STUDY ON THE PREVALENCE OF THYROID DESEASE IN HEALTHCARE WORKERS AT THE HOSPITAL OF PISA IN RELATION WITH OCCUPATIONAL EXPOSURE TO IONIZING RADIATION

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Abstract
This study analyzes the prevalence of thyroid disease in healthcare workers who have worked at the University Hospital in Pisa. They underwent a health surveillance protocol from 2nd January 2005 to 1st July 2009 with particular regard to occupational exposure to ionizing radiation.
Data of health care workers were obtained by consulting Asped 2000: computerized medical records used by the University Hospital in Pisa for health surveillance of workers exposed to occupational risk. This population consisted of 6658 people: 4391 women and 2267 men. Among these, 546 people were found to have thyroid disease. Radiological exposure interested 2226 people. 213 out of 546 workers suffering from thyroid diseases were exposed to ionizing radiation. For thyroid diseases overall and for each type of thyroid disease the fraction of patients professionally exposed has been calculated. A statistical analysis was done to determine the exposure that could be a risk factor for the development of these diseases. Only for healthcare workers exposed to ionizing radiation and affected by thyroid cancer, dosimetric charts folders were collected. For thyroid diseases in general the odds ratio resulted to be 1.30 with a 95% confidence interval (CI 95%) between 1.09 and 1.55. Thyroiditis was present in 187 cases including 79 exposed subjects and 108 non-exposed subjects with an odds ratio of 1.47 (CI 95%, 1.10-1.97). No statistical significance was achieved for the other thyroid diseases analyzed (goiter, C-cell hyperplasia, hyperthyroidism, hypothyroidism, Graves' disease, nodular disease and cancer). Thyroid cancer was present in 37 cases including 14 exposed and 23 non-exposed. The odds ratio was 1.21 (CI 95%, 0.62-2.36). It is very important to say that the classification in exposed or non-exposed workers is not based on the real exposure to ionizing radiation but on a susceptibility of exposure, according to radioprotection principles

Key words: ionizing radiation, thyroid disease, health surveillance, health care workers

1. Introduction

1.1 Ionizing radiation in hospital

In hospital, ionizing radiation is used for diagnostic and therapeutic procedures. Non-corpuscular ionizing radiation sources are represented by X-rays and corpuscular radiation are represented by beta and gamma radiation generated by radionuclides such as technetium 99 (^{99}Tc) and iodine 131(^{131}I).
Health care workers exposed to ionizing radiation are those who carry out their activities in the traditional X-ray areas departments as radiology and radiotherapy and nuclear medicine but also those who carry out their activity in some surgical departments as cardiovascular hemodynamics and orthopaedics (plaster room and surgery room). These workers, as well as patients, are exposed to low dose radiation [1]. The current consensus held by international radiological protection organizations about health risks from ionizing radiation is the linear-non-threshold (LNT) model, a dose-response model which is based on the assumption that, in the low dose range, radiation doses greater than zero will increase the risk of excess cancer in a simple proportionate manner [2,3]. All the radioprotection measures applied in hospital are based on the optimization principle, that is the process of determining what level of protection and safety makes exposures, and the probability and magnitude of potential exposures, as low as reasonably achievable, economic and societal factors being taken into account [4]. The medical surveillance of health care workers classified as susceptible to exposure to ionizing radiation has two purposes: diagnosis of deterministic damage, like radio dermatitis and lens opacities, today very infrequent, and the early detection of cancer, that is a stochastic effect[5].

