Obesity and Thyroid Cancer: Is Leptin the (Only) Link?

Antonio Di Cristofano
Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York 10461

Thyroid cancer is the most common endocrine malignancy and ranks as the fifth most common cancer diagnosed in women. In the past 4 decades, the incidence of thyroid cancer has maintained a steady upward trend, and 60,000 new cases are expected in 2013 (1). This rise cannot be explained only by the increased detection of small tumors thanks to the use of neck ultrasounds and ultrasound-guided fine needle aspiration biopsies, because the upward trend started well before these screening practices became so common, and also because there is an increase in the prevalence of larger tumors.

The notion that in the same timeframe the prevalence of obesity has increased in parallel to that of thyroid cancer has led to several studies testing the hypothesis that the two might be causally linked. However, although obesity has been positively associated with a growing number of tumor types (reviewed in Refs. 2–5), its connection with thyroid cancer has not been firmly established.

Several large-scale prospective studies suggest that there is a positive association between body mass index and thyroid cancer risk, especially in women (6–8). However, another study failed to establish a relationship between obesity and more aggressive histological features of thyroid cancer (9).

The article by Kim and colleagues (10) in this issue of Endocrinology addresses in vivo, in a relevant mouse model, the link between obesity and thyroid cancer development.

By comparing the incidence and biological behavior of follicular thyroid tumors in \(Thrb^{Pv/Pv},Ptne^{-/-}\) mice fed regular chow or a high-fat diet (HFD), the authors establish a direct role of diet-induced obesity in increasing the aggressiveness of these tumors, as measured by tumor size, proliferative index, and presence of foci of anaplasia. Notably, they found no differences in the overall prevalence of hyperplasia and capsular invasion. This would suggest that obesity impacts the biological behavior of already established thyroid lesions, rather than their initiation rate (ie, risk). However, it must be noted that the prevalence of hyperplasia and invasion are already close to 100% in the control group, thus precluding any further increase. Future studies should be designed to analyze the prevalence at earlier time points to assess the rate of tumor initiation.

From a mechanistic point of view, the authors provide evidence of increased serum levels of leptin and of activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) 3 cascade, one of leptin’s downstream effector pathways.

Thus, for the first time, a direct link is shown between obesity-induced signals and thyroid cancer-promoting effectors. Earlier reports have associated increased STAT3 activation with anaplastic thyroid cancer, underlining the relevance of the findings presented in this paper. It is interesting, however, that STAT3 activation has recently been inversely associated with papillary thyroid cancer behavior, both in clinical specimens (11) and in mouse models (12). It is thus possible that the mechanisms proposed by Kim and colleagues (10) apply to a distinct subset of thyroid tumors, i.e., follicular carcinomas and their dedifferentiated derivatives.

Additional studies in which HFD effects are studied in models of papillary thyroid cancer will address this issue.

Although Kim and colleagues (10) emphasize in their mouse model the association between obesity, increased leptin levels, and activation of the JAK/STAT pathway, it is important to underline that there are a number of additional leptin-mediated pathways that might further contribute to the increased aggressiveness of thyroid tumors in

---

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.
Copyright © 2013 by The Endocrine Society
Received June 17, 2013. Accepted June 21, 2013.

For article see page 2936


Endocrinology, August 2013, 154(8):2567–2569 2567


Abbreviation: HFD, high-fat diet; JAKSTAT, Janus kinase/signal transducer and activator of transcription; PI3K, phosphatidylinositol-3 kinase.

Downloaded from https://academic.oup.com/en/endo/article-abstract/154/8/2567/2423572 by guest on 10 February 2018
a predisposed environment. Future studies leveraging the \( \text{Thrbb}^{Pv/Pv},\text{Pten}^{+/-} \) strain or additional available models of thyroid cancer (13–15) will have to address the influence of these pathways on thyroid cancer risk and aggressiveness.

One leptin-initiated signaling cascade that has not been tackled by this study leads to the activation of nuclear factor \( \kappa B \) and, among others, to the downstream induction of VEGF (16). The notion that nuclear factor \( \kappa B \) and vascular endothelial growth factor are two established markers of increased aggressiveness of thyroid cancer (17, 18) underlines the potential relevance of this link between obesity and tumor behavior.

Increased leptin levels also induce aromatase expression (19), leading to increased production of estradiol (20). Accordingly, early studies on mice subjected to HFD showed a 2-fold increase in estrogen levels (21). Based on the recent in vivo evidence of the direct effect of estradiol on thyrocyte proliferation and thyroid cancer development (15), it is conceivable that thyroidal estrogen receptor activation might contribute to the aggregate increase in thyroid cancer risk or aggressiveness.

However, leptin increase may be only one aspect of the whole picture.

The increase in circulating insulin and in circulating and bioavailable IGF-1 in obese individuals represents an additional logical contributing factor, especially in view of the key role of IGF-1 signaling in thyroid proliferation (22). The elevated basal activation status of the phosphatidylinositol-3 kinase (PI3K)/AKT pathway in the \( \text{Thrbb}^{Pv/Pv},\text{Pten}^{+/-} \) thyroids is probably the reason for the absence of a measurable increase in IGF1R/PI3K signaling reported in this study. Thus, the possibility of such a connection needs to be addressed in different models, not relying on constitutive PI3K activation.

Our own studies suggest yet another possible concurrent mechanism for the increased thyroid cancer risk in the setting of obesity. Obesity, through a variety of mechanisms, including hyperinsulinemia, leads to the inactivation of AMPK (23). Impaired AMP-activated protein kinase function in the thyroid, in turn, reduces the activity of PPAR-gamma coactivator-1\( \alpha \) and leads to the coordinated down-regulation of the expression of Krebs cycle and oxidative phosphorylation genes, impairing mitochondrial function and inducing a compensatory glycolytic switch that favors the transformation process (24).

Thus, the study by Kim and colleagues (10) establishes a formal direct link between obesity and biological behavior of thyroid cancer, setting the ground for future studies that will extend these observations not only to the wide range of additional leptin targets but also beyond leptin signaling, adding to our understanding of the complex link between obesity and thyroid cancer risk.

Acknowledgments

Address all correspondence and requests for reprints to: A. Di Cristofano, Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Price Center for Genetic and Translational Medicine, 1301 Morris Park Avenue, Room 302, Bronx, New York 10461. E-mail: antonio.dicristofano@einstein.yu.edu.

Funded by National Institutes of Health Grants CA128943 and CA167839. A.D.C. is a recipient of the Irma T. Hirschl Career Scientist Award.

Disclosure Summary: The author has nothing to disclose.

References


Save the Date for Endocrine Board Review (EBR),
www.endo-society.org/CEU2013