

## A pooled analysis of case-control studies of thyroid cancer

### I. Methods

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### Abstract

**Objective:** Because the etiology of thyroid cancer is not well described, we conducted a pooled analysis of all published case-control studies, as well as two identified unpublished studies. This paper describes the major characteristics of the 14 studies included in the analysis, as well as the statistical methods employed. Four studies were conducted in the United States (1 each in Washington State, California, Connecticut and Hawaii), 8 in Europe (3 in Sweden, 2 in Norway, 1 in Switzerland, 1 in Italy and 1 in Greece), and 2 in Asia (1 in China and 1 in Japan).

**Methods:** The original datasets were obtained and restructured in a uniform format. Data on socio-demographic characteristics, anthropometric measures, smoking and alcohol consumption, history of benign thyroid diseases and of other selected medical conditions and treatments, family history of cancer and of benign thyroid conditions, occupation, residence in endemic goitre areas, and dietary habits were analyzed. For women, we also analyzed menstrual and reproductive factors and use of female hormones. Radiotherapy and, in Japan, exposure to the A-bombs were considered as potential confounding factors.

**Results:** A total of 2,725 cases (2,247 females and 478 males) and 4,776 controls (3,699 females and 1,077 males) were included in this study. Of the cases, 79% were classified as papillary thyroid carcinomas, 14% as follicular, 2% medullary, 1% anaplastic, 1% other histologies, and 3% histological type unknown. Each of the datasets was checked for outliers and consistency. Data were analysed separately by study center, gender, and the two major histologic types (papillary, follicular). Frequency tables and simple statistics were computed for each variable under study. Conditional logistic regression was used to compute odds ratios. For matched studies, the original matching was preserved, whereas, for unmatched ones, five-year age groups were used for matching. Study-specific analyses were computed, and then the data from all the studies were pooled conditioning on study. Heterogeneity between studies, geographic areas and study designs was assessed, and the modifying effect of age was also evaluated.

## Introduction

Thyroid cancer is relatively rare: world standardized incidence rates are generally lower than 3/100,000 for men and about 5/100,000 for women [1]. Women develop these cancers about three times more often than men. The majority of thyroid malignancies are well differentiated and five-year survival rates are extremely high. Papillary carcinomas comprise between 50% and 80% of all thyroid cancers and follicular carcinomas between 10% and 40%. Given the indolent behavior of papillary and follicular carcinomas, differences in levels of national health care and availability of early detection screening programs may explain part of the variation in incidence observed over time and geographical areas [2, 3]. Anaplastic carcinoma is less common (5–10%), usually occurs in the sixth to seventh decade of life, is histologically undifferentiated, and highly malignant. Medullary carcinoma arises from parafollicular or C cells. Approximately 20% of medullary carcinoma are familial, often occurring as part of multiple endocrine neoplasia (MEN) types 2A or 2B. The different histological types of thyroid cancers vary in biological behavior, prognosis, and etiology [2].

Ionizing radiation is the only well-defined risk factor for thyroid cancer. A pooled analysis of seven studies demonstrated a strong linear relationship with dose when exposure occurred during childhood [4]. A history of benign thyroid disease, particularly thyroid nodules, is associated with an elevated risk of thyroid cancer, but the causal relationship is unclear. Iodine deficiency and residence in endemic goitre areas also increase the risk of follicular and anaplastic thyroid cancer. In contrast, high levels of iodine are associated with an increased risk of papillary carcinoma. The role of diet, with special attention to iodine-rich fish and seafood and goitrogenic vegetables, has been evaluated, but the data are sparse and results are inconclusive. The most consistent finding is a protective effect of high vegetable intake [2, 3]. An increased risk of papillary carcinoma has been reported in some families [5]. Unlike the pattern observed for breast cancer, pregnancy and early menopause appear to enhance the risk of thyroid cancer [2, 6, 7].

Several thyroid cancer case-control studies have been conducted, but the number of cases was small in most studies. The largest published study included slightly less than 400 cases. By pooling the data from all identified case-control studies of thyroid cancer, we can increase the statistical power to detect risk factors and to identify consistent patterns of risk. The major hypotheses to be explored are: hormonal and reproductive factors influence the development of thyroid cancer; benign thyroid diseases, particularly nodules, increase the risk of

thyroid cancer; cruciferous vegetables are protective; iodine intake increases the risk of papillary carcinoma and iodine deficiency increases the risk of follicular thyroid cancer. In this paper, we describe the studies included in the pooled analysis and the methods used in data collection, editing, and statistical analysis.

## Methods

### *Identification of the studies*

A MEDLINE search was conducted to ascertain case-control interview studies of thyroid cancer published between 1980 and 1997 in English. Unpublished studies were found through personal contact with investigators. In total, 15 case-control studies were identified. Four studies were conducted in the United States (1 each in Washington State, California, Connecticut and Hawaii), 8 in Europe (3 in Sweden, 2 in Norway, 1 in Switzerland, 1 in Italy, and 1 in Greece), and 2 in Asia (1 in China, and 1 in Japan). Another study in Washington State in the United States was ongoing at the time of data collection and, therefore, could not be included. A first meeting was held, in which study hypotheses and practical issues (*e.g.* data quality control, statistical analysis, variables to be studied, *etc.*) were discussed, and the responsible person(s) for each study were selected. In the following description, as well as in all tables, studies are ordered by geographical area and, within area, by the number of female cases.