1.2 Effects of ionizing radiation on thyroid gland

Irradiation of the thyroid gland produces both functional and proliferative alterations in the follicular cells. At low doses, radiation effects are compensated by a feedback control system, while high doses of radiation sterilize the proliferative capacity of the follicular cell and very high doses lead to the ablation of the gland. The radiation-induced biological effects in humans against the thyroid are divided into three groups: acute effects (thyroiditis, early hypothyroidism), non-acute effects (late hypothyroidism) and late effects with stochastic character (thyroid tumour). Acute radiation thyroiditis usually occurs two weeks after exposure of the thyroid to ^{131}I and it is characterized by symptoms of inflammation and possibly by necrosis of all or part of thyroid cells. A threshold dose of 200 Gy was estimated for the onset of thyroiditis by ^{131}I. This incidence increases by 5% for each additional 100 Gy increment above the threshold. According to the International Commission on Radiological Protection (ICRP), hypothyroidism from external irradiation requires a dose of 45 Gray (Gy) for its appearance. A full-blown incidence of hypothyroidism was found in approximately 20% of patients with Hodgkin's disease therapeutically irradiated on the neck with doses between 35 and 45 Gy. Hypothyroidism from internal irradiation, however, is largely due to the treatment of hyperthyroidism with radioactive iodine [6].

Radiation-induced thyroid cancer can be classified according to the type of exposure: external irradiation, radioactive iodine isotopes for medical reasons, radioactive fallout. Differentiated thyroid cancer, generally papillary, represents an important consequence of the therapeutic irradiation of head and neck, especially in childhood for benign disease (tinea capitis, chronic tonsillitis, acne, cutaneous hemangiomas, thymic hypertrophy) [7]. There is a wide range of doses that appears to promote carcinogenesis, from about 0.1 to 10 Gy. Data from five cohort studies (atomic bomb survivors, children treated for tinea capitis, two studies of children irradiated for enlarged tonsils, and infants irradiated for an enlarged thymus gland) and two case-control studies (patients with cervical cancer and childhood cancer) showed that for childhood exposures, the pooled excess relative risk per Gy (ERR/Gy) was 7.7 (95% CI = 2.1- 28.7) and the excess absolute risk per 100000 PY Gy (EAR/10(4) PY Gy) was 4.4 (95% CI = 1.9-10.1) [8].

The thyroid cancer after exposure to external radiation occurs with a latency of at least 5 years and maximum up to 40 years after exposure. The main factors that increase the risk of developing this cancer are female sex and young age) [9]. The contribution of a genetic predisposition was also hypothesized. In fact, those people who are affected by a radiation-induced cancer are more susceptible to the development of another radiation-induced cancer. Nuclear medicine uses ^{131}I for diagnostic and therapeutic purposes: this radioisotope has a half-life of 8.02 days, and decays by emitting beta radiation with a mean energy of 191 keV (kilo-electron-Volt) and gamma radiation with an average energy of 364 keV. The therapeutic effect of ^{131}I, that is secondary to the radiation-induced damage on thyroid cells, is due primarily (over 90%) to beta radiation, which have an average distance in tissue of 0.36 mm. Gamma radiation, which is very penetrating, represents the 10% of the total dose of radiation received by the gland. Currently, it is not possible to assign an exact risk value to ^{131}I exposure. Epidemiological studies of subjects, for most adults, exposed to diagnostic doses of ^{131}I (in the order of 100 cGy), have shown no significantly increased risk for thyroid cancer. When administered in therapy for hyperthyroidism in adults doses of ^{131}I in the order of 100 Gy are used. However, even in these cases a significantly increased risk of thyroid cancer has not been demonstrated 10].

Epidemiological data concerning the nuclear accident in Chernobyl have shown a significant increase in the incidence of adenocarcinoma in children, more frequently in those who were less than 5 years, or even in uterus at the time of the accident. Even without official and accurate dosimetric assessments, a very high average radiation was estimated in the thyroid, in the order of several Gy. The papillary histotype was the most frequent among observed tumours, above all in young people, showing a lower latency (only 4 years after exposure), no association with gender, but a strong association with autoimmunity. This histotype is more aggressive than other thyroid tumors, but the

