ORIGINAL CONTRIBUTION

Risk Factors of Thyroid Cancer among Women in Tokai, Japan

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To analyze the risk factors of thyroid cancer among Japanese women who generally consume much more iodine than Europeans, we conducted a hospital-based case-referent study at Aichi Cancer Center Hospital (ACCH) in Nagoya, Japan. Ninety-four female patients aged between 20-79 years with papillary or follicular carcinoma of the thyroid, and 22,666 female outpatients without cancer were used. Past history of benign thyroid mass or goiter (odds ratio: OR=13.9) and hyperthyroidism (OR=5.0) showed increased ORs of thyroid cancer. Thyroid cancer cases consumed coffee less frequently (OR=0.5) and had had more experience of delivery than referents (≥3 times; OR=2.5). Western style breakfast (OR=0.5) also decreased the OR. For the multivariate analysis, past history of thyroid diseases (OR=4.3) was positively associated with the risk of thyroid cancer and everyday coffee consumption (OR=0.6) tended to decrease the risk. These results suggest that thyroid hormone-related factors may be involved in the risk of thyroid cancer in Japan, too. To clarify the risk involved in Japanese food, another comparative study including detailed information on iodine intake between countries and individuals is required.

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Thyroid cancer is more common in women than in men1,2, and reproductive factors have been found to be associated with increased risk of thyroid cancer3-6. A history of thyroid disease, especially goiter, has been shown to be involved in an increased risk of thyroid cancer, and thyroid stimulating hormone (TSH) has been suggested to be related to this factor7,9-11. Dietary factor seems to be different between iodine-deficient regions and iodine-rich regions. Iodine-rich food seems to decrease the risk of thyroid cancer in iodine-deficient inland regions9,10, and to increase the risk in iodine-rich coast regions6. Ionizing radiation has also been found to increase the risk of thyroid cancer5,8.

In Japan, the incidence rate of thyroid cancer is not high, and not much different from those of many European countries5. However, histological variation of thyroid cancer is apparently different between European countries and Japan2,12-15. The proportional distribution of the histological types depends on the daily iodine intake13. Papillary carcinoma is proportionally more common in iodine-rich regions including Japan5,14, and contrariwise, the rate of follicular and anaplastic carcinoma increases in iodine-deficient regions such as Switzerland12. It is interesting to compare the risk factors of thyroid cancer between iodine-deficient European countries and iodine-rich Japan, but few studies have been conducted in Japan other than of atomic bomb survivors15 and of irradiated young people16. The present study is a hospital-based case-referent study of thyroid cancer to investigate the risk factors of thyroid cancer among Japanese women in general.

SUBJECTS AND METHODS

Since 1988, a self-administered questionnaire has been completed by first-visit outpatients at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan to get information on lifestyle and disease history before the onset of the current symptoms. Questionnaire details and data collection procedures are described elsewhere17-18. In brief, all first-visit outpatients are asked to complete a questionnaire before diagnosis. An expert

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Interviewer checks all written responses at the time of collection. Included, are questions on demographic information, past history, family history, smoking, alcohol consumption, general health, reproduction, and beverage and food intake.

Between 1988 and 1993, 43,759 (91.4%) of all first-visit outpatients (n=47,895) responded to the questionnaire. The remaining respondents were excluded because of: absence of the interviewer (n=1,568, 3.3%); being aged under 18 years old (n=530, 1.1%); inability to collect the questionnaire (n=460, 1.1%); refusal to participate (n=17, 0.04%); various other reasons (n=1,561, 3.3%). Among them, 6,143 (14.0%) were diagnosed as having cancer and registered with the hospital cancer-registry system of ACCH; malignant neoplasms were ruled out in the remaining 37,616 (86.0%) outpatients.

From 1988 to 1993, 27 men and 99 women were histologically diagnosed as having thyroid cancer. Among them, 27 men, one woman over 80 years old, and four women with medullary or anaplastic carcinoma were excluded from the cases, because the number of male patients is small and the biological characteristics of these two carcinomas are different from those of papillary or follicular carcinoma. Papillary/follicular carcinoma of the thyroid was included in papillary carcinoma.