Table 1 provides information on thyroid cancer incidence rates (age-standardized, world standard) in the study or neighboring areas, for the period 1983–87. In most areas, incidence rates were between 1 and 2.5/100,000 in males and between 4 and 6/100,000 in females. Incidence was highest in Hawaii, mostly in Filipino and Chinese, and lowest in Shanghai, China.

### *Description of the studies (Table 2)*

#### *America – North: United States*

*Study 1 – Los Angeles County, California.* This study of female thyroid cancer cases under age 55 at the time of their diagnosis between 1980–83 was conducted in Los Angeles County. Data from cases, who were diagnosed in 1980–81 at age 40 years or less, have been published [6]. A total of 292 Caucasian women with incident, histologically confirmed thyroid cancer were identified through the Los Angeles County Cancer Surveillance Program and were interviewed by telephone (1980–81 pairs) or in person (1982–83 pairs). For each case a neighborhood control, whose birth date was within five

Table 1. Incidence rates<sup>a</sup> of thyroid cancer in the period 1983–87, standardized for age on the world population, recorded in cancer registries located in (or near to) the studies' areas

Registration area	Incidence/100,000	
	Males	Females
America – USA		
Los Angeles		
Spanish surname whites	2.1	5.8
Other whites	2.3	5.9
Seattle	2.1	5.9
Hawaii		
White	2.7	8.7
Japanese	4.3	6.3
Hawaiian	5.4	9.6
Filipino	6.6	24.2
Chinese	8.1	11.3
Connecticut (white)	1.8	4.8
Asia		
Japan		
Hiroshima <sup>b</sup>	1.9	5.6
Nagasaki	2.2	5.2
Shanghai, China	0.9	2.2
Europe – North		
Sweden	1.6	3.8
Norway	1.6	5.1
Europe – South		
Italy, Varese	2.0	4.9
Vaud, Switzerland	1.8	4.3

<sup>a</sup> From Cancer Incidence in Five Continents [1].

<sup>b</sup> Data are for the period 1981–85.

years of that of the index case and who was at least as old at interview as the case was at diagnosis, was selected and interviewed. The questionnaire included information on socio-demographic factors, occupational history, history of selected personal and family medical conditions (including a history of selected medication use), therapeutic and diagnostic radiation exposure, menstrual, reproductive and hormonal factors, and use of female hormones. The questionnaire used in 1982–83 varied slightly from the one used in 1980–81.

*Study 2 – Western Washington State.* This study included 185 women with papillary or follicular thyroid carcinomas diagnosed between 1974 and 1979. Study subjects were between 18 and 80 years of age at the time of diagnosis and had to speak English and have telephones. Cases were identified through the Cancer Surveillance System of Western Washington, and 65% were interviewed. No independent pathology review was conducted. For each case, an attempt was made to select and interview two women, aged 18 to 80 years, with the same three-digit telephone prefix as the case. Of the 478 eligible controls, 393 (82%) women were interviewed.

Eighty-seven percent were white. Interviews were conducted by telephone in 1980–81. The interview included questions about socio-demographic variables, medical history, menstrual and reproductive factors, use of oral contraceptives, hormone replacement therapy and other selected drugs, and therapeutic and occupational radiation exposure [8–10].

*Study 3 – Hawaii (Oahu).* In Oahu, Hawaii, 140 women and 51 men who were 18 years of age or older when their thyroid cancer was diagnosed between 1980 and 1987, were studied. Cases were ascertained through the Hawaii Tumor Registry. To confirm the diagnosis pathology slides were reviewed by the study pathologist. Individuals from the main ethnic groups in Hawaii (Caucasians, Japanese, Filipinos, Hawaiians and Chinese) were included in the study. Controls (328 female and 113 male) were selected from people participating in the Health Surveillance Program of the Hawaii Department of Health. The questionnaire was administered at home for both cases (79% response rate) and controls (74% response rate), and focused on diet (over 150 food items), radiation exposure, medication use, occupational exposures, physical activity, reproductive history, and past illnesses [11, 12].

*Study 4 – Connecticut.* The Connecticut study included 109 women and 50 men of all races who had thyroid cancer before age 80 years. Cases diagnosed between 1978 and 1980 were identified from the Connecticut Tumor Registry and pathology slides were reviewed by the study pathologist. Controls (208 females and 76 males) were frequency matched to the cases on sex and year of birth, within 5-year categories. Random digit dialing was used to select controls less than 65 years of age, while controls over 65 years of age were chosen from Medicare rosters. Study subjects were interviewed in person in 1981–82. The response rate was 80% for cases and 63% for controls. The questionnaire included information on place of residence, source of drinking water, usual occupation, radiation exposure, medical history, family occurrence of cancer, and diet. For female subjects, questions on reproductive events were also included [13].

