52.4	2	25.3	3.1–91.4	2	13.4	1.6–48.3
Respiratory organs	3	1.7	0.3–4.9	15	2.9	1.6–4.8	18	2.6	1.5–4.1
Bone	0	0.0	0.0–158.1	2	13.2	1.6–47.6	2	11.4	1.4–41.2
Breast	0	0.0	0.0–1146.0	5	1.4	0.4–3.2	5	1.3	0.4–3.1
Uterus				4	0.9	0.3–2.4	4	0.9	0.3–2.4
Ovary				0	0.0	0.0–1.9	0	0.0	0.0–1.9
MLN	1	2.0	0.1–11.4	4	1.4	0.4–3.5	5	1.5	0.5–3.4
Thyroid	22	950.6	595.7–1439.2	78	199.7	157.8–249.2	100	241.7	196.6–294.0
Kidney	0	0.0	0.0–29.0	1	2.0	0.1–11.3	1	1.6	0.0–9.0
Urinary bladder	0	0.0	0.0–24.9	1	1.9	0.0–10.5	1	1.5	0.0–8.2
CNS	1	26.0	0.7–144.7	4	14.7	4.0–37.7	5	16.1	5.2–37.6

MLN, myelo- and lympho-proliferative neoplasm; CNS, central nervous system.

The observed numbers of deaths and the SMRs according to major causes are shown in Table II. As expected, there was no risk excess for cerebrovascular diseases (SMR=1.1) or heart diseases (SMR=1.0). The SMR for malignant neoplasms other than thyroid cancer was significantly elevated in females (SMR=1.7, CI=1.4–2.1), while such a risk increase was unclear in males (SMR=1.3, CI=0.7–2.3). Almost all of the excess deaths in this cohort were due to higher mortality from malignant neoplasms.

Table III presents the observed numbers of deaths and the SMRs according to cancer site. Significantly elevated risks were observed for the larynx (SMR=13.4, CI=1.6–48.3), respiratory organs (SMR=2.6, CI=1.5–4.1), bone (SMR=11.4, CI=1.4–41.2), and central nervous system (SMR=16.1, CI=5.2–37.6) as well as for the

Table IV. Observed Number of Deaths (Obs) and Standardized Mortality Ratio (SMR) with 95% Confidence Interval (95% CI) according to Cancer Site and Years after Operation

		Years after operation			
		5–9	10–14	15–19	20+
All sites except thyroid	Obs	40	27	21	15
	SMR	1.7	1.6	1.9	1.2
	95% CI	1.2–2.3	1.1–2.3	1.2–2.9	0.7–2.0
Respiratory organs	Obs	5	3	4	6
	SMR	2.1	1.7	3.2	4.2
	95% CI	0.7–4.8	0.3–4.9	0.9–8.3	1.5–9.1
Central nervous system	Obs	2	1	2	0
	SMR	17.2	12.1	37.5	0.0
	95% CI	2.1–62.1	0.3–67.4	4.5–135.6	0.0–64.0

Table V. Adjusted Rate Ratio with 95% Confidence Interval (95% CI) for Mortality from Selected Cancers in Relation to Radiation Therapy among Patients with Papillary Adenocarcinoma of Thyroid

Cancer site	Radiation	Number of subjects	Number of deaths	Rate ratio[a)]	95% CI
All sites except thyroid	No	355	9	1.0	
	Yes	2307	78	1.02	0.72–1.46
Respiratory organs	No	355	1	1.0	
	Yes	2307	16	1.47	0.52–4.18
Central nervous system	No	355	1	1.0	
	Yes	2307	4	0.68	0.22–2.10

a) Adjusted for sex and age at operation.

thyroid (SMR=241.7, CI=196.6–294.0). The risk for myelo- and lympho-proliferative neoplasms was slightly elevated (SMR=1.5, CI=0.5–3.4), although the increase was not significant. No increased risks were evident for the breast and urogenital organs.

The above risk increase for thyroid cancer suggested a possible contamination of deaths related to the original thyroid cancer even after exclusion of the deaths within 5 years after operation. Therefore, it was necessary to examine whether observed risk increases for the above sites (larynx, respiratory organs, bone and central nervous system) were truly due to second primary neoplasms. Thus, we tried to review all medical records of the patients who had died of these cancers. Histological findings were available for 6 (4 adenocarcinomas and 2 small cell carcinomas at lung) of 18 deaths from cancer of the respiratory organs and 2 (one meningioma and one astrocytoma in the brain) of 5 deaths from cancer of the central nervous system. As shown, we found no histological evidence of metastatic thyroid cancer for those cases available for histological confirmation. Medical records of 2 deaths from laryngeal cancer and 2 deaths from bone cancer revealed local invasion and/or metastasis from the original thyroid cancer at the time of operation.

The risk patterns for cancer of the respiratory organs and central nervous system as well as that of all sites except thyroid were evaluated according to the time since operation (Table IV). The risk for malignant neoplasms other than thyroid was significantly elevated for as long as 20 years after operation. More specifically, however, the increased risk for the respiratory organs persisted longer than 20 years after operation (SMR=4.2, CI=1.5–9.1), whereas the elevated risk for the central nervous system was observed within 20 years after operation (SMRs: 17.2, 12.1 and 37.5 for 5–9 years, 10–14 years, and 15–19 years, respectively).

Table V shows the rate ratios associating radiation therapy with mortality from cancer of the specific sites described above. To eliminate a possible confounding effect of histological type of the original thyroid cancer, only the patients with papillary adenocarcinoma, who accounted for 83.5% of the total subjects, were included in the analysis, while sex and age at operation were adjusted for through the proportional hazard model. The

patients who were lost to follow-up or died within 5 years after operation were excluded from the analysis. Radiation treatment was not significantly associated with increased risk for any category of the cancer sites.

