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ORIGINAL ARTICLE

Dental x-rays and the risk of thyroid cancer: A case-control study

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Abstract

The thyroid gland is highly susceptible to radiation carcinogenesis and exposure to high-dose ionising radiation is the only established cause of thyroid cancer. Dental radiography, a common source of low-dose diagnostic radiation exposure in the general population, is often overlooked as a radiation hazard to the gland and may be associated with the risk of thyroid cancer. An increased risk of thyroid cancer has been reported in dentists, dental assistants, and x-ray workers; and exposure to dental x-rays has been associated with an increased risk of meningiomas and salivary tumours. *Methods.* To examine whether exposure to dental x-rays was associated with the risk of thyroid cancer, we conducted a population-based case-control interview study among 313 patients with thyroid cancer and a similar number of individually matched (year of birth ± three years, gender, nationality, district of residence) control subjects in Kuwait. *Results.* Conditional logistic regression analysis, adjusted for other upper-body x-rays, showed that exposure to dental x-rays was significantly associated with an increased risk of thyroid cancer (odds ratio = 2.1, 95% confidence interval: 1.4, 3.1) (p = 0.001) with a dose-response pattern (p for trend < 0.0001). The association did not vary appreciably by age, gender, nationality, level of education, or parity. *Discussion.* These findings, based on self-report by cases/controls, provide some support to the hypothesis that exposure to dental x-rays, particularly multiple exposures, may be associated with an increased risk of thyroid cancer; and warrant further study in settings where historical dental x-ray records may be available.

The thyroid gland is highly susceptible to radiation carcinogenesis and exposure to high-dose ionising radiation, particularly in childhood and adolescence, is the only established environmental cause of thyroid cancer [1–3]. Evidence for an association between exposure to high-dose ionising radiation and thyroid cancer has come from studies of children who had received x-ray treatment, for benign conditions such as enlarged tonsils or thymus gland, haemangioma, ringworm of the scalp (*tinea capitis*), skin disorders, and painful arthrosis and spondylosis of the cervical spine [1,4]. Similar evidence has also come from radiation treatment of children with a range of malignancies, where the treatment field included the thyroid. Important additional evidence has come from the study of Japanese survivors of the American atomic bombs of 1945 and the Chernobyl nuclear power plant accident in 1986 [2,5].

For the general population, medical diagnostic x-rays of the head and neck, particularly dental x-rays, are an important source of ionising radiation to the thyroid gland. The anatomic position and the relatively high radiosensitivity of the thyroid gland make it an organ of concern in dental radiography. Given the high lifetime prevalence and frequency of exposure to dental x-rays, even a small increase in thyroid cancer risk would be of considerable public health importance. At present, there is limited epidemiological data on thyroid cancer risk associated with low-dose radiation exposures from common diagnostic x-rays. Low-dose radiation has been associated with thyroid dysfunction such as thyroid autoimmunity among young females, thyroid cysts in females of all ages [6], and papillary thyroid cancer in younger women [7]. In several studies, dental radiography has also been associated with an increased risk of

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meningioma [8–11], brain cancer [12,13], tumours of the parotid gland [1,10,14,15] and breast cancer [16]. An increased risk of thyroid cancer has also been reported in dentists/dental assistants [7,17], diagnostic x-ray workers [18–20] and radiologic technologist [21] suggesting that multiple low-dose exposures in adults may also be important.

The incidence of thyroid cancer has increased in many countries over the past 30 or so years [22–24]. Much of this increase is probably due to increased ascertainment of subclinical cases, but other contributing factors should be considered. In most populations, thyroid cancer accounts for approximately 1–6% of all cancers in females and <2% in males; the World age-standardised incidence rates (per 100 000 population) vary from about 1–23 in females and 0.5–6 in males [25]. Since the late 1970s, thyroid cancer has consistently been the second most commonly recorded neoplasm (after breast) among Kuwaiti women. During the period 1998–2002, it accounted for 7.3% of all cancers among Kuwaiti and 6.3% among non-Kuwaiti (expatriate) women. The average annual World age-standardised incidence rate (per 100 000 population) was 7.3 in Kuwaiti and 5.0 in non-Kuwaiti women. Similarly high relative frequency and rates of thyroid cancer among women have also been reported from other Arab countries in the Gulf region (Bahrain, Oman, Qatar, Saudi Arabia, United Arab Emirates) [26].

