HORMONES 2013, 12(2):312-314

Letter to the Editor

Iodine-131 administration and risk of cancer: "Appearances can be deceptive"

Massimo Salvatori,[1] Giorgio Treglia,[2] Germano Perotti,[1] Luca Giovanella[2]

[1]Institute of Nuclear Medicine, Catholic University of the Sacred Heart, Rome, Italy, [2]Department of Nuclear Medicine and Thyroid Centre, Oncology Institute of the Southern Switzerland, Bellinzona, Switzerland

Dear Sir,

Radioactive iodine (^{131}I) is a radiopharmaceutical widely used in diagnosis and therapy of benign and malignant thyroid diseases. The possible risk of cancer induced by ^{131}I administration is a topic widely debated in the literature.

Recently, an interesting meta-analysis concerning the risk of cancer in patients submitted to ^{131}I administration for diagnosis or therapy of benign thyroid diseases has been published by Hieu and co-workers.[1] These authors examined seven studies including 22,029 exposed subjects in the therapeutic cohorts and 24,799 in the diagnostic cohorts, summarizing data on 64 different organs or organ group subsets. Outcome was pooled as the relative risk (RR) using both standard and bias adjusted methods. While no increase in the overall burden of cancer was observed, a higher and significant risk for kidney (RR 1.70, 95%CI: 1.15-2.51) and thyroid cancer (RR: 1.99, 95%CI: 1.22-3.26) was demonstrable in the group of patients submitted to ^{131}I administration.

This study was well conducted and the meta-analytic approach is formally correct, but the authors did not refer to a serious limitation which is present in most articles evaluating the supposed carcinogenic effect of ^{131}I therapy, including all but one of the seven studies selected by this meta-analysis. In fact, all published studies assessed whether ^{131}I administration in patients with benign thyroid disease (almost exclusively for hyperthyroidism) could influence cancer development and did not specifically assess the association of thyroid function with cancer risk or mortality. In other words, there are well-grounded suspicions that hyperthyroidism per se could probably account for the small increased cancer risk found in hyperthyroid patients undergoing ^{131}I administration. We would like to summarize the evidence of the literature in this regard.

Thyroid hormones are important in a multitude of physiologic processes throughout the body. It has therefore been suggested that thyroid hormones could stimulate tumor growth and thus be associated with increased risk of cancer, whereas hypothyroid function could lead to a reduced risk and a more favorable prognosis in patients with cancer.[2] Among the biological mechanisms that could mediate the association of hyperthyroid function with the risk of certain cancers, integrin $\alpha v\beta 3$ may be of major significance. This is a membrane receptor for iodothyronines which is overexpressed in many tumors and represents the initiation site for hormone-directed complex cellular events, such as cell division and angiogenesis. Via the integrin receptor, the hormone signal is transduced by MAPK (ERK1/2) into angiogenesis in endothelial cells

Address for correspondence:
Giorgio Treglia, MD Department of Nuclear Medicine and Thyroid Center, Oncology Institute of Southern Switzerland, Via Ospedale, 12, CH-6500, Bellinzona, Switzerland,
Tel.: +41 918118672, Fax: +41 918118250,
E-mail: giorgiomednuc@libero.it

Received 31-03-2013, Accepted 10-04-2013

and cell proliferation of tumor cell lines and tumor xenografts.[3] Alternative or adjunctive mechanisms by which thyroid hormones may stimulate cancer cell proliferation include potentiation of the action of EGF on tumor cells and an antiapoptotic effect supporting cancer cell proliferation.[3]

