SHORT COMMUNICATION

Reproductive factors and risk of thyroid cancer. A prospective study of 63,090 women from Norway

L.A. Akslen¹, S. Nilssen² & G. Kvåle²¹Department of Pathology, The Gade Institute, and ²Department of Hygiene and Social Medicine, University of Bergen, Bergen, Norway.

Summary This prospective study of 63,090 Norwegian women with 124 cases of thyroid cancer diagnosed during 1961–1989 revealed no strong associations with reproductive factors. Late last birth was related to increased risk, whereas no association was noted with parity. A long reproductive period was related to increased risk of papillary carcinomas, whereas a decreased risk of follicular carcinomas and other adenocarcinomas was observed in women with early menarche and late menopause. The risk of thyroid cancer was significantly increased among women in the occupational category 'fishing, ships officers and crew'. Our results are consistent with a modest effect of certain reproductive factors upon thyroid cancer development.

A striking female predominance is present in most series of differentiated thyroid carcinomas, especially below the age of 50 years (Cady *et al.*, 1976; Akslen *et al.*, 1990). Hormonal or other factors related to reproduction may, in part, explain this sex difference. Previous case-control studies have suggested that certain reproductive variables may influence the development of thyroid cancer (McTiernan *et al.*, 1984; Ron *et al.*, 1987; Preston-Martin *et al.*, 1987; Franceschi *et al.*, 1990a). In autopsy studies, no significant sex and age contrasts in the frequency of occult microcarcinomas seem to be present (Fukunaga & Yatani, 1975), and these findings suggest that hormones may influence the growth of such early lesions in some patient groups. To further explore the etiology of thyroid cancer, associations with reproductive variables have been examined in a prospective study of Norwegian women.

Materials and methods

In connection with a screening program for breast cancer in Norway in 1956–1959, detailed data on reproductive factors were collected through personal interviews. The cohort and the methods of follow-up and statistical analysis have previously been described in detail (Kvåle *et al.*, 1987). Of 85,063 women aged 32–74 years by 1 January, 1961 in the three counties of Nord-Trøndelag, Aust-Agder and Vestfold, 63,090 women attended the screening program and were interviewed. The official registration number served as a unique identification of the record for each woman and was used to link follow-up information to our files. Complete information concerning emigrations and deaths was obtained from the Central Bureau of Statistics. Data on cancer registrations, including date of diagnosis and histological type, were supplied by the Cancer Registry of Norway.

A total of 124 cases of thyroid cancer (ICD 7th Revision, 194) were diagnosed during the follow-up period from 1 January, 1961 through 1989. Of these, 50 cases were originally reported as papillary carcinomas, whereas 48 were coded as follicular carcinomas or adenocarcinomas, not otherwise specified. In the remaining group of 26 patients, 12 medullary

carcinomas, poorly differentiated carcinomas, other histological types and cases without histological confirmation were present. The histological slides were, however, not reviewed for this study. Separate analyses were carried out for the two largest histological groups.

On the basis of the total number of cases included in any particular analysis, the expected number was found for each level of the study variable, assuming no association with cancer (Thomas & Gart, 1983). Of the 63,090 participants, 25,783 died and 139 emigrated in the period 1961–1989. Times of death and emigration were taken into account in the calculation of expected numbers (Tarone, 1975). The analyses were adjusted for age at the start of follow-up (with 5-year age groups), county and in special cases other demographic and reproductive variables. The adjustments were made by forming a stratum for each combination of covariables. The analyses also produced two-tailed *P*-values for linear trend. *Stratified logistic regression* analyses were carried out according to the procedure described by Thomas and Gart (1983). In the estimation procedure, a correction for death and emigration was introduced by decreasing the initial number at risk by half the number of such events occurring among those who did not develop thyroid cancer. Due to missing values for certain reproductive variables, the number of cases varied somewhat between analyses.

The majority of the women aged 49 years or less at the start of the follow-up were premenopausal at the time of interview. Consequently, the information on number of births will be incomplete for some participants in this age category. Therefore, in addition to the analyses that included all age groups, separate analyses were performed based on the participants aged 49 years or less and those aged 50 or more at the start of follow-up. Separate analyses were also carried out in subgroups according to age at diagnosis, ≤ 54 , 55–69, ≥ 70 years.