The reference group in the present study comprises women outpatients aged 20-79 years, confirmed to be cancer-free by diagnostic procedure at ACCH. As the Japanese medical system for outpatients is quite different from that of other countries, and most Japanese hospitals, including ACCH, permit outpatients to visit outpatient-departments without doctor’s referrals, we collected much information on non-cancer respondents from ACCH outpatients. The actual number of outpatients with doctor’s referrals was 4,476, being 11.9% of all non-cancer outpatients. To assess the proportional distribution of clinical diagnosis among non-cancer outpatients, we randomly sampled 10 percent of those outpatients (n=2,997) between 1988 and 1992 and confirmed their final diagnosis by medical records. Forty-four percent were found to have no abnormal findings by examination; 13 percent had benign tumors or non-neoplastic polyps; and the other 35 percent were confirmed to have benign and nonspecific diseases. Furthermore, 467 women who had had a past history of cancer were excluded from the referents. According to these procedures, information on eligibility from questionnaires was available in 94 cases and 26,666 referents.

The proportional distribution of places where cases and referents were living was 94.7% and 97.7% in the Tokai area (Aichi, Gifu and Mie prefectures), and 31.9% and 41.7% in Nagoya city, respectively.

Respondents were asked to answer the question on their past disease history and family disease history of first and second degrees of their relatives. As the question on past history did not include the age at which the first lesions were detected, the medical records were reviewed to confirm the age of the onset of benign thyroid mass or goiter. The information on benign thyroid mass or goiter was accepted if the complaints had been made more than 10 years before the diagnosis of thyroid cancer, because it is difficult to distinguish benign lesions from thyroid cancer which usually grows slowly.

Dietary items were divided into four or five groups according to respondent intake frequency. To look for a dose-response relationship, the intake frequency of selected food items was divided into tercile subgroups comprising approximately one third of referents (low, medium and high). As the Japanese have two types of breakfast (Japanese type: rice and miso soup, Western type: bread and coffee), we asked respondents what kind of breakfast they used to consume before symptom onset: 1)rice, 2)rice or bread (mixed), 3)bread, 4)others. The intake frequency of Western type breakfast was divided as follows: low: rice, medium: mixed, high: bread. To clarify the cross association on intake frequency between breakfast type and some dietary items (coffee, milk, and miso soup), Mantel-Haenszel Chi-square test was used for referents.

For data analysis, odds ratio (OR) and 95% confidence interval (CI) of all items for cases and referents were calculated using unconditional logistic regression models, adjusted by age and year of visit (continuous). The P value for trend corresponded to the estimate of the slope derived from the logistic model. To control the effect of confounding factors, multivariate logistic regression models, adjusted by age and year of visit, were used for analysis among the items which showed statistically significant OR by unconditional logistic regression models. Procedure LOGISTIC from SAS was used for calculation.

RESULTS

Age distribution among both cases and referents showed very similar trends and both peaks clustered between the ages of 40-49 years. No case had a medical occupational history. Of histological types, most cases were classified as papillary carcinoma (97%), follicular carcinoma being very rare (3%) (Table 1). Table 2 shows the comparison of women with thyroid cancer to referents by past history of thyroid disease and family history of cancer. History of benign thyroid mass or goiter suffered more than 10 years before thyroid cancer diagnosis (OR=13.9), and history of hyperthyroidism (OR=5.0) revealed higher ORs of thyroid cancer. Cases and referents were not different in family history of cancer. One case and 60 referents had family history of thyroid cancer, but the difference was not statistically significant.