We conducted a population-based case-control study in Kuwait to examine major aetiological hypotheses for thyroid cancer. In this report, we aimed to assess the hypothesis that dental radiography, a common source of radiation exposure in the general population that is often overlooked as a source of radiation to the gland, may be associated with the risk of thyroid cancer.

Subjects and methods

Study population

The study population and methods are described in detail elsewhere [26,27]. In brief, Kuwait has a population of about 2.8 million people and a government-funded national health service that includes all residents. Health care at all levels, including dental services, is provided by the Ministry of Health. For administrative purposes, the country is divided into six governorates; which are sub-divided into residential districts. Medical services in each governorate comprise a network of primary health care clinics (at least one in each district) and a general hospital. Dental treatment is provided free of charge through a network of general and specialist dental care clinics, and dental radiography is widely used. In addition, there are a number of speciality hospitals, including the Kuwait Cancer Control Centre (KCCC); which provides cancer treatment and follow-up services to the whole population. Due to the relatively high incidence of thyroid cancer in Kuwait, a special follow-up clinic is held every week at the centre for thyroid cancer patients. A population-based cancer registry (the Kuwait Cancer Registry), established at the centre since 1979, regularly contributes data to the monograph *Cancer Incidence in Five Continents* compiled by the International Agency for Research on Cancer [25].

Thyroid cancer patients were identified from the records of the population-based Kuwait Cancer Registry. Cases were defined as patients with a primary thyroid cancer, entered in the cancer registry using the International Classification of Diseases for Oncology (ICD-O) topography codes (C73), who were alive, aged ≤70 years, and resident in the country. The district of residence was determined for each thyroid cancer patient and a suitably matched population control subject was selected from the corresponding local primary health care clinic. Kuwait has a distinctive network of primary care clinics in terms of accessibility and the wide range of services offered; and all residents in the district have an equal opportunity to visit the local clinic [27]. One control subject was individually matched to each thyroid cancer patient, based on year of birth (±three years), gender, nationality, and district of residence. Subjects were considered eligible to serve as controls if they were visiting the primary care clinic for minor complaints (upper respiratory tract infection, skin rash/infection, acute gastrointestinal complaints, headache, back/joint pain, minor trauma/injuries and lower urinary tract infection) or accompanying such persons (e.g., a person accompanying child/spouse/friend) or visiting for any other purpose (e.g., travel vaccinations, to collect medication). The study finally included 313 patients with thyroid cancer and 313 individually matched control subjects.

Exposure assessment and statistical analysis

The study protocol was approved by the respective ethics committees in KCCC and Kuwait University. Informed consent was obtained from all participants. A bilingual female interviewer, proficient in Arabic and English languages, and not aware of the epidemiology of thyroid cancer, obtained information from all the participants through a personal interview. The data were recorded in a structured questionnaire which included information on: (*i*) sociodemographic characteristics; (*ii*) gynaecological and reproductive history; (*iii*) medical history (including exposure to diagnostic x-rays of head, neck, and chest, dental x-ray, radiotherapy, and number of exposures); (*iv*) family history (including thyroid disease and cancer); (*v*) habitual diet (frequency of consumption of 13 dietary items); and (*vi*) clinical and histopathological information (abstracted from the records of the cancer registry and KCCC). The consistency of self-reported dental x-ray exposures was assessed in a validation study (using telephone interviews) which included a random sample of 49 cases and 42 controls. The participants of the validation study were also questioned about their age (<20 years or ≥20 years) at first dental x-ray exposure.

