Original Article

Risk factors of thyroid cancer in Babol, Northern Iran

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Received: 11 Dec 2010
Revised: 15 Jan 2011
Accepted: 1 March 2011

Abstract

Background: *Thyroid cancer is the most common endocrine malignancy. Several risk factors were found to play a role in thyroid cancer. The purpose of the study was to determine the risk factors for thyroid cancer, in Babol, north of Iran.*

Method: *80 patients with thyroid cancer were selected as case group and 160 people living in the neighborhood of the patients as control group. Risk factors in both groups were collected and compared. The odds ratio (OR) as well as the marginal logistic regression model were used to estimate the possible risk factors.*

Result: *X-ray exposure, radioactive exposure, family history of thyroid cancer, history of hyperthyroidism, hypothyroidism and thyroid resection were found to be the risk factors of thyroid cancer ($p<0.05$). Passion exposure, OCP user, history of hysterectomy, history of thyroid nodule were not correlated to thyroid cancer ($p>0.05$).*

Conclusion: *History of goiter or other benign thyroid diseases are among the thyroid cancer risk factors in some community-based interventions to prevent or treat the disease in early stages are recommended in our region.*

Key words: *Thyroid cancer, risk factors, case - control study, odds ratio.*

Casp J Intern Med 2011; 2(1): 171-177.

According to American Cancer Society, the number of new thyroid cancer cases are estimated to be 30180 (7590 males and 22590 females) and the number of deaths from the disease 1500 (630 males and 870 females) (1). Thyroid cancer is the most common endocrine malignancy including 91.2% of all endocrine new cancers and 56.5% of endocrine cancer deaths in 2002. The difference between the total number of thyroid-originating endocrine cancers and the ratio of total endocrine cancer deaths due to thyroid cancer are 91.2% and 56/5% respectively, showing a relatively weak and sluggish nature of most thyroid malignancies and their long-term survival (2-4). Thyroid gland exposure to radiation in childhood, age, female gender, and family history are known risk factors in the increasing and well-differentiated thyroid cancer (5).

Well-differentiated thyroid cancer is almost 2.5 times more common in women and is related to papillary and follicular carcinoma of thyroid. The mean age of cancer diagnosis is earlier in women than men, and papillary carcinoma occurs earlier than follicular cancer in both sexes (5). Several studies showed an inverse relationship between the increased risk of thyroid cancer and the age of radiation exposure (6-8). Latent period after child exposure is at least three to five years and in most cases occurs 20 to 40 years after the exposure (9,10). There is no evidence showing that iodine 131 intake for diagnostic purposes, increases the risk of thyroid cancer (11). In addition, iodine 131 therapy to treat hyperthyroidism, is considered to be associated with a very small increase in thyroid cancer appearance (12).

Epidemiologic studies have been identified 4 to 10 times increase in well differentiated thyroid cancer risk among blood relatives developing this class of neoplasm (13). Thyroid cancer has increased gradually in the past decade.

However, most people with thyroid cancer have no obvious risk factors and others with one or more have not developed the disease; even in patients with thyroid cancer and the presence of one or more risk factors, it is impossible to determine how such risk factor has collaborated on cancer development (3).

Thyroid cancer (almost 9 in 100 thousand a year) increases with age and reaches a constant level after 50 years of age. Age is also an important prognostic factor for thyroid cancer, since it is associated with a worse prognosis in younger (under 20) or older ages (over 65). Thyroid cancer is two to three times more common in women than men, but is associated with worse prognosis in males (4,14). Considering the importance of cancer research and particularly its risk factors and since there has not been any study in thyroid cancer in the city of Babol, as well as the presence of equipped medical diagnostic centers and easy access to patients. We aimed to implement a research in order to determine thyroid cancer risk factors in the city of Babol.

Methods

The study population were patients with thyroid cancer living in the city of Babol. Study samples were those with thyroid cancer, who are still alive, collected and recorded by the research station; for each patient two neighbors were selected as the control group. Preliminary studies show that people with thyroid cancer develop goiter approximately 30 percent and it is nearly 10% in those without the cancer. Therefore, a sample size of 80 with 95% confidence and strength test equal to 80 % could be responsive to the study. Two fold samples were chosen for the control group. Data were collected through a questionnaire completed by a trained interviewer.

