

Short communication

Thyroid cancer pooled analysis from 14 case–control studies: what have we learned?

Susan Preston-Martin¹, Silvia Franceschi², Elaine Ron³ & Eva Negri⁴

¹Norris Comprehensive Cancer Center, School of Medicine, Department of Preventive Medicine, University of Southern California, 1441 Eastlake Avenue, M/S 44, Los Angeles, CA 90033-0800, USA; ²Unit of Field and Intervention Studies, International Agency for Research on Cancer, Lyon, France; ³Radiation Epidemiology Branch, National Cancer Institute, Rockville, MD, USA; ⁴Laboratory of General Epidemiology, Mario Negri Institute, Milan, Italy

Thyroid cancer accounts for only about 1% of all incident cancers in the United States, and five year survival rates are extremely high. However, it is relatively frequent among women under age 45, and in the United States is the fourth most common cancer in this group after breast cancer, melanoma of the skin, and cancers of the cervix [1].

The etiology of thyroid cancer has been studied in numerous relatively small (<400 cases) case–control studies, as well as a few cohort studies. The only established cause of thyroid cancer is exposure to ionizing radiation, particularly in infancy or early childhood [2]. An association between thyroid cancer and a history of several benign thyroid diseases has been observed in most studies, although the strengths of these associations have varied across studies [2]. Because thyroid cancer incidence rates in women are consistently two–three times higher than those in men, some studies in various geographic areas have focused on women in an attempt to identify hormonal factors that might explain this excess. But, findings related to menstrual and reproductive factors as well as to exogenous hormone use have been inconsistent as have findings related to diet and to anthropometric and lifestyle factors [2]. We conducted a pooled analysis of 14 case–control studies of thyroid cancer in an attempt to further describe its etiology. Papers reporting on various aspects of this analysis have appeared in *Cancer Causes and Control* beginning in 1999; another such paper appears in the present issue [3].

Thirteen studies published in English from 1980 to 1997 and one unpublished study were identified. Four studies were conducted in the United States including one each in California [4], Washington State [5–7], Connecticut [8], and Hawaii [9, 10]; eight in Europe including one each in Italy [11], Greece [12] and Switzerland [13], two in Norway [14–16] and three in Sweden [17–20]; and two in Asia including one in China [21] and one in Japan. Original datasets were obtained and restructured in a uniform format [22]. Data on

socio-demographic characteristics, personal history of benign thyroid disease, family history of benign thyroid disease and cancer, anthropometric measures, dietary habits, and smoking and alcohol consumption were analyzed. For women, data on reproductive history and use of exogenous hormones also were evaluated. Prior radiotherapy, and in Japan A-bomb exposure, were considered as potential confounders. Data on radiographic exposures were not analyzed because they were absent or of inadequate quality in most studies.

A total of 2725 cases (2247 females and 478 males) and 4776 controls (3699 females and 1077 males) were included [22]. Of the cases, 79% were papillary thyroid carcinomas, 14% follicular, 2% medullary, 1% anaplastic, 1% other histologies, and 3% histological type unknown. Each of the datasets was checked for outliers and consistency and the data were compared with the published papers. Data were analyzed separately by study center, gender, and the two major histologic types (papillary and follicular). As a first step, study-specific analyses were conducted, and then the data from all the studies were pooled conditioning on study. Heterogeneity among studies, geographic areas and study designs were assessed, and the modifying effect of age was also evaluated.

In the pooled analyses, goiter and benign nodules/adenomas were shown to be the strongest risk factors for thyroid cancer apart from radiation in childhood [23]. In women, the pooled odds ratios (OR) were 5.9 for goiter and 38.3 for benign nodules/adenomas. Elevated risks were observed for men and women and in relation to both major histologic types. No significant heterogeneity was seen across geographic areas or across studies. The excess risk was greatest within two–four years prior to thyroid cancer diagnosis, but an elevated OR was present 10 years or more before cancer. Prior hyperthyroidism was related to a small, statistically non-significant increase that was reduced after allowance for a history of goiter. A history of hypothyroidism was not associated with cancer risk.

Associations between thyroid cancer and menstrual or reproductive factors were generally weak, but appeared stronger among women diagnosed with thyroid cancer at younger ages [24]. Parity, spontaneous or induced abortions, and history of infertility were not associated with thyroid cancer risk, although risk was increased among women who had miscarriage as the outcome of their first pregnancy (OR = 1.8 *versus* nulligravidae). Women who had undergone an artificial menopause showed an OR of 1.8. Thyroid cancer risk was weakly increased with later menarche and later age at first birth. No significant heterogeneity across studies or geographic areas emerged.