For each control subject a 'pseudo-diagnosis' date was determined – the date on which the subject was the same age as his/her matching case was at the time of diagnosis. The analysis of data on exposure to radiation was restricted to events before the diagnosis (cases) or pseudo-diagnosis (controls) date. We used conditional logistic regression methods to assess the association between exposure to dental x-rays and thyroid cancer risk. Results are presented as odds ratios (OR) with 95% confidence intervals (95% CI), adjusted for confounding variables where necessary. We also examined the dose-response pattern according to the number of exposures to dental x-rays. Subgroup analyses were conducted to determine the risk of thyroid cancer according to age (at the time of diagnosis), gender, nationality, level of education, parity, and histology. In this paper, all p-values are two sided, and statistical significance was determined at the $p<0.05$ level. Unless otherwise indicated, all statistical tests are based on the likelihood ratio test procedure; and for the trend in odds ratio are based on a χ^2 test for trend. All data management and analyses were performed using the SPSS and STATA statistical packages.

Table I. Distribution of 313 thyroid cancer patients in Kuwait by age at diagnosis, gender, nationality, and histology.

	No. (%)
Age at diagnosis (years)	
5–14	6 (1.9)
15–24	51 (16.3)
25–34	88 (28.1)
35–44	93 (29.7)
45–54	53 (16.9)
55–64	19 (6.1)
65–70	3 (1.0)
Gender	
Female	238 (76.0)
Male	75 (24.0)
Nationality	
Kuwaiti	172 (55.0)
Non-Kuwaiti (expatriates)	141 (45.0)
Arabs*	71 (50.4)
Southeast Asian	37 (26.2)
Bedouin Arabs†	28 (19.9)
Other	5 (3.5)
Histology	
Papillary	186 (59.4)
Papillary/follicular variant	75 (24.0)
Follicular	27 (8.6)
Medullary	3 (1.0)
Other	4 (1.3)
Unknown	18 (5.8)

*Arabs from Middle East and North Africa.
†"Stateless" Arabs resident in Kuwait.

Results

The distribution of 313 thyroid cancer patients (238 females, 75 males; gender ratio: 3.2:1) according to selected variables is shown in Table I; 172 (55%) were Kuwaiti nationals, the remainder non-Kuwaitis. Among the latter, the majority (70%) were from Arab countries and 26% were from Southeast Asia. Most cases (74%) were diagnosed at a relatively young age (15–44 years). The average age at diagnosis (standard deviation) was 34.7 (11) years (range 10–65 years) in women and 39 (13.4) years (range 6–69 years) in men; the median age was 35 and 38 years, respectively. There was no difference in the average age at diagnosis between Kuwaiti and non-Kuwaiti patients. Papillary carcinoma (including cases classified as mixed papillary/follicular variant) was the most common histopathological type accounting for approximately 83% of all cases.

Table II shows the risk of thyroid cancer associated with exposure to dental x-rays. There was an approximately two-fold increased risk of thyroid cancer in individuals who were exposed to dental x-rays (OR=2.1, 95% CI: 1.4, 3.1) ($p=0.001$). There was also a statistically significant dose-response pattern which showed an increasing trend in risk with increasing number of dental x-rays (p for trend <0.0001). This association between dental x-rays and the risk of thyroid cancer was observed across all investigated subgroups, i.e., age (at the time of diagnosis), gender, nationality, level of education, and parity (Table III). As for the histological subtypes, the association was essentially observed with papillary carcinoma (including cases classified as mixed papillary/follicular variant).

Discussion

In the present investigation, exposure to dental x-rays was associated with a significantly increased risk of thyroid cancer. In individuals who were exposed to dental x-rays, the risk of thyroid cancer increased with increasing number of exposures. The increased risk found in the study was consistent across all the investigated subgroups.

Considering that the thyroid gland is highly susceptible to radiation carcinogenesis, relatively few studies have examined the plausible adverse effects of low-dose radiation received through dental x-rays. Three cases-control studies (all from Sweden) have

Table II. Association between exposure to dental x-rays and risk of thyroid cancer.