DISCUSSION

This study had the following advantages in assessing the risk patterns for second primary neoplasms in thyroid cancer patients. Firstly, the study population is very large, and this would increase the statistical power to detect possible associations with relatively rare malignant neoplasms such as cancer of the central nervous system. In fact, the sample size of this study exceeds that of most previous epidemiologic studies of thyroid cancer,[34, 35, 38–41] and is comparable to that of two recent follow-up studies in Norway and Sweden.[36, 37] Secondly, we followed the study subjects for a very long time, and thus we could evaluate the long-term risk changes extending for more than 20 years after operation. The observation period of this study is longer than that of any other previous study. Thirdly, this cohort study has an excellent follow-up rate (98%), which reduced possible bias arising from loss to follow-up. The vital status of the study subjects was precisely determined by utilizing the "koseki" registration system in Japan. As regards the reliability of the causes of deaths, we should consider the accuracy of the underlying causes of death on death certificates. Several previous studies assessing agreement between the underlying causes of death on death certificates and autopsy diagnosis among the general population revealed that confirmation and detection rates of death certificates in Japan reached more than 90% and more than 75%, respectively, for malignant neoplasms.[45–47]

On the other hand, the major limitation of this study lies in the point that we could not completely eliminate possible contamination of cancer deaths related to the original thyroid cancer, although we tried to reduce this contamination by excluding deaths during the initial 5 years after operation. The notable risk excess for thyroid cancer, persisting longer than 5 years after operation, was probably attributable to the recurrence of the original thyroid cancer rather than to the occurrence of second primary thyroid cancer.[31] After reviewing medical records, we consider that excess risks for cancer of the larynx and bone (4 cases) were probably due to local invasions or metastases from the original thyroid cancer. Another limitation is that our study is based on mortality data. It appears inappropriate to draw conclusions as regards second primary neoplasms with a favorable prognosis such as breast and urogenital cancers, for which previous follow-up studies detected elevated risks based on incidence data.[2, 36, 37, 39–41]

This study has shown that the overall risk for malignant neoplasms other than thyroid cancer is significantly elevated in female subjects (SMR = 1.7). Since the number of male subjects is quite small, the risk increase (SMR = 1.3) for males may not have attained statistical significance owing to chance fluctuation. Furthermore, the risk increase for both sexes combined lasted up to 20 years after operation. The possible explanations for this long effect include: 1) second primary neoplasms occurred in the thyroid cancer patients more frequently than expected from the rates for all Japan; 2) late recurrence of the original thyroid cancer caused metastases and/or local invasions, which were misdiagnosed as primary neoplasms. As stated earlier, we believe that both factors contributed to the noted excess mortality, but we could not make a precise assessment as to the extent of the influence of each factor.

One of the most important findings in this study is that the risk for cancer of the central nervous system was significantly elevated; 2 out of 5 deaths from this cancer were definitely due to second primary neoplasms. Even if only these two deaths are taken into account in calculating the SMR, the risk is still elevated (SMR = 6.5, 95% CI = 0.8–23.3). This finding is consistent with the results from previous studies. A Swedish cohort study reported a significant risk increase for this cancer (standardized incidence ratio [SIR] = 2.86).[37] A similar risk increase was found for female patients in a Norwegian study (SIR = 1.75), although it was not statistically significant.[36] Studies in Iceland also reported a significant risk excess of brain cancer in patients with papillary adenocarcinoma of the thyroid (SIR = 4.0).[41]

Several factors possibly contributory to the risk excess for the central nervous system should be considered. Adverse effects of treatments for initial thyroid cancer, including chemotherapy and radiotherapy, both of which are known to have carcinogenic properties, cannot account for this, since all subjects who received chemotherapy were excluded from the analysis initially, and radiotherapy was not associated with increased risk. Other possible candidates include hormonal factors that may influence the development of both thyroid cancer and cancer of the central nervous system. Several studies pointed out an association between reproductive events and thyroid cancer,[20–24] while a few studies reported that increasing parity decreased the risk of brain cancer.[48, 49] Genetic predisposition may also affect susceptibility to these cancers. It is reported that congenital immunodeficiencies may be related to the development of multiple primary neoplasms including primary central nervous system lymphoma and thyroid cancer.[50, 51]

In this study, we found a significantly elevated risk for cancer of the respiratory organs, which persisted longer than 20 years after operation. This finding has not been

noted in previous studies.[34–41] Although we do not have information on smoking habits, there is no reason to consider that the prevalence of smokers in our study population much exceeds that in the general population of Japan. Furthermore, none of the 6 patients who died of lung cancer and for whom histological findings were available had squamous cell carcinoma, which is strongly associated with tobacco smoking. Radiation exposure was strictly limited to the neck at the hospital, and this exposure was not significantly associated with increased risk, as shown in Table V. Thus, unidentified risk factors other than smoking and radiation appear to play a role in the above finding. However, some uncertainty still exists in our results because of the limitation of this study as mentioned before. Metastatic lung cancers might possibly develop more than five years after initial operations. We could confirm only one-third of the deaths from cancer of the respiratory organs histologically, although there is no *a-priori* reason to suppose that availability of medical records is related to second primary or metastatic lung cancers. Further epidemiologic studies are needed to confirm our results.

In summary, our results suggest a high susceptibility of thyroid cancer patients to the development of second primary neoplasms, in particular, cancer of the central nervous system and lung cancer. Because of the several limitations and unavailability of information on possible etiologic factors, including hormonal measurements and genetic predispositions, in this study, further investigations are required to elucidate the risk factors responsible for our findings.

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