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Thyroid Cancer after X-ray Treatment of Benign Disorders of the Cervical Spine in Adults

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While there is very good epidemiological evidence for induction of thyroid cancer by radiation exposure in children, the risk for adults after exposure is still uncertain, especially when concerning relatively small radiation doses. A cohort of 27415 persons which in 1950 through 1964 had received x-ray treatment for various benign disorders in the locomotor system (such as painful arthrosis and spondylosis) was selected from three hospitals in Northern Sweden. A proportion of this cohort, consisting of 8144 persons (4075 men and 4069 women), had received treatment to the cervical spine and thereby received an estimated average dose in the thyroid gland of about 1 Gy. Standard incidence rates (SIR) were calculated by using the Swedish Cancer Register. In the cervical spine cohort, 22 thyroid cancers were found versus 13.77 expected (SIR 1.60; CI 1.00–2.42). The corresponding figures for women were 16 observed cases versus 9.60 expected cases (SIR 1.67; CI 0.75–2.71). Most thyroid cancers (15 out of 22) were diagnosed >15 years after the exposure. In the remaining part of the total cohort, i.e. those without cervical spine exposure, no increased risk of thyroid cancer was found (SIR 0.98; CI 0.64–1.38). The study strongly suggests that external radiation exposure of adults at relatively small doses increases the risk of thyroid cancer but also that this increase is very much lower than that reported after exposure in children.

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That the thyroid gland in children is particularly sensitive to carcinogenic effects has been demonstrated in several epidemiologic studies which concern both exposure to external radiation (A-bomb survivors, exposure to x-ray therapy for various benign conditions) and to internal radiation from radioiodine nuclides (the Chernobyl accident). The findings have been summarized in several recent reviews (1–4).

The risk of thyroid cancer after radiation exposure in adults is considerably less well documented. Large cohorts of adults exposed to diagnostic or therapeutic activities of ^{131}I have so far failed to show an increased risk of thyroid cancer (5). Concerning external radiation exposure in adults, it is obvious that large doses in the order of 40 Gy given as mantle treatment for Hodgkin's disease substantially increase the risk of thyroid cancer (6). However, owing to the partial destruction of the thyroid tissue, doses of this magnitude often cause overt or subclinical hypothyroidism (6) and it is possible that increased thyrotropic stimulation in combination with the mutagenic effect of the radiation has played a role in the development of thyroid cancer. More interesting from a general radiation protection point of view is the question of whether relatively small doses can increase the risk of thyroid cancer. Epidemiologically useful data on adult exposure with relatively small doses of external radiation are only available in two studies, one concerning atomic bomb survivors (7) and the other one a large international cohort of patients treated with radium for uterine cervical cancer (8). In the A-bomb cohort no significant excess risk of thyroid cancer was found among persons above 20 years of age at the time of the study (7) but further analyses nevertheless suggested a dose-response relation (4). Similar evidence was found in the large international cohort study of second cancers following radiation treatment for cervical cancer (8). A case-control study within this cohort was performed in order to assess individual radiation doses (9). A non-significant twofold risk of thyroid cancer was then found; the estimated average dose in this study was of 0.11 Gy (range 0.01–0.24). The mean thyroid dose in the A-bomb cohort was estimated to 0.26 Gy (range 0.01–3.99).

In our paper we report on a cohort of persons who during the period 1950 through 1964 in adult age (>15 years) had been given x-ray treatment for benign conditions in the cervical spine and thereby received a rather well-defined radiation dose in the thyroid gland at an average of about 1.0 Gy.

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MATERIAL AND METHODS

Up to the beginning of the 1960s it was quite common in Sweden to treat painful conditions in the locomotor system (mainly arthrosis and spondylosis) with x-rays in doses in the order of a few Gy. To study the possible risk of cancerogenic effects of this type of treatment a cohort of 20800 persons was collected from two hospitals in northern Sweden. In this cohort the mean absorbed red bone marrow dose and the risk of various haematological malignancies were calculated and reported (10, 11). This cohort now been increased by about 7700 persons from a third hospital in northern Sweden. Information about personal identification and treatment for the whole cohort was obtained from the original treatment records held at each hospital. The person data had to be supplemented with the Swedish 10-digit person number in order to accomplish computer linkage with the Swedish Cancer Register and the Swedish Cause of Death Register. Complete person numbers could not be found for 691 persons and these were therefore withdrawn from the study. A search for the remaining persons in the cohort (97%) was conducted in the National Population Register and the Swedish Cause of Death Register to find out whether they were still alive and currently living in Sweden. A total of 328 persons could not be found in any of these registers and they were therefore also withdrawn from the study. These persons had either died before 1952 or had emigrated from Sweden before 1996. The final cohort therefore comprised 27415 patients (7529, 12467 and 7419 from the hospitals in Umeå, Gävle and Skellefteå, respectively).