Several animal studies showed that thyroid hormone deprivation slows solid tumor growth rates, reduces the tendency to metastasize and improves survival, whereas thyroid hormone supplementation increases tumor growth rates and the tendency to metastasize.[4-7] A complete remission of mammary adenocarcinoma in C3H mice made hypothyroid by treatment with propylthiouracil (PTU) and a significantly high development of mammary tumors in euthyroid and hyperthyroid mice was reported.[4,5] Moreover, a significant enhancement of tumor growth and metastatic index in the thyroxine-treated group of mice compared to the untreated control group was observed;[6] induced hypothyroidism by treatment with ^{131}I showed the reverse effect on both tumor systems. In a study from the University of New Orleans, subcutaneous lung and prostate xenografts grew significantly more slowly in hypothyroid mice treated with PTU than in euthyroid or hyperthyroid mice, regardless of treatment with PTU.[7] Tumors grew well in groups of mice that were changed from a hypothyroid state to a euthyroid state by withdrawal of oral PTU. In vitro and in vivo data indicated that this was not a result of an interaction of the tumor cells with PTU, but rather a result of the hypothyroid state.[7]

The association between thyroid benign disease with or without hyperthyroidism and risk of cancer has been the subject of several clinical studies, including retrospective and prospective analyses of large cohorts of patients, as well as studies with a small number of patients, and even anecdotal reports.

The risk of cancer was examined in a cohort of 57,326 individuals who were discharged from a Danish hospital with a diagnosis of benign thyroid diseases, including myxedema, thyrotoxicosis or nontoxic struma. Although the overall risk of cancer in this cohort was only slightly elevated, the risk of several specific cancers, including cancer of the thyroid, urinary tract, and hematopoietic system, was increased.[8]

In a recent prospective study of almost 30,000 individuals without known thyroid disease at baseline and followed for 9 years, subjects with thyrotropin (TSH) levels suggestive of hyperthyroid function (TSH <0.5 mU/l) were at higher risk of cancer compared with others, including those with suggested hypothyroid function.[9] The higher cancer risk in patients with hyperthyroid function was mainly driven by effects on lung [hazard ratio (HR): 2.60] and prostate cancer (HR: 1.96) and was elevated both in those with subclinical hyperthyroid function and, more strongly, in patients with biochemically overt hyperthyroid function. Hypothyroid function was not associated with cancer risk.[9]

The largest to date longitudinal cohort study evaluating cancer risk in patients hospitalized for Graves' disease (GD) was published in 2010 by Shu et al.[10] In this cohort of 18,156 GD patients, a total of 1,495 who developed cancers during a median follow-up period of 17 years was observed (overall incidence ratio: 1.13, 95%CI: 1.07-1.19). The overall excess of all cancers (13%) was largely attributable to cancers of the thyroid, other endocrine glands, upper aerodigestive tract, and breast.[10]

The relationship between benign thyroid diseases and breast cancer is a long-debated issue that has been investigated for over 50 years and a disparity in results appears relatively commonly throughout the literature. A recent meta-analysis has been written with the purpose of collating and analyzing available data from 28 studies, calculating a pooled odd ratio (OR) of the risk of breast cancer in patients diagnosed with benign thyroid diseases.[11] The study demonstrated significant evidence of an increased risk of breast cancer in patients with autoimmune thyroiditis (OR: 2.92, 95%CI: 2.13-4.01). Besides the biological mechanisms reported above, the presence of the sodium-iodide symporter (NIS) in both breast and thyroid tissue led to the hypothesis that the uptake and oxidation of iodine may play a role in the development of breast cancer.

Apart from breast cancer, other tumors have been associated with thyroid benign diseases. In a population-based case-control study, Ness et al. evaluated several risk factors on the hypothesis that inflammation may play a role in ovarian cancer risk.[12] Comparing 767 patients with a recent diagnosis of epithelial ovarian cancer to community controls, hy-

perthyroidism was identified as a significant ovarian cancer risk factor (OR: 1.8).