In this study, we entered patients with thyroid cancer who were diagnosed according to pathology report and were registered in Babol research station during 2002 to 2005. Patients with thyroid cancer diagnosis confirmed by pathologist and living in Babol were studied as the case group. For each case, two neighbors, matched with the patient's sex and age (±2 years) at the time of diagnosis, were selected as controls. In fact, cases and controls were matched together in terms of age, sex and residence.

The possible risk factors are (age, sex, number of x-ray exposure, women age at first birth, occupation, family (blood relatives) history of cancer, goiter, thyroid nodules, smoking, contraceptive pill use and exposure to radioactive materials). List of patients with thyroid cancer and their addresses were prepared by Babol research station and questionnaires were completed as well.

The questionnaire was prepared by investigating recent papers and scientific resources under a professor's supervision; content validity was also used to prove scientific accuracy of the questionnaire. To observe ethical considerations, patients obtained verbal consent to complete the questionnaire after being oriented about the nature of this research; Information confidentiality was observed.

Data analysis were done in two methods. In addition, for data descriptive analysis, all independent risk factors variables were studied using Chi-square and Fisher tests; the presence or absence of a possible risk factor was investigated and the p-value less than 0.05 was considered significant.

The analytical analysis regarding matching for investigating the risk factors marginal logistic regression (MLR) method for the data correlation was considered, and conditional logistic regression was used to modeling thyroid cancer risk factors in addition to MLR. Odds ratio (OR) and 95% confidence interval were estimated using conditional maximum likelihood method.

Results

The characteristics of the patients and the studied risk factors are shown in table 1.

Table 1: Absolute and relative frequency distribution of case and control groups based on demographic information

Profile	Group Status	Case		Control	
		Number	Percentage	number	percentage
Age Groups (years)	15-24	9	11.3	20	12.5
	25-34	7	8.8	17	10.6
	35-44	19	23.8	32	20
	45-54	17	21.3	35	21.9
	55-64	8	10	13	8.1
	65-74	13	16.3	29	18.1
	>= 75	7	8.8	14	8.8
Sex	Male	18	22.5	35	21.9
	Female	62	77.5	125	78.1
Marital Status	Single	12	15	28	18.1
	Married	60	75	115	74.2
	Widowed	6	7.5	11	7.1
	Divorced	2	2.5	1	0.6
Education	Illiterate	20	26	41	26.8
	Primary school	28	36.4	50	32.7
	Secondary school	13	16.9	35	22.9
	High school	12	15.6	20	13.1
	Associate degree	1	1.3	1	0.7
	Bachelor	3	3.9	6	3.9
Occupation	Homemaker	55	69.6	111	69.4
	Student	6	7.6	14	8.8
	Employee	7	8.9	4	2.5
	Driver	0	0	5	3.1
	Jobless	3	3.8	7	4.4
	Farmer	4	5.1	10	6.3
	Tradesman	1	1.3	4	2.5
	Worker	3	3.8	0	0
Family size	1-3	27	33.8	52	32.7
	4-6	38	47.5	84	52.8
	>= 7	17	18.8	23	14.5
Maritan age	11-18	0	0	2	1.9
	19-25	40	75.5	75	71.4
	>= 26	13	24.5	28	26.5
Number of pregnancies in married women	1-3	15	29.4	44	43.6
	4-6	22	43.1	37	36.6
	7-9	12	235	19	18.8
	>= 10	2	3.9	1	1
Number of children in married women	1-3	21	39.6	49	47.1
	4-6	23	43.4	35	33.7
	>= 7	9	17	20	19.2
Marriage duration	1-5	3	6	13	12.9
	6-10	20	40	37	36.6
	11-15	23	46	41	40.6
	16-20	4	8	10	9.9
Place of residence	Rural	54	67.5	114	71.3
	urban	26	32.5	46	28.8

