Children and Thyroid Cancer: Interpreting Troubling Trends

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In this issue of *Cancer*, Bernier et al reported that the rates of pediatric thyroid cancer have risen 4.43% each year for the 16 years ending in 2013.[1] A large body of work in adult thyroid cancer has identified overdiagnosis as the dominant reason for the increasing incidence in the United States and elsewhere.[2-4] Overdiagnosis is an epidemiologic term defined as the detection of cancers that, had they not been found, would have been unlikely to go on to cause harm to the person.[5] Supporting the hypothesis of overdiagnosis as the dominant reason for the increasing incidence of thyroid cancer, when the American Thyroid Association modified their guidelines for needle biopsy of nodules to discourage sampling of small lesions, a corresponding decrease in incidence rates was observed, suggesting that, indeed, overdiagnosis was the culprit.[6,7]

Although Bernier et al acknowledged this, they asserted that their findings provide evidence that there also is a true increase in the incidence of thyroid cancer,[1] and appeared to be working to extend their findings from 2017, in which they came to similar conclusions for the adult population.[8] Although we agree that a true increase in the incidence of thyroid cancer is possible, and in fact one of us reported in the past on this concern, we also are once again concerned that the inferences being drawn from the US cancer epidemiology data may be artifactual.[9-11]

First, the authors reported that there is not a reservoir of clinically silent cancers in the pediatric population.[1] Until recently, we might have agreed, but current strong evidence argues otherwise. After the nuclear power plant accident in Fukushima, Japan, in 2011, the Japanese government undertook a population-level screening program to which all children of Fukushima Province were invited. Because the radiation exposure was so low, the cancers were found so soon after the accident, and the growth patterns suggested the identified cancers actually were falling into an arrest pattern, it now is believed that the "high prevalence of childhood thyroid cancer detected in this four year study in Fukushima can be attributed to mass screening."[12-15] The work from Fukushima strongly refutes the premise that there is *not* a reservoir of clinically silent cancers in the pediatric population.

Second, the authors reported that overdiagnosis does not occur in the pediatric population because "…medical imaging of the neck would not be usually performed."[1] Computed tomography (CT) imaging rates for pediatric patients more than doubled between 1996 and 2010.[16] Therefore, similar to the adult population, given that we now know there is a reservoir of clinically silent thyroid cancers, it is likely they are being detected through the increased use of CT scans. Furthermore, it has been established that there is a strong linear relationship between CT imaging and the population incidence of thyroid cancer.[17] Given that the study by Bernier et al reported that approximately one-half of the cases in their cohort were diagnosed within the past 6 years,[1] we believe their data support a hypothesis that the increasing incidence could be due to the rapidly increasing use of medical imaging in the pediatric population. Although CT scans in children are associated with an increased incidence in later cancers, the incidence of later cancer is not large enough to be responsible for the rate of change observed in this cohort.[18] Last, in the adult population, it has been shown that not just small cancers but also larger asymptomatic ones can be found incidentally on imaging performed for other reasons.[19]

Third, the authors asserted that the increased incidence is in not just local but also regional and distant disease, and suggested this means that overdiagnosis is less likely.[1] As noted above, larger cancers also can be picked up incidentally, but there is an additional possibility: stage migration, sometimes called the "Will Rogers effect."[20] As diagnostic tests increase in sensitivity, cases that previously would have been labeled as localized are classified as regional, and so on. The increasing use of ultrasound and cross-sectional imaging generally, the advent of positron emission tomography scans,

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and the rising use of thyroglobulin as a marker of biological disease all reasonably could be expected to contribute to stage migration in this cohort.

Finally, without mortality data, it is impossible to determine whether the reported increase in incidence rates is clinically significant (ie, whether it is a true increase) or not. In epidemiology studies, comparing incidence with the concurrent trends in mortality is one of the key tests of whether the trends are due to a true increase in disease. However, given that the 30-year cancer-specific survival for papillary thyroid cancer in children diagnosed with local or regional disease is approximately 99% to 100% irrespective of sex, procedure type, or tumor size at diagnosis, and that there is only a minimal decrease in survival (97%) for patients with distant metastasis, this will always be a difficult task: the number of deaths is so small it would be hard to detect trend line changes.[21,22] Recent population-based work by Jensen et al has demonstrated similar survival outcomes in young adults.[23] In their study of 297 children and young adults in Denmark from 1980 through 2014, no change in incidence for children and adolescents (those aged birth-17 years) was noted. However, increased incidence rates (average annual percentage change, 3.7%) were observed among young adults (those aged 18-24 years). The 15-year overall survival for patients with papillary thyroid cancer remained unchanged at >99%.

The excellent survival noted for thyroid cancer diagnosed in children and adolescents does point to the larger issue: the significant duty we have as physicians to protect patients from overdiagnosis and overtreatment, which are substantial risks when a disease has both a subclinical prevalence and a very low mortality rate. Although we appreciate the concerns of Bernier et al[1] that there may be a new genetic, environmental, or dietary cause of thyroid cancer, we believe that first it is most important to closely examine the reasons for the increase that could be attributable to overdiagnosis, given this appears to be a likely explanation. If it appears to be a true increase, then efforts need to be made to determine new theories of causation. However, if it is due to the detection of subclinical disease, then efforts are necessary to curb the use of CT scans, the inappropriate use of ultrasound, and needle biopsies, in much the same way that it has been implemented in the adult population.

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