Some forms of exogenous hormone use were marginally related to thyroid cancer risk [25]. No increase was seen for use of hormone replacement therapy. The relationship of ever use of oral contraceptives (OCs) to thyroid cancer risk was weak (OR = 1.2) and of borderline statistical significance; however the risk was stronger for papillary cancers (OR = 1.6) and current users (OR = 1.5), which may relate to increased medical surveillance among current OC users. No increase was seen 10 or more years after discontinuing OC use. Small increases in ORs were also seen among women who took drugs for lactation suppression or fertility drugs, although this later association was not statistically significant. No significant heterogeneity was evident across studies or geographic areas.

Height and weight at diagnosis appeared to be directly associated with a small increase in thyroid cancer risk, but there was significant heterogeneity across studies [26]. Height was more strongly related to risk in males, but trends of increasing risk with increasing height were observed in both genders. Height, weight, and body mass index slightly increased thyroid cancer risk in women, but not men.

Dietary data varied considerably in completeness across the 13 studies which collected such data, and the number of food items queried in each study ranged from 4 to over 150 [27]. Therefore, the pooled analyses focused only on fish/seafood [27] and cruciferous and other vegetables [28]. Fish was not associated with thyroid cancer risk in all studies combined, but there was a suggestion of reduced risk in endemic goiter areas. It was reassuring to note that high levels of fish consumption did not appreciably increase risk in iodine-rich areas, and fish consumption was inversely related to thyroid cancer risk in endemic goiter areas. Cruciferous vegetables, which contain goitrogenic substances as well as several constituents which can inhibit carcinogenesis, were weakly and non-significantly related to reduced risk of thyroid cancer. Results were similar in studies from iodine-rich areas and endemic

goiter areas, as well as in analyses restricted to papillary cancer or women.

Cigarette smoking, particularly current cigarette smoking, was associated with a reduced risk of thyroid cancer; and current smokers had a 40% reduction in risk [3]. This association was evident in both men and women, in the two major histological groups, papillary and follicular cancers, and in the diverse geographic regions covered in the 14 studies. Our data also demonstrate a trend of decreasing risk with both smoking intensity and duration. In contrast, no association was noted between thyroid cancer and level of consumption of alcohol after controlling for smoking or intake of coffee or tea.

We also conducted a separate analysis on the 67 medullary cancers included in the pooled analysis after selecting five controls per case from the total control group, matched to cases on study, gender, and age [29]. We found that risk was directly related to height, history of thyroid nodules, and a few other medical conditions, *i.e.*, hypertension, allergy, and gallbladder disease. The risk was inversely related to number of cigarettes smoked per day among current smokers, and to age at first birth among women. Thus, in spite of the small number of cases, we were able to detect a few significant associations for medullary thyroid cancer. Although there was little evidence for familial occurrence in our study, some of the risk factors (*e.g.*, hypertension and height) may represent components of an underlying multiple endocrine neoplasia type 2 syndrome.

In summary, we have gained a few new insights about possible causes of thyroid cancer from our pooled analyses; we were able to conduct separate analyses for some histological types (*e.g.*, follicular and medullary) and for males, on whom virtually no data were previously available. The large female excess of papillary and follicular thyroid cancer is not strongly related to any identifiable menstrual or reproductive factors or to use of exogenous hormones. The strong association with a history of benign nodules/adenoma or goiter may explain some of the female excess, as these conditions are more common in women compared with men, but the reason for this female excess of benign thyroid disease is unknown.

We found no evidence that thyroid cancer risk is elevated among people, male or female, with a relatively high intake of iodine from fish and seafood. Therefore, unless fermented fish sauces such as patis, which are used heavily in various Asian populations, have extraordinarily high iodine levels, the strikingly high incidence of thyroid cancer among Filipino and some other Asian populations remains unexplained. Overall, our findings are reassuring with respect to concerns that