Results

Demographic factors

Table I shows the distribution of cases according to demographic variables. The risk of thyroid cancer was highest in the counties of Aust-Agder and Trøndelag, whereas no urban/rural gradient was observed. Increased risk was observed in the occupational category *fishing, ships officers, crew* (odds ratio estimate, based on stratified logistic regression: 2.14, 95% CI: 1.30–3.54 for the total series).

Table I Distribution of respondents, observed number of cases with thyroid cancer and observed/expected ratio by demographic variables

	Respondents	O	Total O/E ^a	Papillary carcinomas		Follicular carcinomas Adenocarcinomas	
				O	O/E ^a	O	O/E ^a
Total series	63,090	124	1.00	50	1.00	48	1.00
Place of residence:							
Urban	13,355	26	1.04	11	1.13	7	0.70
Rural	49,735	98	0.99	39	0.97	41	1.08
County:							
Vestfold	27,627	42	0.77	14	0.63	19	0.90
Aust-Agder	13,780	34	1.25	15	1.39	12	1.13
Nord-Trøndelag	21,683	48	1.13	21	1.23	17	1.04
Occupational category: ^b							
Fishing, ship officers, crew	5,361	19	1.92	7	1.83	8	2.01
Other and unspecified	57,729	105	0.92	43	0.93	40	0.91

^aAdjusted for age at start of follow-up and county. ^bOwn or husband's occupation.

Reproductive factors

There were no statistically significant associations between reproductive variables and risk of thyroid cancer (Table II). However, *late last birth* was associated with increased risk on the border of statistical significance ($R = 1.7$; $P = 0.06$). This association was strongest for the papillary type. *Parity* was not associated with thyroid cancer in this cohort. However, an upper 95% confidence limit of 1.5 for the odds ratio estimate for women with ≥ 3 vs 1–2 births is still consistent with a certain adverse effect. In addition, the relative odds estimate tended to increase among the older part of the cohort (Table III). The interaction between parity and age at start of follow-up was statistically significant. *Late menar-*

Table III Occurrence of thyroid cancer by parity in subgroups according to age at start of follow-up and age at diagnosis

	Number of cases	Odds ratio Parity: ≥ 3 vs 1–2	(95% C.I.)
Total	97	1.01	(0.67–1.52)
Age at start of follow-up ^a			
< 50	55	0.65	(0.37–1.17)
≥ 50	42	1.75	(0.91–3.37)
Age at diagnosis			
≤ 54	18	0.86	(0.31–2.37)
55–69	40	1.00	(0.53–1.90)
≥ 70	41	1.11	(0.59–2.09)

^aTest for interaction with age at start of follow-up: $P = 0.03$.

Table II Occurrence of thyroid cancer by parity, abortions, age at first and last birth and age at menarche and menopause. Observed (O) number of cases, observed/expected ratio (O/E) and relative odds estimate (R) by histological groups

	Total		Papillary carcinomas		Follicular carcinomas Adenocarcinomas	
	O	O/E	O	O/E	O	O/E
Parity ^a : Nulliparous	23	1.02	11	1.20	8	0.91
Parous	97	1.00	39	0.96	38	1.02
R (parous vs nulliparous with 95% CI)	0.97	(0.61–1.54)	0.79	(0.40–1.56)	1.12	(0.52–2.41)
Parity ^b : 1–2	51	1.00	19	0.91	18	0.90
≥ 3	46	1.01	20	1.10	20	1.11
R (parity ≥ 3 vs 1–2 with 95% CI)	1.01	(0.67–1.52)	1.21	(0.64–2.32)	1.25	(0.64–2.41)
Abortions ^c : 0	96	1.02	43	1.06	34	0.99
≥ 1	22	0.94	7	0.73	10	1.05
R (≥ 1 abortions vs 0 with 95% CI)	0.91	(0.57–1.46)	0.67	(0.29–1.51)	1.08	(0.52–2.22)
Age at first birth (years) ^d : ≤ 24	36	1.03	13	0.91	18	1.27
≥ 25	55	0.98	23	1.06	17	0.82
R (age at first birth ≥ 25 vs ≤ 24 with 95% CI)	0.96	(0.61–1.50)	1.19	(0.57–2.49)	0.60	(0.30–1.23)
Age at last birth (years) ^e : ≤ 34	29	0.81	9	0.71	15	0.86
≥ 35	38	1.23	16	1.30	14	1.21
R (age at last birth ≥ 35 vs ≤ 34 with 95% CI)	1.71	(0.99–2.95)	2.17	(0.86–5.51)	1.52	(0.67–3.44)
Age at menarche (years) ^f : ≤ 13	32	0.96	19	1.30	8	0.66
14	44	1.15	19	1.16	13	0.92
≥ 15	42	0.91	12	0.63	23	1.30
R ² (age at menarche ≥ 15 vs ≤ 13 with 95% CI)	0.94	(0.60–1.48)	0.50	(0.25–1.00)	2.01	(0.92–4.40)
Age at menopause (years) ^g : ≤ 47	17	1.25	5	0.97	10	1.90
48–51	13	0.67	6	0.81	4	0.47
≥ 52	12	1.32	5	1.48	4	0.95
R ² (age at menopause ≥ 52 vs ≤ 47 with 95% CI)	0.95	(0.40–2.27)	1.58	(0.38–6.51)	0.31	(0.08–1.26)

