commentaries

Are We Missing the Elephant in the Room? A Case for Thyroid Cancer Overdiagnosis As the Etiology for Its Increasing Incidence in India

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The incidence of differentiated thyroid cancers, especially the papillary subtype, has been increasing worldwide. The SEER database from the United States showed a three-fold increase in thyroid cancer incidence from 1975 to 2010, with a relatively stable thyroid cancer–specific mortality rate.[1] Similarly, in South Korea, thyroid cancer incidence increased by seven-fold from 1999 to 2009.[2] India is not an exception to this trend.[3] Several regions of India have seen an increase in incidence of thyroid cancer.

Women are predominantly affected by this trend.[1] The majority of newly diagnosed thyroid cancers are small and of the papillary histologic type.[4,5] In countries where the incidence is rapidly increasing, the increase has been attributed to a disproportionate increase in diagnosis of small papillary thyroid cancers.[6] Approximately one sixth of computed tomography scans and magnetic resonance images show incidental thyroid nodules, of which the majority are smaller nodules.[7,8]

On the basis of such information, several studies from developed regions of the world have concluded that overdiagnosis is the leading cause of this astounding increase in the incidence of thyroid cancer.[9,10] The influence of environmental and other risk factors on this increased incidence is controversial and, if present, likely marginal. An increase in the prevalence of risk factors such as obesity and tobacco use could contribute to an increased incidence of thyroid cancer. However, why are women in India, who have lower rates of obesity and smoking, also experiencing an increase in thyroid cancer diagnosis?

We recently reported that overdiagnosis could be the reason for the doubling of thyroid cancer incidence in the state of Kerala in southern India.[3] In this region, the incidence of thyroid cancer is at least four-fold the incidence seen in other regions of India. In the population-based cancer registry (PBCR) based in the city of Thiruvananthapuram in Kerala, the incidence of thyroid cancer doubled over a decade. The age-adjusted incidence rate in 2005 to 2008 was 6.9 per 100,000 women; this rate increased to 13.3 per 100,000 women in 2012 to 2014. However, the mortality rate remained stable. Similar trends in thyroid cancer–specific mortality were also noted in other PBCRs based in major cities such as Delhi, Mumbai, Bangalore, and Chennai. It is this mismatch between the increased incidence rate and stable mortality rate of thyroid cancer that points to the contribution of overdiagnosis.

However, a recent editorial in the *Indian Journal of Cancer* overlooked the putative role of overdiagnosis in the increasing incidence rate of thyroid cancer in India.[11] The editorial suggests that the rate of larger thyroid cancers has increased in India and that the thyroid cancer–specific mortality rate has also increased. To our knowledge, there are no data from India that confirm an increase in incidence of larger tumors. The PBCRs of India do not report data on tumor size or proportion of patients with differentiated thyroid cancer diagnosis. In addition, available data suggest that the thyroid cancer–specific mortality rate is stable in India.

The editorial points to three putative factors responsible for the increase in thyroid cancer rates. First, there is a link between radiation exposure and thyroid cancer. Could the background radiation from the thorium-rich sand in Kerala be contributing to an increase in thyroid cancer rates? This is unlikely; exposure to radiation at the level of a nuclear disaster needs to occur in the region for incidence rates to increase at such a rapid pace. Second, thyroid autoimmune diseases may elevate an individual's risk

for differentiated thyroid cancer. However, such diseases have not been shown to have increased in incidence over time. Third, could an increase in iodine exposure through dietary sources be elevating the risk for thyroid cancer? Once again, this hypothesis remains just another oft-cited theory and is unlikely to have contributed to the dramatic increase in thyroid cancer rates.

Although all of these putative risk factors cannot be ignored, they do not explain the dramatic increase in incidence of thyroid cancer. Even if increasing rates of obesity or tobacco exposure result in an elevated risk for thyroid cancer, the strength of such an association would have to be profound to result in such a significant increase in the incidence rate of thyroid cancer. One other factor that could possible result in an increase the incidence rate is poor quality of diagnosis documentation in the registry in the initial years. However, even if this was the case, why would the incidence in Kerala be four times that seen in Delhi, Mumbai, Chennai, or Bangalore? The reality of overdiagnosis as the leading cause of the increase in incidence of thyroid cancer cannot be pushed under the rug.