the addition of iodine to salt and dairy products may increase the risk for papillary thyroid cancer [30]. Such fears may weaken the efforts to fight iodine deficiency, which is the single largest cause of preventable brain damage and mental retardation in the world [31]. Iodine deficiency is still an issue in various areas in Europe [32]. It is unfortunate that no study of thyroid cancer is available from areas of Central Asia and Africa where conditions of extreme iodine deficiency still exist [31]. While it is possible that individuals and populations vary considerably in their susceptibility to the tumorigenic effects of high (or low) iodine intake, based on our findings, much of the variation observed across the 14-pooled studies is likely to reflect random variation and differences in diagnostic standards. Even our large dataset was inadequate to evaluate many potentially interesting interactions between weak risk factors. Unless new compelling hypotheses emerge which can be tested in studies of this rare disease, it seems that the causes of most thyroid cancers will remain unknown.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM (2001) *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0*. IARC CancerBase no. 5. Lyon: IARC Press.
2. Ron E (1996) Epidemiology of thyroid cancer. In: Schottenfeld D, Fraumeni JR Jr., eds. *Cancer Epidemiology and Prevention*. Oxford: Oxford University Press, pp. 1000–1021.
3. Mack WJ, Preston-Martin S, Dal Maso L, et al. (2003) A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control* **14**: 773–785.
4. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE (1997) Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Int J Cancer* **55**: 191–195.
5. McTiernan AM, Weiss NS, Daling JR (1984) Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. *Nat J Cancer Inst* **73**: 575–581.
6. McTiernan AM, Weiss NS, Daling JR (1987) Incidence of thyroid cancer in women in relation to reproductive and hormonal factors. *Am J Epidemiol* **120**: 423–435.
7. McTiernan AM, Weiss NS, Daling JR (1984) Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. *Cancer Res* **47**: 292–295.
8. Ron E, Kleinerman RA, Boice JD Jr., et al. (1987) A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* **79**: 1–12.
9. Kolonel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW (1990) An epidemiological study of thyroid cancer in Hawaii. *Cancer Causes Control* **1**: 223–234.
10. Goodman MT, Kolonel LN, Wilkens LR (1990) The association of body size, reproductive factors and thyroid cancer. *Br J Cancer* **66**: 1180–1184.
11. D'Avanzo B, La Vecchia C, Franceschi S, Negri E, Talamini R (1995) History of thyroid diseases and subsequent thyroid cancer risk. *Cancer Epidemiol Biomarkers Prev* **4**: 193–199.
12. Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA (1989) Does coffee consumption protect against thyroid disease? *Acta Chir Scand* **155**: 317–320.
13. Levi F, Franceschi S, Guile C, Negri E, La Vecchia C (1993) Female thyroid cancer: the role of reproductive and hormonal factors in Switzerland. *Oncology* **50**: 309–315.
14. Glatte E, Haldorsen T, Berg JP, Stensvold I, Solvoll K (1993) Norwegian case-control study testing the hypothesis that seafood increases the risk of thyroid cancer. *Cancer Causes Control* **4**: 11–16.
15. Galanti MR, Hansson L, Lund E, et al. (1996) Reproductive history and cigarette smoking as risk factors for thyroid cancer in women: a population – based case-control study. *Cancer Epidemiol Biomarkers Prev* **5**: 425–431.
16. Galanti MR, Hansson L, Bergstrom R, et al. (1997) Diet and nutrients as risk factors for papillary and follicular thyroid carcinoma. *Cancer Causes Control* **8**: 205–214.
17. Wingren G, Hatschek T, Axelson O (1993) Determinants of papillary cancer of the thyroid. *Am J Epidemiol* **138**: 482–491.
18. Hallquist A, Hardell L, Degerman A, Boquist L (1993) Occupational exposures and thyroid cancer: results of a case-control study. *Eur J Cancer Prev* **2**: 345–349.
19. Hallquist A, Hardell L, Degerman A, Boquist L (1994) Medical diagnostic and therapeutic ionizing radiation and the risk for thyroid cancer: a case-control study. *Eur J Cancer Prev* **3**: 481–488.
20. Hallquist A, Hardell L, Degerman A, Boquist L (1994) Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. *Eur J Cancer Prev* **3**: 259–267.
21. Preston-Martin S, Jin F, Duda MJ (1993) A case-control study of thyroid cancer in women under the age of 55 in Shanghai (People's Republic of China). *Cancer Causes Control* **4**: 431–440.
22. Negri E, Ron E, Franceschi S, et al. (1999) A pooled analysis of case-control studies of thyroid cancer. I. Methods. *Cancer Causes Control* **10**: 131–142.
23. Franceschi S, Preston-Martin S, Dal Maso L, et al. (1999) A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* **10**: 583–595.
24. Negri E, Dal Maso L, Ron E, et al. (1999) A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. *Cancer Causes Control* **10**: 143–155.
25. LaVecchia C, Ron E, Franceschi S, et al. (1999) A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control* **10**: 157–166.
26. Dal Maso L, La Vecchia C, Franceschi S, et al. (2000) A pooled analysis of thyroid cancer studies. V. Anthropometric factors. *Cancer Causes Control* **11**: 137–144.
27. Bosetti C, Kolonel L, Negri E, et al. (2001) A pooled analysis of case-control studies of thyroid cancer. VI. Fish and shellfish consumption. *Cancer Causes Control* **12**: 375–382.
28. Bosetti C, Negri E, Kolonel L, et al. (2002) A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables. *Cancer Causes Control* **13**: 765–775.
29. Negri E, Ron E, Franceschi S, et al. (2002) Risk factors for medullary thyroid cancer: a pooled analysis. *Cancer Causes Control* **13**: 365–372.
30. Hedinger C (1981) Geographic pathology of thyroid disease. *Pathol Res Pract* **171**: 285–292.
31. Micronutrient deficiencies: eliminating iodine deficiency disorders. WHO website, <http://www.who.int/nut/idd.htm>, November 2002.
32. Delange F, Dunn JT, Glinioer D (1993) *Iodine in Europe: A Continuing Concern*. New York: Plenum Press.