	Case/Control	Cases %	Controls %	OR	95% CI	P-value
Dental x-ray						
No	208/255	66.7	81.7	1.0	–	
Yes	104/57	33.3	18.3	2.1	1.4–3.1	0.001
Number of dental x-rays						<0.0001*
1–4	75/43	72.2	75.4	2.2	1.4–3.5	0.001
5–9	16/4	15.4	7.0	4.6	1.4–14.7	0.01
10+	11/3	10.6	5.3	5.4	1.1–26.7	0.037

Conditional logistic regression analysis adjusted for upper-body (head, neck, and chest) x-rays.
One case-control pair was excluded from the analysis because the case had received radiotherapy. Information on no. of x-rays was missing for two cases and seven controls.
Baseline for ORs was taken as those subjects who had not reported any dental x-ray exposure.
*P for trend.

examined the association between diagnostic x-rays and the risk of thyroid cancer. In a questionnaire-based study including 93 women with papillary cancer, multiple (10+) dental x-rays exposures were associated with a significantly increased risk of the cancer (OR=2.8, 95% CI: 1.1, 7.5); increased risk was also found for diagnostic x-rays, particularly those of the head, neck and upper back/chest region [28]. In another study including 123 women with thyroid cancer, a positive association with dental x-rays was found only for those aged ≤50 years (OR=6.4, 95% CI: 1.3, 33) [29]. In a subsequent study, the authors complemented the questionnaire data with medical records [30]. Overall, this study did not show an increased risk for thyroid cancer in relation to previous medical diagnostic x-rays; whereas in subgroup analysis, a positive (but non-significant) association was found for younger women who were aged ≤50 years at diagnosis [30]. The authors noted that the collection of historical x-ray records was not complete and the results, which could be related to selective bias, must be treated with caution [30]. In a more recent paper, the authors cast doubt over the safety of their recall data and highlight the importance of reducing

Table III. Association between exposure to dental x-rays and risk of thyroid cancer by age at diagnosis, gender, nationality, level of education, parity, and histology.

	Cases %*	Controls %*	OR	95% CI	P-value
Age at diagnosis/ pseudo-diagnosis (years)					
≤35	32.6	15.8	2.1	1.1–3.8	<0.05
35+	33.9	20.6	1.9	1.0–3.4	0.05
Gender					
Females	33.2	19.0	2.0	1.2–3.3	<0.01
Males	33.3	16.0	2.4	1.0–5.6	0.05
Nationality					
Kuwaiti	32.2	19.9	2.0	1.1–3.6	<0.05
Non-Kuwaiti	34.8	16.3	2.1	1.2–3.9	<0.05
Education (years)					
No formal education	27.4	8.2	4.6	1.3–16.3	<0.05
1–12+	36.6	22.0	1.7	1.0–3.1	<0.05
Number of live births†					
1–4	38.8	24.4	1.8	0.9–3.6	NS
5+	33.6	12.8	2.7	1.3–5.9	<0.05
Histology					
Papillary**	34.5	18.0	2.3	1.4–4.0	0.002
Follicular	30.8	19.2	0.9	0.2–4.7	NS

Conditional logistic regression analysis adjusted for upper-body (head, neck, and chest) x-rays.
One case-control pair was excluded from the analysis because the case had received radiotherapy.
Baseline for ORs was taken as those subjects in the respective subgroup who had not reported any dental x-ray exposure.
NS=Not significant.
*Percentage exposed to dental x-rays.
†Includes only ever-married women; ORs based on unconditional logistic regression analysis, adjusted for age, nationality, district of residence, and upper-body x-rays.
**Includes cases classified as mixed papillary/follicular variant.