It is important to look at examples from other regions that have seen similar trends in increasing incidence of thyroid cancer. The implementation of a national cancer screening program in South Korea led to providers offering thyroid screening for a low fee and thus an explosion of new thyroid cancers. Thyroid cancer incidence in Korea increased slowly in the 1990s and then increased meteorically in 2011 to 15 times that observed in 1993. Ahn and Welch[12] clearly caution the rest of the world on the basis of their experience with thyroid cancer screening in South Korea. Ignoring this warning and underplaying the importance of overdiagnosis in India could lead to the same situation as that seen in South Korea, especially as diagnostic laboratories and imaging modalities increase in India. In South Korea, widespread national attention and media coverage called for revision of existing practices, and as a result, a decrease in incidence rates has been reported.[12]

Overdiagnosis was thought to be a problem specific to developed nations, but with an epidemiologic transition from communicable diseases to chronic noninfectious diseases, this phenomenon could occur in developing countries also. Diagnostic laboratories and imaging facilities are increasing in India. In fact, Kerala, with its high socioeconomic and educational status, has health care quality that matches that of a developed region. This may be the only reasonable explanation for why the thyroid cancer incidence rate in Kerala is four times that seen in other parts of India and why it doubled in a decade.

Why is it important that we identify the reason for this phenomenon? A large proportion of patients diagnosed with thyroid cancer are women younger than 50 years old, and treatment of thyroid cancer could result in an increased risk for hypertension, heart disease, stroke, nutritional deficiencies, and osteoporosis.[13] To fulfill the vow that we took when we became doctors to do no harm, it is imperative that we see the elephant in the room for what it is. Overdiagnosis could be the most plausible hypothesis for the dramatic increase in thyroid cancer in Kerala and several other regions in India.

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REFERENCES

1. Davies L, Welch HG: Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 140:317-322, 2014
2. Ahn HS, Kim HJ, Welch HG: Korea's thyroid-cancer "epidemic": Screening and overdiagnosis. N Engl J Med 371:1765-1767, 2014
3. Mathew IE, Mathew A: Rising thyroid cancer incidence in southern India: An epidemic of overdiagnosis? J Endocr Soc 1:480-487, 2017
4. Brito JP, Morris JC, Montori VM: Thyroid cancer: Zealous imaging has increased detection and treatment of low risk tumours. BMJ 347:f4706, 2013
5. Davies L, Welch HG: Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 295:2164-2167, 2006
6. Leenhardt L, Bernier MO, Boin-Pineau MH, et al: Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 150:133-139, 2004
7. Yoon DY, Chang SK, Choi CS, et al: The prevalence and significance of incidental thyroid nodules identified on computed tomography. J Comput Assist Tomogr 32:810-815, 2008
8. Youserm DM, Huang T, Loevner LA, et al: Clinical and economic impact of incidental thyroid lesions found with CT and MR. AJNR Am J Neuroradiol 18:1423-1428, 1997
9. Vaccarella S, Franceschi S, Bray F, et al: Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med 375:614-617, 2016
10. Vaccarella S, Dal Maso L, Laversanne M, et al: The impact of diagnostic changes on the rise in thyroid cancer incidence: A population-based study in selected high-resource countries. Thyroid 25:1127-1136, 2015
11. Aravindan KP: Papillary thyroid cancer: Why the increase and what can be done? Indian J Cancer 54:491-492, 2017
12. Ahn HS, Welch HG: South Korea's thyroid-cancer "epidemic": Turning the tide. N Engl J Med 373:2389-2390, 2015
13. Blackburn BE, Ganz PA, Rowe K, et al: Aging-related disease risks among young thyroid cancer survivors. Cancer Epidemiol Biomarkers Prev 26:1695-1704, 2017