The ORs did not increase with smoking (current or ex-), nor habitual drinking. Frequent coffee consumption was associated with decreased OR for thyroid cancer by the test for gradient (p=0.037) (Table 3).
Table 1. Distribution of women thyroid cancer cases and women non-cancer-referents according to age, occupation and histological type, Aichi Cancer Center Hospital (ACCH), 1988-1993.

| Age          | Cases | (%) | Referents | No. | (%) |
|--------------|-------|-----|-----------|-----|-----|
| 20-29        | 7     | (7) | 2,545     |     | (10)|
| 30-39        | 14    | (15)| 5,226     |     | (20)|
| 40-49        | 36    | (38)| 9,599     |     | (36)|
| 50-59        | 19    | (20)| 5,594     |     | (21)|
| 60-69        | 15    | (16)| 2,858     |     | (11)|
| 70-79        | 3     | (3) | 844       |     | (3) |
| Total        | 94    | (100)| 26,666   |     | (100)|

| Occupational history | Cases | (%) | Referents | No. | (%) |
|----------------------|-------|-----|-----------|-----|-----|
| Office worker        | 20    | (21)| 4,291     |     | (16)|
| Medical staff        | 0     | (0) | 1,009     |     | (4) |
| Homemaker            | 32    | (34)| 9,265     |     | (35)|
| Others               | 42    | (45)| 12,101    |     | (45)|

| Histological type | Cases | (%) | Referents | No. | (%) |
|-------------------|-------|-----|-----------|-----|-----|
| Papillary         | 91    | (97)| -         |     |     |
| Follicular        | 3     | (3) | -         |     |     |

Table 2. Comparison of women with thyroid cancer to referents by past history of thyroid disease and family history of cancer.

|                         | Cases/referents | OR \(^a\) | 95% CI \(^b\) |
|-------------------------|-----------------|-----------|--------------|
|                         | No   | Yes   | No   | Yes   |
| Thyroid benign mass or goiter\(^c\) | 87/26297\(^d\) | 4/86   | 1.0  | 13.9 | 5.0-38.7 |
| Hyperthyroidism         | 87/26297\(^d\) | 2/123   | 1.0  | 5.0  | 1.2-20.6 |
| Family history\(^e\) of cancer | 64/17933 | 30/8733 | 1.0  | 0.9  | 0.6-1.4 |
| Family history\(^e\) of thyroid cancer | 93/26606 | 1/60   | 1.0  | 4.8  | 0.7-35.4 |

|                         | OR\(^a\) | 95% CI\(^b\) |
|-------------------------|-----------|--------------|
| Smoking                 |           |              |
| Never                   | 1.0       | 0.3-1.2      |
| Current or ex-alcohol consumption | 0.6    |              |
| Sometimes or less       | 1.0       |              |
| ≥4 times/week           | 0.7       | 0.3-1.5      |
| Coffee consumption      |           |              |
| Less sometimes          | 1.0       |              |
| Sometimes               | 0.9       | 0.5-1.9      |
| Everyday                | 0.5       | 0.3-1.0      |
| Test for gradient       | p=0.037   |              |

\(^a\) Odds ratio adjusted by age and year of visit.  
\(^b\) Confidence interval.  
\(^c\) >10 years before the diagnosis of thyroid cancer.  
\(^d\) Among first or second degree of relatives.  
\(^e\) No past history of thyroid diseases.

Table 3. Comparison of women with thyroid cancer to referents by factors of smoking, alcohol consumption, and coffee consumption.

| Smoking                  | Cases/referents | OR\(^a\) | 95% CI\(^b\) |
|--------------------------|-----------------|-----------|--------------|
| Never                    | 84/22303        | 1.0       |              |
| Current or ex-alcohol consumption | 10/4337 | 0.6    | 0.3-1.2      |
| Sometimes or less        | 73/18990        | 1.0       |              |
| ≥4 times/week            | 6/2485          | 0.7       | 0.3-1.5      |

Coffee consumption

| Less sometimes          |               | 1.0       |              |
| Sometimes               | 14/3095        | 0.9       | 0.5-1.9      |
| Everyday                | 22/9151        | 0.5       | 0.3-1.0      |

Test for gradient p=0.037

\(^a\) Odds ratio adjusted by age and year of visit.  
\(^b\) Confidence interval.
In Table 4, cases and referents were compared by reproductive factors. Cases had more experience of delivery (≥3 times; OR=2.5) than referents, but trend test for number of delivery was not statistically significant (p=0.056). Age at menarche and at first delivery showed no significant difference between cases and referents.