response to therapy is very good and the cure rate is very high even in the presence of distant metastases. The Chernobyl experience cannot be comparable to the conditions of occupational exposure for a complex of reasons (age-related factors, factors related to the particular type of exposure and countermeasures such as iodine prophylaxis and dosimetric factors). Numerous studies have been conducted on the population exposed to the Chernobyl nuclear accident of 1986, particularly on the inhabitants of Ukraine, Belarus and Russian Federation. A large increase in the incidence of thyroid cancer has been found among children and adolescents that were exposed. This increase has been linked to the release of iodine radioactive isotopes including the ^{131}I which has a half life of about 8 days and decays by emitting beta radiation. The lack of iodine in the diet promoted the absorption of radioactive iodine [11,12,13].
A cohort study carried out by the Atomic Bomb Casualty Commission and by Radiation Effects Research Foundation (RERF), contains about 120000 people who survived the bombing of Hiroshima and Nagasaki in 1945. This population is large, checked by the only criteria about the proximity to the epicenter of the two explosions. The population study was followed over a long period ranging from 1950 to 2000. According to the results of this study, thyroid cancer risk has been well described by a linear dose-response function and has shown a strong dependence on the age of exposure. In fact there is little evidence of a dose-response relationship for those exposed in adulthood, while the Excess of Relative Risk (ERR/Sv) for those exposed in childhood is wide (9.5 if under the age of 10 and 3.0 for those who were exposed between 10 and 19 years) [14]. One hundred and twelve cases of thyroid cancer diagnosed during the period 1958-79 among the extended Life Span Study cohort in Hiroshima and Nagasaki were studied. There was a statistically significant association between thyroid cancer incidence and exposure to atomic bomb radiation. The adjusted excess relative risk (ERR) per gray was 1.1 (95% CI= 0.3-2.5) and the adjusted absolute risk per 10^4 PYGy was 0.59 (95% confidence interval = 0.2-1.7) [15].

2. Materials and methods

The population of this study is represented by health care workers who have worked at the University Hospital in Pisa and underwent health surveillance protocol from 2nd January 2005 to 1st July 2009. This population consisted of 6658 persons: 4377 women and 2281 men.
The data were exported from the health surveillance database (Asped 2000) in Access format and, through the function "query", information and regarding name, sex, date of birth, medical history, age at pathology and occupational hazards were taken. The query results were exported as a table to a spreadsheet to be reworked. For each worker the presence or absence of any thyroid disease and the presence or absence of exposure to ionizing radiation in the workplace were detected, so the number of people belonging to these categories could be identified. The classification of exposed workers was based on an estimate of risk that was not necessarily accompanied by a concrete actual exposure.
Thyroid diseases were then classified into 11 categories thyroid adenoma, changes in thyroid hormone, goiter, C-cell hyperplasia, hyperthyroidism, hypothyroidism, Graves' disease, nodular pathology, thyroiditis and cancer. For each type of thyroid disease, patients exposed and those not exposed to ionizing radiation were identified. A particular interest was placed in cases of cancer and thyroid nodular disease, characterized by the presence of a cold nodule in doubt of a possible evolution to carcinoma. For all these people the medical history and the work history were checked again. Histological reports were consulted to verify and investigate the cancer diagnosis of these patients. As regards the cases, further information was collected, in particular, the year when they began to be exposed, the departments where they worked and how long they were exposed before the diagnosis of thyroid cancer was verified. For these patients personal dosimetry charts were consulted.
A statistical analysis was done to determine whether the exposure to ionizing radiation could have been a risk factor for the development of thyroid diseases overall and for each type of thyroid disease.

3. Results

The population of this study, health care workers who have worked at the University Hospital in Pisa, consisted of 6658 people. They underwent a health surveillance protocol between 1st January 2005 and 1st July 2009. 546 workers resulted affected by thyroid disease and were called "cases" and 6112 were not affected by thyroid disease and were called "controls". Out of 546 cases, 213 (39%) were classified susceptible to exposure to ionizing radiation; out of 6112 controls, 2013 (32.9%) resulted susceptible to exposure to ionizing radiation. 2226 (33.4%) people resulted susceptible to exposure to ionizing radiation. The population of people classified susceptible to exposure to ionizing radiation and the population classified not susceptible to exposure to ionizing radiation were homogeneous in terms of the distribution of sex and age. To simplify we called people susceptible to exposure to ionizing radiation "exposed" and the population classified not susceptible to exposure to ionizing radiation "not exposed".

Analyzing the distribution of cases and controls in relation to the exposure to ionizing radiation, the odds ratio was 1.30 with a 95% confidence interval (95%IC) between 1.09 and 1.55(Table 1).