the potential for recall bias in case-control studies [31]. In a pooled analysis of these studies (which included 186 female papillary thyroid cancer patients) 10+ dental x-ray exposures were associated with an increased risk of thyroid cancer (OR=3.5, 95% CI: 1.6, 7.6) [7]. A relatively higher risk was observed among women who had had ≥three pregnancies (OR=4.7, 95% CI: 1.5, 14.8) [7]. Diagnostic x-ray exposures generally were also associated with increased risk and a significant dose-response pattern [7]. In another study, including 484 patients with thyroid cancer, information on exposure to medical diagnostic x-rays was obtained from hospital charts. The study found no evidence of an association between medical diagnostic x-rays of the head and neck region and thyroid cancer [32]. Information on dental x-rays, however, was obtained from a subgroup of cases and controls (123 matched pairs) through telephone interviews. A total of 23 cases and 11 controls reported having had one or more Panorex or full-mouth series of dental x-rays (Relative Risk (RR)=2.3, 95% CI: 1.1, 4.8) [32]. The findings of our study, which is the largest case-control study on the subject, provides further evidence for the possible association between dental x-rays and the risk of thyroid cancer.

Case-control studies are subject to a verity of biases. These may include issues of case and control ascertainment, misclassification, representativeness and participation rates; recall and information bias between cases and controls and survival bias. The strengths of this study include relatively large number of thyroid cancer cases, the unbiased selection of cases and controls from the population-based national cancer registry and primary-care settings, a high participation rate among both cases (93.2%) and controls (92.1%), and availability of information on potential confounders such as parity, level of education, diagnostic and/or therapeutic x-rays of head, neck, and chest, radiotherapy (to any part of the body), and number of exposures. To ensure non-differential ascertainment of exposure among cases and controls, the analysis of data on exposure to radiation and parity was restricted to events before the diagnosis (cases) or pseudo-diagnosis (controls) date. Like most case-control studies that have examined the association between dental x-rays and head and neck cancer, our study was based on self-reporting by the participants as comprehensive historical dental x-ray records had not been maintained at the dental clinics. It was deemed almost impossible to assemble dental records because it is not common practice to register with one specific dentist in Kuwait, and dentists do not tend to keep historical records. An additional difficulty, with regard to the non-Kuwaiti (expatriates) subjects in the study, was that many of their past x-ray might not have been taken in Kuwait. As noted in Table I, the large majority of expatriates were from Arab countries and Southeast Asia. We were therefore unable to obtain information on dosimetry and age at first exposure. To our knowledge, lead collars or aprons were not commonly used during the calendar years for which dental x-rays were self-reported. To assess the consistency of reporting of dental x-ray exposure, we conducted a validation study amongst a random sample of 49 cases and 42 controls. These telephone interviews did not find material difference in consistency of reporting between cases and controls and there was no evidence that controls were more likely to change their answers than cases.

The literature on high-dose radiation and thyroid cancer shows a marked age related sensitivity, with the youngest at exposure being the most sensitive. While we did not have information on age at first exposure, it is noteworthy that cases were more likely to be exposed to dental x-rays at younger ages compared with controls. Among the cases aged <25 years at diagnosis, about 27% were exposed vs. 18% of the controls; and at age <20, about 22% were exposed vs. none of the controls. Furthermore, the median age for women with thyroid cancer was 35 years; and the younger cases at diagnosis showed a slightly higher risk than older cases (Table III). In the validation study, a relatively greater proportion of exposed cases than exposed controls (57% vs. 45%) reported that their first dental x-ray exposure was before the age 20 years.

The interviewer was not aware of any possible link between dental x-rays and thyroid cancer, and the information about dental x-rays was one of many questions asked. Recall bias in general and differential recall bias between cases and controls may be correlated with sociodemographic factors (gender, nationality/ethnic background, level of education), type of exposure, and age at diagnosis of the disease – it is noteworthy that we found a similar association between dental x-rays and thyroid cancer risk across all these categories (Tables II and III). As in most interview-based case-control studies, a general recall bias must be considered, but is unlikely to wholly account for the significant dose-response pattern found in our study. In an unrelated dental x-ray validation study, which compared information from patient interviews and dental charts, recall was found to be unbiased since the measures of agreement between interview and dental charts data were similar for cases and controls. The authors concluded that interview data alone may be used for case-control comparisons of dental x-ray exposure and would, because of unbiased misclassification, tend to underestimate the relative risks [10,33].