*Asia – East: Japan, China*

*Study 5 – Hiroshima and Nagasaki, Japan.* A study of 307 women and 58 men diagnosed with thyroid cancer between 1970 and 1985 and identified through the Hiroshima and Nagasaki Tumor Registries was conducted in Hiroshima and Nagasaki. Controls were matched to cases on sex, age, area of residence, and

Table 2. Selected study characteristics: pooled analysis of thyroid cancer case-control studies

Study number, location and references	Cases			Controls			Notes
	Age range	Year of diagnosis	Year of diagnosis	Type	Females	Males	
America – USA							
1. Los Angeles [6]	15–55	1980–83	292	Neighborhood	292	–	Individually matched by age and residence.
2. Western Washington [8–10]	18–80	1974–79	185	RDD <sup>a</sup>	393	–	Individually matched by telephone prefix
3. Hawaii [11, 12]	16–80	1980–87	140	Population	328	113	54 cases and 172 controls were Japanese, 32 and 144 Caucasian, 15 and 21 Chinese, 51 and 32 Filipino, and 39 and 72 Hawaiian
4. Connecticut [13]	20–76	1978–80	109	RDD <sup>a</sup>	208	76	
Asia							
5. Hiroshima and Nagasaki, Japan	23–74	1970–85	307	Population	307	58	Individually matched by sex, age, city of residence and A-bomb exposure
6. Shanghai, China [14]	18–54	1981–84	207	Resident's Registry	207	–	Individually matched by age
Europe – North							
7. Southeastern Sweden [15]	21–60	1977–87	149	Population	187	200	
8. Uppsala, Sweden [16, 17]	17–72	1985–93	133	Population	203	54	Individually matched by sex, birth year and county of residence
9. Northern Sweden [18–20]	22–71	1980–89	123	Population	240	85	
10. Norway, NHSS [21]	11–64	1955–89	71	NHSS <sup>b</sup>	355	105	Cases and controls answered the health screening questionnaire of the NHSS <sup>b</sup>
11. Tromsø, Norway [16, 17]	20–72	1985–93	58	Population	138	58	Individually matched by sex and date of birth
Europe – South							
12. Northern Italy [22]	16–72	1986–92	291	Non cancer patients	427	190	
13. Vaud, Switzerland [7]	12–72	1988–90	100	Non cancer patients	318	94	
14. Athens, Greece [23]	14–88	1989–93	82	Non cancer patients or visitors	96	44	

<sup>a</sup> Random Digit Dialing.<sup>b</sup> National Health Screening Survey.

atomic-bomb dose. The questionnaire included information on socio-demographic factors, smoking, history of selected medical conditions, family history of cancer, and about 50 dietary items. Data on menstrual and reproductive history were collected for women. Study results have not yet been published.

*Study 6 – Shanghai, China.* This study included 207 women listed in the Shanghai Cancer Registry as having a histologically confirmed thyroid cancer between the ages of 18 and 54, and diagnosed between 1981 and 1984. For validation, pathology review was conducted on 20% of the cases. The 207 control women were randomly chosen from the general population of the Shanghai urban area using the Shanghai Residents' Registry. The controls were individually matched to cases by year of birth. Over 90% of eligible subjects were interviewed. Interviews were conducted in subjects' homes. The focus of the study was on menstrual and reproductive factors, but the questionnaire also included a few dietary items and personal and family history of thyroid disease and cancer [14].

*Europe – North: Sweden, Norway*

*Study 7 – Southeastern Sweden.* This study included 149 female and 26 male thyroid cancer cases, aged 20 to 60 years, residing in three counties of southeastern Sweden. Cases were diagnosed between 1977 and 1987 and were identified from the regional tumour register. In a review of about 70% of the cases, the confirmation rate for the original diagnosis was 100%. Controls included 187 women and 200 men in the same age range as the cases randomly selected from the 1979, 1982 and 1985 regional population register. The response rates to the mailed questionnaire were 88% for cases and 78% for controls. The questions focused on socio-demographic factors, reproductive history, lifetime residence and occupation, leisure-time exposures, personal medical history, diseases among relatives, smoking and some dietary habits. Study subjects were interviewed in 1990 [15].

*Study 8 – Uppsala, Sweden.* Cases diagnosed with differentiated papillary or follicular thyroid cancer between 1985 and 1993, and living in the Uppsala-Örebro Health Care Region were identified from the national (1985–90) or regional (1991–93) cancer registries. Cases were histologically confirmed. Two controls for each case were selected from the national Population Registry, and were matched on sex, year of birth, and county of residence. At the time of data collection, study subjects had to be between the ages of 18 and 75. 86% of the cases and 70% of the controls completed a mailed question-

naire, between 1993 and 1994. Of these, 170 cases (133 women and 37 men) and 257 controls (203 women and 54 men) were included in the present analysis. The questionnaire included information on life and work environment, dietary habits (56 items), personal and family medical history, and hormonal and reproductive history. A telephone interview was performed in case of incomplete or unreliable information [16, 17].