Cases and referents were compared by various food items in Table 5. A decreased OR was revealed in high frequency of Western type breakfast (OR=0.5), and the test for gradient was also statistically significant (p=0.014). Frequent green veg...
Table 6. Multivariate comparison of women with thyroid cancer to referents by four significant items of past history of thyroid disease, coffee consumption, Western type breakfast and delivery experience.

|                        | OR  | 95% CI          |
|------------------------|-----|-----------------|
| Past history of thyroid disease* | 4.3 | 1.02-17.7       |
| Coffee consumption*    | 0.6 | 0.3-1.04        |
| Western style breakfast* | 0.7 | 0.4-1.4         |
| Ever had a birth*      | 1.5 | 0.8-2.7         |

a) Odds ratio adjusted by age and year of visit.
b) Confidence interval.
c) Thyroid benign mass, goiter or hyperthyroidism vs. no.
d) Everyday vs. less.
e) Bread vs. rice or mixed style.
f) ≥3 times vs. less.

Table intake tended to increase the OR, but the trend test was not statistically significant (p=0.111). Other dietary items were not significantly associated with increased or decreased ORs for thyroid cancer.

When the intake frequency of Western type breakfast was compared with that of selected food items, Western type breakfast was positively related to frequent intake of coffee (p<0.001) and milk (p<0.001), and negatively related to intake frequency of miso soup (p<0.001) by Mantel-Haenszel test (data is not shown in table).

To control the effect of confounding factors, multivariate logistic regression models, adjusted by age and year of visit, were used for the analysis of the items of past history of thyroid disease, Western type breakfast, coffee consumption, and delivery experience. These results showed a positive association with past history of thyroid disease (OR=4.3) (Table 6). The OR of everyday coffee consumption decreased to 0.6 but was not statistically significant (95% CI; 0.3-1.04).

**DISCUSSION**

As we used non-cancer outpatients as the reference group, selection bias should be discussed. ACCH is a cancer hospital but open to anyone, with or without doctor’s referrals. Therefore, malignant neoplasms were ruled out in 86% of all outpatients, and 44% of outpatients among all non-cancer patients were diagnosed as being disease free. Moreover, some specific diseases such as tobacco-related diseases were less frequent (<1%) among randomly selected referents. Cases tended to come from more distant places than referents. However, the difference on the distribution of living place between cases and referents did not significantly influence the results. From these facts, the character of the referents in the present study is closer to that of the general population than that of cancer. Furthermore, we used all eligible non-cancer outpatients for referents. A large number of referents reduces the selection bias and gives a steadier estimate than matched analysis. The information bias is small in the present study, because subjects answered in the questionnaire before diagnosis was made.

Many epidemiological studies, including the present study, have found an increase in risk of thyroid cancer associated with past history of thyroid disease. These past histories include goiter, benign hyperplastic thyroid diseases, and benign thyroid nodules. These positive associations have been observed both in iodine deficient regions and in iodide rich regions. On these items, some recall or rumination bias could not be neglected, because cases themselves suffered from thyroid diseases. Moreover, thyroid cancer has a higher prevalence of occult cancer than other common cancers. Therefore, it is possible that some thyroid cancer had been diagnosed as benign thyroid nodules or goiter in the past. To reduce this bias, we accepted this information if the complaints had been made more than 10 years before the diagnosis of thyroid cancer.

Thyroid tumors have been produced by iodine deficient diets, by blocking thyroid hormone synthesis, by administering TSH directly, and by chemical goitrogens. Furthermore, suppression of TSH release by administration of thyroxin is often an effective treatment for thyroid cancer. Therefore, it seems reasonable that some common risk factors producing excess or imbalanced TSH secretion play an important role in the growth of thyroid benign tumor and thyroid cancer.