	Cases (%)	Controls (%°)	Total (%)
Exposed	213 (**39%**)	2013 (32,9%)	2226 (33,4%)
Not exposed	333 (61%)	4099 (67,1%)	4432 (66,6%)
Total	**546** (100%)	6112 (100%)	6658 (100%)

OR = 1.30
CI (95%) = 1.09-1.55

Table 1: *Prevalence of thyroid disease (cases)*

The cases were classified according to the specific thyroid disease in 11 categories. Alterations in thyroid hormone were present in 3 cases including 2 exposed and 1 non-exposed. For goiter category there were 50 people: 15 patients (30%) were exposed and 35 patients (70%) were not exposed. The odds ratio was 0.85 with CI 95% (0.46 to 1.56). The C-cell hyperplasia was found in one worker that was exposed to the ionizing radiation. Hyperthyroidism regarded 22 cases of which 10 exposed (45.45%) and 12 non-exposed (54.55%). The odds ratio was 1.66 with CI (0.72 to 3.89). Hypothyroidism was present in 45 cases: 15 exposed (33.33%) and 30 non-exposed (66,67%). The odds ratio was 1.00 with CI (95%) = (0.50 to 2.03). Graves' disease is present in 26 cases: 10 exposed (38.46%) and 16 non-exposed (61.54%). The odds ratio was 1.25 with CI (95%) = (0.57 to 2.76). The nodular disease affected 170 persons including 68 exposed (40%) and 102 non-exposed (60%). The odds ratio was 1.34 with 95% CI = (0.98 to 1.83). The unspecified thyroid disease was present in 4 cases, all non-exposed. Thyroiditis was present in 187 cases: 79 exposed (42.25%) and 108 non-exposed (57.75%). The odds ratio was 1.47 with CI (95%) = (1.10 to 1.97) (Table 2).

	Thyroiditis	Not thyroiditis	Total
Exposed	79	2147	2226
Not exposed	108	4325	4432
Total	187	6472	6658

OR = 1.47
CI (95%) = 1.10-1.97

Table 2: *Prevalence of thyroiditis*

Thyroid cancer was present in 37 cases including 14 exposed (0,63% of the exposed workers) and 23 non-exposed (0.52% of the non-exposed workers). The odds ratio was 1.21 with CI (95%) = (0.62 to 2.36) (Table 3).

	Cancer	Not cancer	Total
Exposed	14	2212	2226
Not exposed	23	4409	4432
Total	37	6621	6658

OR = 1.21
CI (95%) = 0.62-2.36

Table 2: *Prevalence of cancer*

For thyroid cancer a classification based on histological examination has been implemented to see if there was a prevalent subtype in the study population in general and in the two groups of exposed and not exposed workers: papillary carcinoma resulted to be the most frequent, as expected from epidemiological data (Table 3).

THYROID CANCER:	N° total cases (%)	N° cases in exposed (%)	N° cases in non-exposed (%)
Papillary ca	29 **(78,38%)**	13 **(92,86%)**	16 **(69,56%)**
Follicular ca	2 (5,41%)	0	2 (8,70%)
Medullary ca	1 (2,70%)	1 (7,14%)	0
Unspecified ca	5 (13,51%)	0	5 (21,74%)
Total	37 (100%)	14 (100%)	23 (100%)

Table 3: *Histological subtypes of thyroid cancer*

Since the papillary histotype is the most frequent type of carcinoma being linked with ionizing radiation, the odds ratio was calculated for this specific histological type, which was 1.62 with CI (0.95%) = (0.78-3.38) (Table 4).

	Papillary ca	Not Papillary ca	Total
Exposed	13	2213	2226
Not exposed	16	4416	4432
Total	29	6629	6658

OR = 1.62
CI (95%) = 0.78-3.38

Table 2: *Prevalence of papillaty thyroid cancer*

The dosimetric charts of the 14 health care workers suffering from thyroid cancer and occupationally exposed to ionizing radiation showed a cumulative dose equivalent to the whole body from external irradiation different than zero only in 4 cases (28,57%). These values ranged from a minimum of 0.22 mSv to a maximum of 1,18 mSv. Three out of the 14 (21.43%) health care workers were also exposed to the risk of contamination by radioactive isotopes. The cumulative committed dose equivalent of these workers was zero in the first case, 1,31 mSv in the second one and 15,36 mSv in the third one. In this last case the value was achieved during a period of 11 years. In none of these cases the thyroid cancer has been recognized as radio induced.