*Study 9 – Northern Sweden.* Using a similar design and the same questionnaire as Study 7 [15] 232 histologically confirmed thyroid cancer cases between 20 and 70 years of age at the time of diagnosis (1980–89), and residing in the four most northern counties of Sweden were ascertained from the Swedish Cancer Registry. Two controls, matched on age and county of residence, were selected from the national Population Registry for each case. The questionnaire, mailed in 1990, was returned by 171 (95%) cases (123 women and 48 men) and 325 (90%) controls (240 women and 85 men controls) [18–20]. The following data were collected: socio-demographic factors, reproductive history, lifetime residence and occupation, leisure-time exposures, personal medical history, family history of disease, smoking, and some dietary habits.

*Study 10 – Norway.* This study was based on linking data from the Norwegian Cancer Registry for 1955 to 1989 with data from questionnaires, mailed between 1974 and 1987 by the National Health Screening Service (NHSS) to approximately 60,000 persons residing in three Norwegian counties. The questionnaire included information on frequency of consumption of about 60 food items, as well as selected data on past diseases. The case series consisted of subjects with thyroid cancer (71 women and 21 men) diagnosed between 1955 and 1989 and who had answered the NHSS questionnaire. For each case, five controls (355 women and 105 men) were randomly selected from the NHSS responders, matched on gender, age and county of residence. Information on parity at the date of diagnosis of the index case was obtained from the National Population Registry [21].

*Study 11 – Tromsø, Norway.* A study using the same questionnaire and methods as study 8 [16, 17] was conducted in Tromsø, in the most northern part of Norway. The thyroid cancer cases aged less than 65 years at diagnosis were selected from the Norwegian Cancer Registry. Histologically confirmed cases diagnosed between 1985 and 1993 were included in the study and interviewed in 1993 and 1994. Four controls per case were selected from the National Population Registry among residents in the region, and matched to

cases by gender, year and month of birth. Interviews were conducted at the same time as those for cases. Response rate was 75% for cases and 56% for controls [16, 17]. Eighty-two cases (58 female and 24 male) and 196 matched controls (138 women and 58 men) were included in the present analysis.

*Europe – South: Italy, Switzerland, Greece*

*Study 12 – Northern Italy.* This study was conducted in the provinces of Milan, Pordenone and Padua, in northern Italy. It included 291 women and 108 men less than 75 years old, with histologically confirmed thyroid cancer, diagnosed between 1986 and 1992 in the major teaching and general hospitals in the Study areas. Controls (427 females and 190 males) were admitted to the same network of hospitals as cases with diagnoses of acute, non-neoplastic, non-hormonal diseases, not related to known or potential risk factors for thyroid cancer. The response rate was over 95% for both cases and controls approached for interview. A structured questionnaire was administered within two years of diagnosis by trained interviewers. It included socio-demographic and anthropometric characteristics; lifestyle habits such as smoking, alcohol and coffee consumption; dietary habits; a problem-oriented medical history; family history of thyroid diseases; gynecological and obstetric history, and use of oral contraceptives and female hormones for other indications [22].

*Study 13 – Vaud, Switzerland.* Study number 13 was conducted in the Swiss Canton of Vaud and included 100 women and 23 men with histologically confirmed thyroid cancer and admitted between 1988 and 1990 to the main university hospital of the Canton of Vaud (CHUV). Controls were 318 women and 94 men admitted to CHUV for acute conditions. Individuals admitted for malignant, hormonal or gynecological disorders were not selected as controls. The questionnaire was administered less than one year after diagnosis and was very similar to that of study 12, except for a few differences in the food list [7].

*Study 14 – Athens, Greece.* The last study was based on 82 women and 32 men with histologically verified cancer of the thyroid, treated at two major university endocrinology departments in Athens, Greece, between 1985 and 1992. Controls (96 women and 44 men) were patients admitted to the same hospitals as the cases, but for non-thyroid conditions, or healthy visitors to the hospital. Questions included socio-demographic characteristics, occupation, medical history, reproductive history, therapeutic irradiation, family history of cancer, smoking,

alcohol and coffee consumption, and dietary habits. Only part of the data has already been published [23].

*Data management*

The original datasets were restructured using a uniform format either by the original study investigators, or by the central coordinators in the Mario Negri Institute for Pharmacological Research and the Aviano Cancer Center in Italy or the National Cancer Institute in the United States. We collected individual data on: socio-demographic characteristics, anthropometric measures, smoking and alcohol consumption, history of benign thyroid disease, radioactive iodine treatments, other radionuclides and external radiotherapy, family history of cancer and of benign thyroid diseases, occupation, residence in endemic goitre areas, and dietary habits. For women, we also obtained data on menstrual and reproductive history and use of female hormones. The participating centers completed forms describing their study methods and variables, and provided supplemental data they thought helpful.