A subcohort of patients who had received roentgen treatment for symptoms of the cervical spine consisted of 8144 persons (4075 men and 4069 women) and constituted the main material for the present study. The mean age at exposure in this subcohort was 53 years (similar in men and women), 82% being 40–69 years of age and none were aged under 15 years (Table 1). The remaining 19271 persons in the cohort had treatment fields which did not include the thyroid gland. This part of the cohort served as an internal control to the group that had received treatment of the cervical spine.

Table 1

Age at exposure

Age (years)	The whole exposed cohort	Thyroid cancer cases
15–39	931 (11%)	2 (9%)
40–49	2137 (26%)	7 (32%)
50–59	2912 (36%)	11 (50%)
60–	2164 (27%)	2 (9%)
Total	8144 (100%)	22 (100%)

The radiation dose

The radiation treatment of the cervical spine was fairly standardized. The x-rays were given using 180–200 kV machines, a focus-skin distance of 50 cm and a filter, which resulted in a half-value lager of 1–3 mm Cu. The treatment was given through a rectangular dorsal field measuring typically 10×15 cm^2 and with a sagittal beam direction, which meant that the whole thyroid gland or at least the main part of it was in most cases included in the primary beam. A treatment series usually consisted of three treatments given at intervals of 2–3 days and a skin dose at each treatment of 100–200 R. Some patients received more than one treatment series, usually at intervals of at least one year. Of the patients who exclusively were given treatment of the cervical spine, 84% had received one treatment series, 13% two series and the remainder three or more series. The absorbed dose in the thyroid depends on both the irradiation parameters and the anatomy of the patient. For estimation of the absorbed dose in the thyroid, it was assumed that, for all patients, the thyroid was located at a depth of 13 cm seen from the posterior direction (12). The absorbed dose at 13 cm depth is taken from the literature (13). Based on irradiation data from 30 randomly selected patients receiving radiation treatment of the cervical spine, a dose conversion factor in terms of thyroid dose per unit skin dose was derived. It was found that the thyroid dose was on average 19% of the skin dose, which corresponds to a dose conversion factor of 1.38 mGy/R. In order to estimate the thyroid dose for each individual in the cohort, this conversion factor is applied to the registered skin dose.

Statistical and epidemiological methods

The number of observed thyroid cancer cases (ICD-7 = 194) for the period 1958–1995 was obtained from the Swedish Cancer Register by computer matching. A similar linkage was also performed using the Swedish Cause of Death Register for the period 1952–1995 to obtain date of death for deceased persons. No register information on cancer incidence data is available before 1958 in Sweden. Therefore a total of 192 persons who had died before 1958 were excluded from the cohort incidence analyses.

The person-years were calculated from the time of first treatment to the date of diagnosis or death, or until the closing date, 31 December, 1995, using the program PYRS (14). Age and calendar year were used as stratification variables in the calculation of person-years. Age was defined by 5-year strata and calendar time by 1-year strata. The expected number of cases was calculated by multiplying the sex, age and calendar-specific incidence rates in the reference population by the corresponding numbers of person-years in the cohort. Separate reference populations were used in the analyses: the county of Västerbotten for patients treated in Umeå and Skellefteå and the county of

Table 2

Risk of thyroid cancer

Cohort	Person years	No. observed	No. expected	SIR	95% CI
Cervical spine cohort	180 399	22	13.77	1.60	1.00–2.42
Men	81 721	6	4.17	1.44	0.52–3.12
Women	98 678	16	9.60	1.67	0.75–2.71
Age at first exposure					
<50 y	90 993	9	5.69	1.58	0.72–3.00
≥50 y	89 406	13	8.09	1.61	0.85–2.75
Time after first exposure					
0–15 y	91 346	7 *	5.83	1.20	0.48–2.47
>15 y	89 053	15	7.94	1.89	1.06–3.12
Total cohort excluding those with cervical spine irradiation	412 922	29	30.28	0.98	0.64–1.38

* One case diagnosed within 2 years.
Abbreviations: SIR = standard incidence ratio; CI = confidence interval.

Gävleborg for those treated in Gävle. The standardized incidence ratio (SIR) was defined as the ratio between observed and expected number of cases.