240 people including 80 cases and 160 controls, (53 were males and 187 females), 168 living in the village and 72 in the city. In fact, the majority of patients participating in the study and consequently the controls were rural women. History of goiter (OR 6.3, p<.001), hyper and hypothyroidism has been in a significant relationship with thyroid cancer (p<0.01) and crude odds ratio of these variables indicates being the risk factor for this cancer (table 2). With regard to marital status, 75% of patients and 74% of controls were married. Although thyroid cancer has been observed in all age groups of the study, about 45% of patients between 35 to 55 years are in their middle age. Approximately 95 and 94 percent of people were non-smokers in patients and control groups, respectively. 38.6% of women patients and 45.8% of controls mentioned the experience of taking oral contraceptive pills (OCP) in an average of five years, in which the difference was not meaningful (p>0.05). Over 82% of patients and less than 1% of controls had a history of goiter which does not show significant correlation with thyroid cancer (p<001). Generally, according to crude odds ratio (OR), there was not a significant relationship between thyroid cancer and marital status education level, patients' occupational records, smoking, family size, marital age and number of children. Therefore, thyroid cancer does not have significant correlation with subjects' profile (p>0.05) (Table 2).

Similarly, there was not a significant difference between thyroid cancer and number of pregnancies, history OCP use, hysterectomy and a history of TAH/BSO in women patients. Over 97% of patients exposed to radioactive materials had a history of thyroid scans performed possibly for cancer diagnosis which can be considered as a confounding factor. Over 97% of controls did not mention radioactive materials exposure (Table 2).
Based on crude odds ratio, history of thyroid nodules, which can be more important, is not associated with thyroid cancer; With regard to completing the questionnaires through interviews and not by performing physical examination or radiologic imaging, diagnosis of thyroid nodule was not possible (Table 2).

Table 2: Absolute and relative frequency distribution of cases and controls based on history of thyroid cancer risk factors

Status / Risk factors (Rf)	Cases						Controls						Test result
	With Rf		Without Rf		Total		With Rf		Without Rf		Total		
	n*	P*	n	p	n	p	n	p	n	p	n	p	
Poison exposure	4	5	76	95	80	100	8	5	152	95	160	100	N m*
Occupational exposure to radioactive materials	0	0	80	100	80	100	1	0.6	157	99.4	158	100	
Smoking history	4	5.1	75	94.9	79	100	10	6.3	150	93.8	160	100	
X-ray exposure	71	88.8	9	11.3	80	100	106	66.3	54	33.8	160	100	p<0.01
Radioactive exposure	78	97.5	2	2.5	80	100	4	2.5	156	97.5	160	100	p<0.01
Family history of thyroid cancer	62	77.5	18	22.5	80	100	58	36.3	102	63.7	160	100	p<0.01
OCP use	22	38.6	35	61.4	57	100	54	45.8	64	54.2	118	100	N m
History of hysterectomy	5	8.6	53	91.4	58	100	13	11	105	89	118	100	
TAH/BSO	6	10.3	52	89.7	58	100	9	7.6	109	92.4	118	100	
History of goiter	65	82.3	14	17.7	79	100	1	0.6	159	99.4	160	100	p<0.05
History of thyroid nodules	2	2.6	74	97.4	76	100	0	0	159	100	159	100	N m
History of hyperthyroidism	54	68.4	25	31.6	79	100	2	1.3	157	98.7	159	100	p<0.001
History of hypothyroidism	24	30.4	55	69.6	79	100	2	1.3	157	98.7	159	100	p<0.001
History of thyroid resection	78	98.7	1	1.3	79	100	0	0	159	100	159	100	p<0.001

n*: number p*: percentage N m*: Not meaningful

Discussion

In the present study, we found a correlation between thyroid cancer and goiter, hyper and hypothyroidism. History of benign thyroid diseases (thyroiditis, goiter, hyper and hypothyroidism) has been associated with the risk of thyroid cancer, since relative risk (RR) for the disease has been estimated about 7.7 (15-17). In addition, simultaneous incidence of thyroid cancer with hyperthyroidism varies from 9% to 21% (18). Factors including age, sex, radiotherapy for cancer treatment, history of head and neck radiation, radioactive exposure, women age at first birth, occupation, family history of cancer, goiter, and contraceptive pills are mentioned as thyroid cancer risk factors (4,18-19), which is not in accordance with our results in regard to occupation, family history, age at first birth and women taking oral contraceptives. In a population-based case-control study performed in America, for thyroid cancer (159 cases and 285 controls), previous radiotherapy has reported 12% cases and 4% of controls risk of the cancer has a converse relationship with age at radiation time. The greatest risk has been associated with children under 10 years of age (4,20).