The data of each study were centrally checked for internal consistency and problems were discussed with the original study's designated contact person. The submitted data were compared with published articles. Data included in the present analysis, however, may differ somewhat from those published because definitions of variables or selection criteria were modified to maintain uniformity among studies (e.g., in the current study some analyses include all events occurring prior to diagnosis, while in some of the published studies events occurring in the year before thyroid cancer diagnosis were excluded).

For each topic, a list of variables (those collected directly and newly created variables to be analyzed) was defined, and a set of tables was prepared. The first included descriptive information such as mean, variance and quantiles. The second table described the distribution frequency according to predefined categories. The corresponding odds ratios (OR) were then computed using conditional logistic regression [24] and summarized in an additional table. For individually matched studies, where age was one of the matching variables, the original matching was used to define strata, while quinquennia of age were used for other studies. For Hawaii, the model was conditioned also on ethnicity. When appropriate, the same variable was analyzed both as a continuous and categorical term. The data were analysed separately by center and gender.

After individual study analyses were completed, the studies were pooled together, and conditional logistic regression was used to estimate pooled odds ratios,

Table 3. Distribution of cases by histological type, study and gender: pooled analysis of thyroid cancer case-control studies

Study number and location	Histology (women:men)					
	Papillary	Follicular	Anaplastic	Medullary	Other	Undefined
America – USA						
1. Los Angeles	243:–	40:–	0:–	1:–	0:–	8:–
2. Western Washington	129:–	49:–	0:–	0:–	0:–	7:–
3. Hawaii	115:47	23:4	0:0	2:0	0:0	0:0
4. Connecticut	88:35	8:7	0:1	5:4	7:1	1:2
Asia						
5. Hiroshima and Nagasaki, Japan	284:51	21:6	1:0	1:1	0:0	0:0
6. Shanghai, China	173:–	29:–	1:–	4:–	0:–	0:–
Europe – North						
7. Southeastern Sweden	117:16	23:7	1:0	2:1	6:2	0:0
8. Uppsala, Sweden	111:31	22:6	0:0	0:0	0:0	0:0
9. Northern Sweden	93:34	21:6	1:1	5:2	3:5	0:0
10. Norway, NHSS	45:17	0:0	0:0	0:0	0:0	26:4
11. Tromsø, Norway	50:23	8:1	0:0	0:0	0:0	0:0
Europe – South						
12. Northern Italy	210:64	50:19	4:4	8:10	3:1	16:10
13. Vaud, Switzerland	75:19	16:2	3:0	5:2	0:0	1:0
14. Athens, Greece	58:21	5:3	0:0	6:4	3:1	10:3
Total	1791:358	315:61	11:6	39:24	22:10	69:19

–, Not collected.

conditioning also on study [25]. All models were adjusted for history of external radiotherapy. To account for possible imbalances in the age distribution of cases and controls within the five-year age categories used for matching, three additional continuous terms for age were included in the logistic models. For continuous and ordinal variables, a test for deviation from linearity was also performed, by introducing a quadratic term in the model, and evaluating its significance by means of Wald's chi square [24].

Analyses also were conducted in strata of geographical area (United States, Asia, Europe-North, Europe-South), and study design (3 groups). The three study design groups were: (i) studies with population controls; (ii) studies with hospital controls; and (iii) studies with prevalent cases.

To test for heterogeneity among studies, geographical area, and study design, we compared the difference between the 2 log likelihood of the model estimating a common OR and of that estimating a specific OR for each group to the chi square distribution with degrees of freedom given by the number of groups minus one. Since tests for heterogeneity among geographical areas and study design were similar, we have reported only the former. When a variable was analyzed in categories, but was ordinal, we tested the heterogeneity between trends in risk, rather than among all separate categories.

Models excluding, in turn, subjects with a history of benign thyroid diseases or of radiotherapy were fitted,

but then results were generally very similar. Analysis by separate age categories (< 35, 36–55, > 55 years) were performed and the modifying effect of age was evaluated by comparing the increase in the 2 log likelihood between the models with and without interaction terms to the chi square distribution with degrees of freedom given by the number of interaction terms. Separate analyses for papillary and follicular cancers were also performed.

For binary variables and for continuous coefficients a graph was prepared, in which a square was plotted for every study whose center projection on the underlying scale corresponded to the estimated OR. The size of the square was proportional to the inverse of the variance of the estimated beta. A diamond was used to plot the pooled odds ratio. Its center represents the odds ratio and the extremes show the 95% confidence interval. These graphs were similar to those used by the Collaborative Group on Hormonal Factors and Breast Cancer [26].