^aAmong women with known parity, adjusted for age at start of follow-up and county. ^bAmong parous women with known parity, adjusted for age at start of follow-up and county. ^cAmong women with known number of abortions and parity, adjusted for age at start of follow-up, county and parity. ^dAmong parous women with known parity and age at first birth, adjusted for age at start of follow-up, county and parity. ^eAmong parous women with ≥ 2 births and known age at last birth, adjusted for age at start of follow-up, county and parity. ^fAmong women with known parity and age at menarche, adjusted for age at start of follow-up, county and parity. ^gAmong women with known parity and age at menopause, adjusted for age at start of follow-up, county and parity.

che was significantly related to decreased risk of papillary carcinomas, whereas the reverse was indicated for patients with follicular carcinomas and adenocarcinomas. This difference in effect according to histological type was statistically significant ($P = 0.01$). A similar, although not statistically significant difference ($P = 0.11$) was observed in the effect of age at menopause according to histological type. Thus, a long reproductive period (early menarche and late menopause) was related to increased risk of papillary carcinomas and decreased risk of follicular carcinomas and adenocarcinomas.

Additional adjustment for occupational category did not change the odds ratio estimates markedly.

Discussion

The marked female excess among differentiated thyroid carcinomas indicate that reproductive factors may be of importance for tumour development. In some recent case-control studies, high parity and abortions as well as use of oestrogen-containing preparations and lactation suppressants have been associated with increased risk (McTiernan *et al.*, 1984; Ron *et al.*, 1987; Preston-Martin *et al.*, 1987; Franceschi *et al.*, 1990a).

In this prospective study of reproductive factors and thyroid cancer, a large number of women were followed for more than 29 years, but the number of cases occurring was still rather small. No significant associations with reproductive variables like parity and age at first birth were observed, in contrast to earlier case-control studies, where parous women have been found to have an increased risk (McTiernan *et al.*, 1984; Ron *et al.*, 1987; Preston-Martin *et al.*, 1987; Franceschi *et al.*, 1990a). However, a non-significant positive association was noted in the older part of the cohort, and the confidence intervals for the odds ratio estimate in the total cohort is consistent with a moderate adverse effect. Further, a positive association with late last birth give some support to similar results presented by Franceschi *et al.* (1990a). Since

information on number of births was incomplete for some of the participants aged less than 50 years at the start of follow-up, we cannot exclude the possibility that misclassification may influence the results in this age group. However, analyses of relationships with parity for other cancers did not reveal any notable differences in estimates between the older and the younger part of the cohort (Kvåle *et al.*, 1987; Kvåle *et al.*, 1988).

The observation in our data that a long reproductive period was associated with increased risk of papillary and a decreased risk of follicular and other adenocarcinomas indicate that oestrogens may influence the two main histological groups differently. However, the histological slides were not reviewed and some misclassification may be expected (Franssila & Saxén, 1972). The results according to histological type should therefore be cautiously interpreted.

Women in the occupational category *fishing, ships officers and crew* were at increased risk of thyroid cancer. Previously, some reports (Ron *et al.*, 1987; Glatte *et al.*, 1990), but not all (Franceschi *et al.*, 1990b), have indicated that high consumption of fish may be a risk factor.

In conclusion, our results are consistent with the hypothesis that certain reproductive factors influence the occurrence of thyroid cancer and may thus, at least in part, explain the marked sex difference. However, larger studies are clearly needed to establish more precisely the magnitude of these associations.

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Note added in proof

Another Norwegian study on this subject has recently been published (Kravdal, Ø., Glatte, E. & Haldorsen, T. (1991)). Positive correlation between parity and incidence of thyroid cancer. *Int. J. Cancer*, 49, 831–836.

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