Dental radiography has also been implicated in other tumours of the head and neck region. In a case-control study from the US, an increased risk of intracranial meningioma was associated with early exposure (age <20 years) to full-mouth dental x-ray series (OR=4.0; p<0.01) [8–10]. Similar findings were reported in another study from the US [11]. A similar association has been reported for glioma [12] and brain cancer [13]. However, the association of diagnostic x-rays with meningioma was not confirmed in a recent study [34], and there was no association between dental radiography (or amalgam filling) and tumours of the CNS in a study from Sweden [35]. Dental x-rays have also been associated with benign and malignant tumours of the parotid gland [10,14,15,36]. In the first study to suggest this association, exposure to diagnostic radiography (dental or head x-ray) before age 20 increased the risk of benign tumours by about two-fold (RR=1.8, 95% CI: 1.1, 2.9). The study also found a dose-related increase in risk of malignant tumours [14]. In a recent study from the US, increased risk of breast cancer was reported for women who had received dental x-rays without lead apron before age 20 years (OR=1.8, 95% CI: 1.1, 2.9) [16].

Increased risk of thyroid cancer has also been reported in dentists/dental assistants [7,17] and diagnostic x-ray workers [18–20]. In a cohort study of 27 000 diagnostic x-ray workers in China, the workers had a 50% higher risk of developing cancer than the other specialists; among the cancers, significantly increased risks were observed for leukaemia (RR=3.5) and cancers of the breast (RR=1.4) and thyroid (RR=2.1). The authors noted that these excesses were observed in workers first employed prior to 1960 (and for ≥10 years) when radiation exposures in China were high [19]. More recently, a cohort study of radiologic technologists in the US showed some evidence of an increased risk of thyroid cancer in technologists who had higher radiation exposures [21]. There has also been a considerable debate on the possible effects of low-dose radiation since the publication of the study by Hujoel et al. [37], which suggested an association between dental radiography during pregnancy and low-birth-weight infants (OR=2.3, 95% CI: 1.1, 4.7). Based on the epidemiological and experimental evidence, the authors proposed that hypothalamus-pituitary-thyroid axis might be involved in the causal pathway. The study, however, has been criticised for not adequately accounting for various confounding factors. These studies of dentists/dental assistants and diagnostic x-ray workers suggest that multiple low-dose radiation exposures in adults may also be important in the aetiology of thyroid cancer.

Conclusions

In conclusion, this case-control study found significant association, with a dose-response pattern, between self-reported dental x-ray exposure, particularly multiple exposures, and the risk of thyroid cancer. The odds ratios of about two in the study (and conservative estimates of 10–40% increased risk based on the lower bounds of the 95% CIs) were similar in magnitude to those found in the two case-control studies in Sweden that were also based on self-reported exposure histories. The validation study did not find evidence of significant differential reporting between cases and controls. As in all questionnaire-based case-control studies, the possibility of recall/reporting bias must be considered, but is unlikely to cause significant dose-response patterns and interaction as indicated in this study; the findings therefore cannot be attributed entirely to the possibility of differential reporting between cases and controls. However, considering the lack of information on dosimetry and age at first exposure, the findings should be interpreted with caution. This leaves open the possibility that thyroid cancer could be caused by multiple low-dose radiation exposures and warrant further study in settings where historical dental x-ray records may be available.

The public health and clinical implications of these findings are particularly relevant in light of (i) the reports of increases in the incidence of thyroid cancer, particularly papillary carcinoma, in many countries over the past 30 or so years; (ii) relatively high life-time prevalence and frequency of exposure to dental x-rays in the general population; and (iii) the guidelines for prescribing dental radiographs which recommend x-rays as a necessary part of evaluation for new patients, including children, and under certain circumstances periodic dental radiography (at 6–12 months interval), particularly for children and adolescents, to screen for increased risk of dental caries or decay. Recent recommendations by the American Dental Association stress the need for shielding of the thyroid [38]. The notion that low-dose radiation exposure through dental radiography, which is a common diagnostic radiation exposure in the general population, is absolutely safe needs to be investigated further, as although the individual risk, particularly with modern equipment is likely to be very low, the proportion of the population exposed is high.

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