#### Summary data description

A total of 2,725 cases (2,247 females and 478 males) and 4,776 controls (3,699 females and 1,077 males) were included in the analyses. Since several of the studies included in this analysis had specific selection criteria, in terms of gender, age, and histological type, the description of the study population reflects these exclusions. The

distribution of cases by histology, study center and gender is shown in Table 3. Papillary thyroid carcinomas (including mixed papillary/follicular) were most common ( $n = 2149$ ; 79%), followed by follicular ones. Anaplastic ( $n = 17$ ; <1%), medullary ( $n = 63$ ; 2%), and cancers with other histologies ( $n = 32$ ; 1%) were rare. In studies that included men and women, the sex ratio (females:males) was over 3 for both papillary and follicular carcinomas, but lower for other histological types. The histological subtype was unknown for 88 (3.3%) cases.

The frequency distribution by age, and the median age of cases and controls, by gender and study, are given in Table 4. The median age of cases and controls was similar in most studies. Since in many studies the subjects included had to be in a given age range, the age distribution and the median age in the various studies reflect these selection criteria. Thus, the median age of female cases was lowest in Los Angeles and Shanghai (32

years) where only women under age 55 were considered. For most studies, the median age was between 40 and 49 years, and the Japanese study had the highest median age for both women (52 years) and men (53 years). Overall, we had for women over 500 cases in each of the first three categories, *i.e.*, below age 31, 31–40 and 41–50, over 400 cases aged 51 to 60, and over 250 cases aged 60 or more. Figure 1 gives the distributions of female and male cases according to age group and histology, which are strongly influenced by the eligibility criteria of the various studies. In women, the category with the highest number of cases is the age class 41 to 45. The higher frequencies were observed between 26 and 45 years for papillary carcinomas, and in the late forties and early fifties for follicular ones. The few anaplastic cancers were generally at older ages. In males, the age categories with largest number of cases were between 51 and 60 years, and both the distribution of papillary

Table 4. Distribution of cases and controls by center, gender and age at diagnosis: pooled analysis of thyroid cancer case-control studies

Study number and location	Gender	Age, years (cases:controls)					Median
		≤ 30	31–40	41–50	51–60	> 60	
America – USA							
1. Los Angeles	F	120:101	89:92	66:68	17:31	–:–	32:34
2. Western Washington	F	60:130	37:95	31:54	24:43	33:71	38:36
3. Hawaii	F	27:71	25:61	37:73	27:64	24:59	45:45
4. Connecticut	M	9:17	9:18	8:15	11:30	14:33	49:53
	F	22:60	32:52	19:40	15:30	21:26	41:38
	M	2:7	13:18	13:22	15:24	7:5	49:48
Asia							
5. Hiroshima and Nagasaki, Japan	F	11:10	53:54	76:76	104:105	63:62	52:52
	M	–:–	8:8	15:15	21:20	14:15	53:53
6. Shanghai, China	F	91:91	55:55	42:42	19:19	–:–	32:32
Europe – North							
7. Southeastern Sweden	F	17:38	38:45	45:57	49:47	–:–	45:43
	M	6:50	3:53	8:49	9:48	–:–	46:40
8. Uppsala, Sweden	F	26:40	33:48	31:51	25:37	18:27	42:42
	M	3:2	5:10	14:21	8:13	7:8	48:47
9. Northern Sweden	F	10:19	22:44	33:64	34:64	24:49	49:49
	M	4:8	12:21	9:15	13:26	10:15	47:47
10. Norway, NHSS	F	9:45	21:105	25:127	14:68	2:10	42:42
	M	2:10	9:45	4:20	5:24	1:6	38:38
11. Tromsø, Norway	F	14:33	13:31	13:33	12:25	6:16	43:43
	M	3:7	7:20	1:2	7:14	6:15	52:48
Europe – South							
12. Northern Italy	F	64:91	56:76	66:88	61:85	44:87	44:47
	M	21:39	18:41	25:42	25:38	19:30	46:45
13. Vaud, Switzerland	F	26:63	18:51	22:57	7:51	27:96	43:48
	M	3:20	5:29	6:18	6:20	3:7	46:40
14. Athens, Greece	F	14:29	20:27	21:19	13:17	14:4	44:37
	M	8:15	4:15	12:9	3:2	5:3	44:36
Total	F	511:821	512:836	527:849	421:686	276:507	42:43
	M	61:175	93:278	115:228	123:259	86:137	48:45

–, Not collected.