A large study involving 532 pancreatic cancer patients found that hyperthyroidism, but not hypothyroidism, was suggestive of excess pancreatic cancer risk (OR: 2.1).[13]

An epidemiologic study demonstrated a relationship between thyroid disease and renal cell carcinoma: women with renal cell carcinoma had a statistically significantly higher percentage of hypothyroidism, benign thyroid disease, and use of thyroid-hormone supplements as compared with the control group.[14]

In a prospective study, Turkyilmaz et al. evaluating 102 sequential patients with oesophageal cancer observed a significant correlation ($p<0.001$) between oesophageal cancer and hyperthyroidism compared to a group of 160 sequential patients without oesophageal cancer.[15]

In conclusion, the general risk of cancer in patients with benign thyroid diseases or high levels of thyroid hormones is only slightly increased and subject to possible biases (e.g. surveillance bias or abnormal thyroid hormones due not to thyroid diseases but to a preclinical cancer). However, a small risk is evident and it counterbalances the same slight risk reported after radioiodine therapy for hyperthyroidism.[1]

To conclusively prove the putative increased risk of cancer or increased mortality to radioiodine therapy, several prospective studies should be done comparing hyperthyroid patients treated with radioiodine to a control group consisting of hyperthyroid patients not treated with radioiodine or treated with antithyroid drugs or surgery.

Declaration of interest

The authors declare no conflicts of interest.

Funding

None

REFERENCES

1. Hieu TT, Russell AW, Cuneo R, et al, 2012 Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: a meta-analysis. Endocr Relat Cancer 19: 645-655.
2. Hercbergs AH, Ashur-Fabian O, Garfield D, 2010 Thyroid hormones and cancer: clinical studies of hypothyroidism in oncology. Curr Opin Endocrinol Diabetes Obes 17: 432-436.
3. Cheng SY, Leonard JL, Davis PJ, 2010 Molecular Aspects of Thyroid Hormone Actions. Endocr Rev 31: 139-170.
4. Shoemaker JP, Dagher RK, 1979 Remissions of mammary adenocarcinoma in hypothyroid mice given 5-fluorouracil and chloroquine phosphate. J Natl Canc Inst 62: 1575-1578.
5. Vonderhaar BK, Greco AE, 1982 Effect of thyroid status on development of spontaneous mammary tumors in primiparous C3H mice. Cancer Res 42: 4553-4561.
6. Kumar MS, Chiang T, Deodhar SD, 1982 Enhancing effect of thyroxine on tumor growth and metastases in syngeneic mouse tumor systems. Cancer Res 39: 3515-3518.
7. Theodossiou C, Skrepnik N, Robert EG, et al, 1999 Propylthiouracil-induced hypothyroidism reduces xenograft tumor growth in athymic nude mice. Cancer 86: 1596-1601.
8. Mellemgaard A, From G, Jorgensen T, et al, 1998 Cancer Risk in Individuals with Benign Thyroid Disorders. Thyroid 8: 751-754.
9. Hellevik AI, Asvold BO, Bjøro T, et al, 2009 Thyroid Function and Cancer Risk: A Prospective Population Study. Cancer Epidemiol Biomarkers Prev 18: 570-574.
10. Shu X, Ji J, Li X, et al, 2010 Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. Br J Cancer 102: 1397-1399.
11. Hardefeldt PJ, Eslick GD, Edirimanne S, 2012 Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast Cancer Res Treat 133: 1169-1177.
12. Ness RB, Grisso JA, Cottreau C, et al, 2000 Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11: 111-117.
13. Ko AH, Wang F, Holly EA, 2007 Pancreatic cancer and medical history in a population-based case-control study in the San Francisco Bay Area, California. Cancer Causes Control 18: 809-819.
14. Rosenberg AG, Dexeus F, Swanson DA, et al, 1990 Relationship of thyroid disease to renal cell carcinoma. An epidemiologic study. Urology 35: 492-498.
15. Turkyilmaz A, Eroglu A, Aydin Y, et al, 2010 A new risk factor in oesophageal cancer aetiology: hyperthyroidism. Acta Chir Belg 110: 533-536.