Other significant risk factors in this study include a history of benign thyroid nodules and goiter (4,21). Clinical significance of thyroid nodules remains standing because of the need to rule out thyroid cancer in 5 to 10% of these nodules. Thyroid cancer occurs depending on age, sex, history of radiation exposure, family history and other factors, (18,22).

Incidence of thyroid cancer varies in hot nodules and has been estimated between 0 to 4% in adults (11,19,23). In addition, there was not a significant relationship between history of nodules and thyroid cancer in this study which can be due to nodules diagnosis with clinical examination or radiological imaging and by a doctor and not by patient history (since this cannot be reliable).

In the same study in America, there was not any significant correlation with some suspected risk factors including diagnostic x-ray, radioisotope scans, occupational radiation exposure, removing the tonsils, the Jewish race, alcohol consumption, smoking, contraceptives pill, milk production suppressants, estrogens during menopause, most prevalent drugs and water sources (4,23,24). In a population-based case-control study performed on 191 cases (lconfirmed in Pathology) and 341 controls (matched in terms of age) in Sweden and Norway, hormonal factors, reproductivity and smoking investigated as causes of papillary and follicular thyroid cancer in women. In this study, there was not any obvious relationship between the number of live births, number of pregnancies, history of incomplete pregnancies, contraceptive pills or using hormone replacement therapy (HRT) with thyroid cancer (19) which is in consistency with our results.

However, considering smoking, hormonal factors and reproductivity in the first delivery (under the age of 20 or less than 5 years after menarche) and the history of artificial menopause compared to spontaneous one, were all associated with an increased risk of thyroid cancer. Smokers also showed low risk compared to nonsmokers which was statistically near to borderline and such reduced risk was especially found in premenopausal women (20).

In conclusion, thyroid cancer has been significantly associated with history of goiter, hyper and hypothyroidism, but not with history of thyroid nodules, which can be more important. This may be due to nodules diagnosis with clinical examination or radiological imaging and by a doctor and not by a patient's history (since this cannot be reliable). According to available resources, most thyroid cancers have euthyroid mode and hypo and hyperthyroidism which are rarely seen (17,15). Furthermore, the relationship examination between thyroid cancer and diseases with diabetes is a matter of high importance, which has not been found in our study owing to few cases; therefore, further studies with higher sample sizes are required to determine these relationships.

Case-control overmatching and Recall bias are among the limitations and shortcomings of this study. Overmatching has occurred during the design and some during the study

implementation. Recall bias happened in numbers of radiation exposure between the cases and the controls.

Acknowledgement

The study, done in a thesis form was a thesis sponsored by Tehran University of Medical Sciences. Also, we thank the Health Research Department especially to Mr. Alijantabar Deldari and Mr. Ebrahimi for their cooperation.