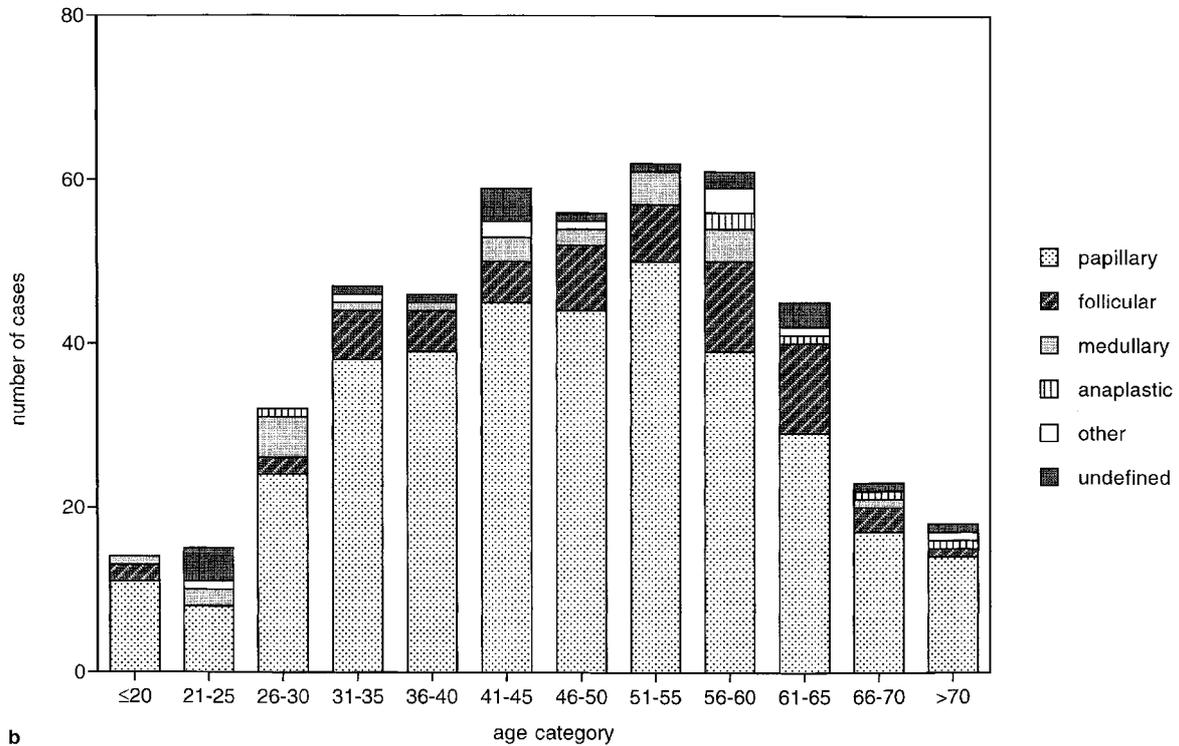
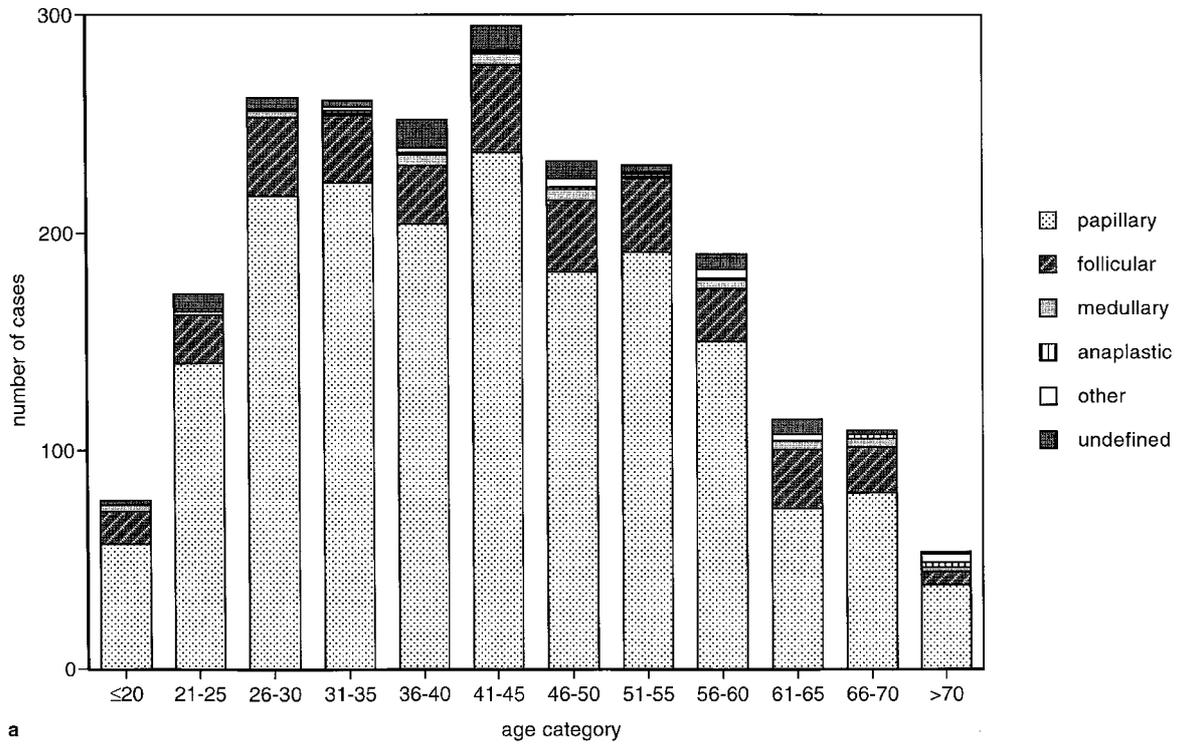


Fig. 1. Distribution of thyroid cancer cases included in the pooled analysis of thyroid cancer case-control studies according to age group and histology. (a) Females ( $n = 2,247$ ); (b) males ( $n = 478$ ).

and follicular cases appeared shifted to the right, as compared to females, and there was a higher proportion of anaplastic and medullary cancers.