Hyperthyroidism associated with thyroid cancer has been observed in several studies, including this study. Although some information of hyperthyroidism may have included a recall bias or symptoms from thyroid cancer, hyperthyroidism may be also involved in developing thyroid cancer, because hyperthyroidism is accompanied with an increased activity of thyroid gland cells and with an unstable level of TSH if the secretion of thyroid hormone is modified by natural clinical course or treatment.
The female-to-male ratios of thyroid cancer incidence in Japan range from 2.9 to 5.9. These same trends have also been shown in other countries. Many studies have shown the association between reproductive factors and the risk of thyroid cancer. Increased risks have been found in women who have been ever pregnant, miscarriage as outcome of the first pregnancy, multiparity, pregnancy soon after puberty, and use of various hormone-containing preparations. The present study also showed that cases tended to have had more experience of delivery than referents. Some of these factors are the same as those of estrogen-related cancer such as breast cancer. In addition to estrogen, TSH may be related to these factors, because estrogen increases the secretion of TSH, and thyroid gland changes its size and activity during the course of a normal menstrual cycle and pregnancy.

Our interest is to analyze the dietary factors among the Japanese who consume much more iodine than Europeans and to compare the risk factors of thyroid cancer between them. In the present study, no dietary factors other than frequent intake of Western type breakfast were associated with the increased OR for thyroid cancer. In northern Italy and Switzerland, starchy foods and animal fats or proteins have been involved in increased risk of thyroid cancer, and dietary iodine including fish, green vegetables and fruit, has been inversely associated with risk. An Hawaiian study has shown a positive association between risk and seafood (shellfish), harm ha (fish sauce) and dietary iodine, and an inverse association between risk and goitrogenic vegetables (primarily cruciferous) in females. In addition, Norwegian and Swedish studies have found an increase in risk associated with cod-liver oil, fish liver and fish, and low intake of cruciferous vegetables. From these studies, it may be concluded that high iodine-containing food seems to decrease the risk of thyroid cancer in iodine-deficient inland regions, and to increase the risk in iodine-rich coast regions.

In a comparative study, Americans have shown a higher mean intake of iodine than Europeans, with Japanese immigrants in Hawaii consuming the most iodine of all Americans. Most Japanese regularly consume iodine rich fish. Some specific iodine-high-rich food items such as kelp consumption should be analyzed for the risk of thyroid cancer in iodine-high-rich regions, because the comparison of common iodine-rich food may reduce the contrast of the difference for consumption, when most subjects consume iodine rich food.

In the present study, frequent intake of green vegetables tended to be associated with an increased risk of thyroid cancer. Green vegetables including crucifers contain goitrogenic compounds (thiocyanates, thiocyanolidones and isothiocyanates) that block the synthesis of thyroid hormone and produce goiter by augmenting secretion of TSH. Goiter, however, occurs with a concentration that would require a dose of 1 g of potassium thiocyanate daily; that is, equal to a daily intake of about 10 kg of cauliflower. Thus, it is unlikely except in unusual circumstances (such as coexistent iodine deficiency) that a diet rich in thiocyanate would produce goiter in humans.

The association of coffee consumption, and benign thyroid diseases or thyroid cancer has been reported in Greece. Franceschi analyzed this relation but found no association in northern Italy. In the present study, to reduce confounding effects, multivariate procedures were applied, and coffee intake still tended to be associated with a decreased risk of thyroid cancer. Linos suggested that the mechanism by which coffee consumption may play a protective role against development of benign or malignant thyroid neoplasms may be the stimulatory effect of caffeine on the intracellular cyclic AMP production, which is known to inhibit cell growth.

The persons who consumed Western type breakfast consumed coffee and milk more frequently than those who took Japanese type breakfast, and consumed miso soup less frequently. Western type breakfast did not show a significant decreased OR when controlled by coffee consumption and other factors. The decreased risk associated with Western type breakfast may be confounded by coffee consumption.

In summary, our results showed that a history of thyroid disease is associated with an increased risk of thyroid cancer and frequent coffee consumption may be involved in a decreased risk. Other dietary factors did not show significant increased or decreased risk. These results suggest that thyroid hormone-related factors may be involved in the risk of thyroid cancer in Japan, too. To clarify the risk of Japanese food, another comparative study including detailed information on iodine intake between countries and individuals is required.

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