References

1. Bandi P, Barber S, Boone M, et al. Cancer Facts and Figures 2006; American Cancer Society. Available at: http://222.cancer.org/downloads/STT/CAFF2006pwsecured.pdf. Accessed March 1, 2006.
2. Halperin EC, Perez CA. Brady LW, et al. Perez and Brady's Principles and Practice of Radiation Oncology. 5 th ed. Philadelphia: Lippincott Williams & Wilkins 2008; vol 2.
3. Sener SF. Disease without Borders. CA Cancer J Clin 2005; 55: 7-9.
4. Harrison's Principles of Internal Medicine 16th Edition-McGraw-Hill Professional-2004. gateway. ut. ovid. com/gw1/ovidweb.
5. DeVita JR, Vincent TJR, Lawrence TS, Rosenberg SA, Depinho RA, Winberg RA. Devita, Hellman, Rosenberg's Cancer: Principles and Practice of Oncology, 8th Ed. Philadelphia: Lippincott willians & willkins; 2008; vol2.
6. Schantz A, Castleman B. Parathyroid carcinoma: a study of 70 cases. Cancer 1973;31: 600-5.
7. Fujimoto Y, Obara T. How to recognize and treat parathyroid carcinoma. Surg Clin North Am 1987; 67: 343-57.
8. Smith JF, Coombs RR. Histological diagnosis of carcinoma of the parathyroid gland. J Clin Pathol 1984; 37: 1370-8.
9. Levin KE, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. Surgery 1987; 101): 649-60.
10. Boice JD, Jr. Radiation-induced Thyroid Cancer - - What's New?. J Natl Cancer Inst 2005; 97: 703-5.
11. Kammori M, Nakamura K, Ogawa T, et al. Demonstration of human telomerase reverse transcriptase (hTERT) in human parathyroid tumours by in situ hybridization with a new oligonucleotide probe. Clin Endocrinol 2003; 58: 43-8.
12. Farnebo F, Svensson A, Thompson NW, et al. Expression of matrix metalloproteinase gelatinase A messenger ribonucleic acid in parathyroid carcinomas. Surgery 1999; 126: 1183-7.
13. Wassif WS, Farnebo F, Teh BT, et al. Genetic studies of a family with hereditary hyperparathyroidism-jaw tumour syndrome. Clin Endocrinol 1999; 50:191-6.
14. Ron E, Kleinerman RA, Boice JD JR, et al. A Population-Based Case-Control Study of ThyroidCancer. J Natl cancer Inst 1987; 79: 1-12.
15. D'Avanzo B, La Vecchia C, Silvia Franceschi S, Negri E, Talamini R. History of Thyroid Diseases and Subsequent Thyroid Cancer Risk. Cancer Epidemiol, Biomarkers Prev 1995; 4: 193-9.
16. Mack WJ, Preston-Martin S, Bernstein L, Qian D, Xiany M. Reproductive and Hormonal Risk Factors for Thyroid Cancer in Los Angeles County Females. Cancer Epidemiol, Biomarkers Prev 1999; 8: 991-7.
17. Horn-Ross PL, Morris JS, Lee M, et al. Iodine and Thyroid Cancer Risk among Women in a Multiethnic Population: The Bay Area Thyroid Cancer Study. Cancer Epidemiol, Biomarkers Prev 2001; 10: 979–85.
18. Huszno B, Szybinski Z, Przybylik-Mazurek E, et al. Influence of iodine deficiency and iodine prophylaxis on thyroid cancer histotypes and incidence in endemic goiter area. J Endocrinol Invest,2003; 26: 71-6.
19. Gerenova J, Buysschaert M, de Burbure CY, Daumerie C. Prevalence of thyroid cancer in Graves' disease: a retrospective study of a cohort of 103 patients treated surgically. Eur J Intern Med 2003; 14: 321-5.
20. Galanti MR, Hansson L, Lund E, et al. Reproductive History and Cigarette Smoking as Risk Factors for Thyroid Cancer in Women: A Population-based Case-

Control Study. Cancer Epidemiol, Biomarkers Prev 1996; 5: 425-31.

21. Daumerie C, Ayoubi S, Rahier J, Busschaert M, Squifflet P. Prevalence of thyroid cancer in hot nodules. Ann Chir 1998; 52: 444-8 (In French).
22. Angusti T, Codegone A, Pellerito R, Favero A. Thyroid cancer prevalence after radioiodine treatment of hyperthyroidism. J Nucl Med 2000; 41: 1006-9.
23. Montella M, Pezzullo L, Cripso A, et al. Risk of thyroid cancer and high prevalence of hepatitis C virus. Oncol Rep 2003; 10: 133-6.
24. Cooper DS, Doherty GM, Haugen BR, et al. Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2006; 16: 109-42.
25. Sadetzki S, Calderon- Margalit R, Modan B, Srivastava S, Tuttle RM. Ret/PTC activation in benign and malignant thyroid tumors arising in a population exposed to low-dose external-beam irradiation in childhood. The J Clin Endocrinol Metab 2004; 89: 2281-9.