The number of cases and controls with a history of external radiotherapy are shown by age at exposure in Table 5. It can be seen that study subjects from Sweden and the U.S. received radiotherapy more often than subjects from other countries and that cases reported radiation exposure more frequently than controls. Overall, 140 (6.2%) female cases and 24 (5.0%) male cases were exposed to radiotherapy, compared to 78 (2.1%) female and 18 (1.7%) male controls.

## Discussion

This paper describes the major characteristics of the studies included in a pooled analysis of thyroid cancer case-control studies, together with the methodology used to collect and analyze the data. The usefulness of

pooled analyses (based on original data) of observational epidemiologic studies is currently a topic of lively debate. Strengths and weaknesses of this approach have been discussed [25, 27–29]. A pooled analysis allows systematic comparison of the data from several studies without the problems of different variable categorization, methods of data analysis, and presentation. It also allows assessment of rare exposures, analysis of subgroups, and evaluation of interactions across variables. Moreover, in a pooled analysis, unpublished studies and variables which were not analyzed earlier can be examined. The large number of cases increases the power to identifying factors, *i.e.*, associations suggested by one study can be strengthened, and weak but relatively consistent associations can be clarified and better quantified. Confirmation of negative results is also a benefit, particularly when dealing with a rare cancer site such as the thyroid.

A degree of heterogeneity across studies is of course expected, given the substantial differences in popula-

Table 5. Distribution of cases and controls by center, gender and age at first external radiation treatment exposure

Study number	Gender	Not treated	Age at treatment		
			< 20	≥ 20	Unknown
America – USA					
1. Los Angeles	F	259:283	25:2	6:6	2:0
2. Western Washington	F	147:379	21:3	13:10	4:0
3. Hawaii	F	–:–	–:–	–:–	–:–
	M	–:–	–:–	–:–	–:–
4. Connecticut	F	92:198	6:6	3:3	1:0
	M	39:74	5:1	3:0	0:0
Asia					
5. Hiroshima and Nagasaki, Japan	F	302:305	5:2	0:0	0:0
	M	57:57	1:1	0:0	0:0
6. Shanghai, China	F	–:–	–:–	–:–	–:–
Europe – North					
7. Southeastern Sweden	F	141:177	3:2	4:3	1:5
	M	23:195	2:1	0:4	1:0
8. Uppsala, Sweden	F	129:198	2:1	2:4	0:0
	M	35:54	1:0	1:0	0:0
9. Northern Sweden	F	114:236	2:0	7:3	0:1
	M	47:82	1:0	0:3	0:0
10. Norway, NHSS	F	–:–	–:–	–:–	–:–
	M	–:–	–:–	–:–	–:–
11. Tromsø, Norway	F	55:138	1:0	2:0	0:0
	M	24:58	0:0	0:0	0:0
Europe – South					
12. Northern Italy	F	279:412	0:0	0:0	12:15
	M	105:186	0:0	0:0	3:4
13. Vaud, Switzerland	F	91:311	0:0	0:0	9:7
	M	21:91	0:0	0:0	2:3
14. Athens, Greece	F	73:91	1:0	8:5	0:0
	M	28:43	1:0	3:1	0:0
Total	F	1682:2728	66:16	45:34	29:28
	M	379:840	11:3	7:8	6:7

–, Variable not collected.

tions studied and methods employed. The presence of heterogeneity may be valuable, since the effort to explain the observed differences among studies may lead to a better understanding of the subject. When analyzing the data in strata of age, geographical region, etc., it must be kept in mind that the influence of the participating studies in different strata may vary. The pooled risk estimates, in fact, essentially are weighted averages of the estimates from the various studies, and reflect, therefore, the different sizes of exposures and populations. We have chosen to give a pooled estimate regardless from the result of the heterogeneity test between studies, since there is no clear cutoff point below which heterogeneity can be ignored. For every estimate, however, the degree of heterogeneity between the studies that concurred in forming it has been quantified, and taken into account in the discussion of results. The analysis in separate strata of geographical area, study design and age at diagnosis can also reveal whether these variables may explain at least part of the heterogeneity between studies.

The studies considered in the present analysis generally included only a few hundred subjects, and the entire dataset is not much larger than one big study of other more common cancers, e.g., breast cancer. Thus, random variation is more influential in this pooled analyses than would be found in analyses based on larger or more studies [26]. Consequently, while this analysis can contribute important and new information of thyroid cancer risk factors, it cannot provide conclusive evidence on many topics. Despite these limitations, this study substantially improves our knowledge of the epidemiology of thyroid cancer.

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