Analyses in this study were also performed using the patients treated in other locations than the cervical spine as a referent group, i.e. an internal comparison. These calculations were made using a multiplicative Poisson regression model with sex and age at first treatment as covariates. This analysis made it possible to investigate the risk of thyroid cancer resulting from treatment of the cervical spine compared to treatment of all other sites, adjusted for sex and age classes of 0–30, 30–40, 40–50, 50–60, 60–70 and 70–99 years.

RESULTS

The total number of person-years at risk in the cervical spine cohort was 81721 for men and 98678 for women. During 1958 through 1995 a total of 22 thyroid cancers in this cohort had been reported to the Swedish Cancer Register compared with 13.77 expected cancers (SIR = 1.60; 95% CI = 1.00–2.42; Table 2) and the excess relative risk per 1 Gy (ERR/Gy) was 0.58. The corresponding figures for females only were 16 thyroid cancers compared with 9.6 expected cancers (SIR = 1.67; 95% CI 0.95–2.71) and ERR /Gy was 0.65. Most thyroid cancers occurred more than 15 years after the exposure, 15 cases compared with the 7.94 expected (SIR = 1.89; 95% CI = 1.06–3.12; Table 2). Sixteen of the 22 thyroid cancers in the cervical spine cohort were differentiated papillary and/or follicular carcinomas.

In the remaining part of the total cohort (i.e. excluding those receiving treatment of the cervical spine) there was no excess of thyroid cancer (29 observed versus 30.28 expected). When this part of the total cohort was used as the referent, the relative risk for thyroid cancer in the cervical spine cohort was 1.64 (95% CI = 0.94–2.85).

DISCUSSION

It is well documented that the thyroid gland is sensitive to carcinogenesis by radiation (3). In a pooled analysis of five studies with persons below 15 years of age at exposure an estimated ERR/Gy of 7.7 (95% CI = 2.1–28.7) was found (4). The epidemiological findings convincingly show, however, that age at exposure influences the risk remarkably (15). This is especially well demonstrated by the large A-bomb cohort, in which there was a dramatic drop in risk with increasing age at exposure from 0 up to 30 years of age (16). No excess risk of thyroid cancer was found among persons above 20 years at exposure in that cohort. It has actually been difficult to obtain definite proof of the existence of radiation-induced thyroid carcinoma after exposure to relatively small doses in adult age (15).

A cohort that could have given excellent information is the well-known British series of patients treated with x-rays for ankylosing spondylitis (17, 18). Many of these patients received treatment of the cervical spine with doses often considerably higher than those used in the present series. However, probably owing to the lack of cancer incidence registers for the relevant observation period, only the mortality data have been published and as the mortality rate from thyroid cancer is low, it is not mentioned among the cancers in heavily irradiated sites. In questionnaire-based case-control studies, an increased risk of thyroid cancer after very low radiation doses has sometimes been reported (19). However, this type of study is unreliable because of recall bias when it concerns common exposures such as dental x-rays and chest x-rays. In a case-control study where the x-ray exposure was reasonably well reconstructed from radiology records from different hospitals, no increased risk of thyroid cancer could be demonstrated (20). This fits well with the findings in the present study; assuming a linear dose-response relation, it is unlikely that effects of the very small radiation doses

from ordinary diagnostic x-ray examinations could be epidemiologically demonstrable.

The results in the present study suggest that external radiation exposure increases the risk of thyroid cancer also in adults, but to a much lower degree than in children. The estimated risk per Gy in the present cohort seems to be of the same order of magnitude as that in the A-bomb cohort. Very likely, the risk after small and medium radiation doses is linearly proportional to the dose, but within the present cohort the exposure was too uniform to allow a study of the dose-response relationship.

Thyroid cancer is often a slow-growing tumour which may be detected incidentally, for instance at health controls. The patients in the present study, however, were initially treated for a benign condition (usually cervical spondylosis) and not subjected to any regular clinical follow-up. It seems unlikely that the finding in this study of an increased risk of thyroid cancer was a 'screening effect'.

For official radiation protection recommendations the International Commission on Radiological Protection (ICRP) has estimated the risk for radiation-induced cancer in a number of different organs (21). For the thyroid, the ICRP estimated that the total lifetime absolute risk for fatal cancer for an absorbed dose of 1 Gy, is 6×10^{-4} for adults. Applying this factor with a fatality rate of 0.1, this would lead to an incidence of 59 thyroid cancers in the present cohort. The ICRP has, in this case, taken the data from the NCRP Report No. 80 (22), which gives an estimate of 1.26 excess cases per 10^6 person-years and Gy after exposure in adults. This assumption would in the present cohort give 27 extra cases compared with the 8 extra cases actually found.

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