4. Discussion

Thyroid disease is characterized by a high prevalence and incidence in Italy, as well as in other developed countries. In Italy one of the most common thyroid disease is goiter which is considered endemic because it affects more than 10% of the population, within estimated costs of diagnosis and therapy of about 150 million Euros per year. In addition to the goiter also thyroiditis, including Hashimoto's thyroiditis, thyroid nodules (5-25% of the population) have a great importance in epidemiology. The differentiated thyroid cancer represents the 1% of all cancers, but it has been the first of epidemiological increasing in the last 10 years and it is also the most frequent endocrinological cancer.

Among the main risk factors for thyroid disease there are ionizing radiation, genetic factors, hormonal factors and other environmental factors such as dietary deficiency (iodine). The quantity of thyroid cancer due to ionizing radiation has increased dramatically in recent decades as a result of nuclear disasters both military (e.g., Hiroshima and Nagasaki) and civil, as in the case of the Chernobyl accident. Among the causes of thyroid irradiation not linked to catastrophic events, there are radiotherapy practices especially in childhood for benign disease, some of which used only a few decades ago. Today, however, ionizing radiation is used for medical purposes and plays a key role in diagnostic imaging, nuclear medicine and surgery being used in numerous diagnostic, therapeutic and interventional techniques [16]. The dose for a single X-ray examination is in the range of low doses, but we have to consider the number of the medical procedures for every single person. While numerous studies on the general population analyze the effects of medical exposure to ionizing radiation on thyroid gland, literature data studying populations of workers occupationally exposed to ionizing radiation, particularly with regard to health care workers, are very limited [17,18,19]. In the population of healthcare workers, subjects of this study, the percentage of recorded thyroid diseases, only on the basis of medical history, was 8,2%. The proportion of thyroid disorders detected in the subpopulation of workers classified as susceptible to exposure to ionizing radiation was, on the contrary, about 10%. It is a quite important percentage. The distribution of thyroid disease ad thyroditis among the two categories of exposed and non-exposed workers was asymmetric with a statistical significance, albeit slight. A positive association but not statistical significant was recorded between hyperthyroidism, Graves' disease, nodular thyroid disease and thyroid cancer and radio exposure. In a study on the healthcare personnel of University Hospital of Bologna it was not find any association between occupational radiation exposure and thyroid nodules[20].

The results of this thesis, however, must be critically evaluated considering all the possible bias that this kind of study may represent. In the first instance it must be emphasized that the two groups of workers compared were similar in age and sex distribution, but definitely not comparable to the diagnostic tests performed. Certainly the population of exposed workers have had a higher level of diagnostic tests (hormone assays, ultrasound investigation) than non-exposed workers, being subjected to mandatory health surveillance protocols for the present Italian regulations (Legislative Decree n° 230/95 and following).

In addition, the statistics of this thesis considers the simple classification in exposed or non-exposed workers based on a forecast of exposure rather than on a real recording of dose as a risk factor. This mode of inquiring due to the “preliminary" purpose of the study, could lead to an overestimate of the risk. Infact out of the 14 workers affected by thyroid cancer and classified as susceptible to exposure to ionizing radiation only 4 people presented a cumulative dose equivalent different than zero. On the other hand also the modalities of dose registration with the current instruments and those used in the past, does not guarantee a perfect adhesion to reality. In this sense, several factors, sometimes directly attributable to the operator (poor compliance of the operator) and sometimes due to the method of irradiation (inadequate positioning of personal dosimeters, difficulties in recording the committed dose etc), can cause an underestimation of the real exposure. It is also important to remember how difficult it is dealing with the problem of fractionated and prolonged exposure to low doses to the limits of detectability of dosimeters used.

The data collected and processed in this thesis, even considering the methodological limitations discussed above, lay the foundations for further investigations regarding this sensitive and certainly interesting theme in terms of Occupational Medicine.

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6. References

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