The utilization of sensitive diagnostic procedures does not completely explain the observed increased incidence in papillary thyroid cancer over three decades

Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784-91.

SUMMARY

BACKGROUND The incidence rates of thyroid cancer in the United States, Europe and other developed areas have been steadily increasing over the past three decades. This is mainly the result of a large rise in the incidence of papillary thyroid cancers smaller than 2 cm, which some have concluded is caused by the use of sensitive diagnostic tools such as ultrasonography and fine-needle aspiration biopsy that does not reflect an increase in the true occurrence of thyroid cancer but instead represents subclinical tumors that do not reflect the true incidence of clinically significant thyroid cancer. However, others have challenged this view in terms of the source and clinical consequences of this finding. The authors of the present study hypothesized that additional studies will be necessary to settle this debate if an analysis of the incidence patterns of thyroid cancer cannot be completely explained by enhanced detection. That is, if the detected cancers are not only localized but are in some cases more advanced, then the underlying cause or causes for the increased incidence of papillary thyroid cancer remain uncertain.

METHODS This study was based on an in-depth analysis of 48,403 patients with thyroid cancer in whom the cancer was diagnosed from 1980 through 2005. Data from this group were collected from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program using data from nine population-based registries in Connecticut, Iowa, New Mexico, Utah, Hawaii, Detroit, San Francisco–Oakland, Atlanta, and Seattle–Puget Sound (the SEER-9 registries), which include approximately 10% of the U.S. population. In 1992, four registries from San Jose–Monterey, Los Angeles, rural Georgia, and Alaska Natives were added to the registry, thus expanding the coverage to 14% of the U.S. population (the SEER-13 registries). The analysis included data from the early years of the SEER-9 database, which provided racial categories of only white and black, and from the SEER-13 database, which became available in 1992, providing data on Hispanic ethnicity and Asian/Pacific Islanders (APIs) who have a high rate of thyroid cancer. The analysis was restricted to patients with malignant thyroid tumors that were microscopically confirmed and not diagnosed solely at autopsy or identified only through death certificates. On this basis, 887 patients (1.8%) were excluded from the analysis, leaving 47,516 patients, 39,706 of whom had papillary thyroid cancer. Thyroid cancer incidence rates vary by sex and race/ethnicity, factors that influence access to and utilization of health care, which were not taken into account in previous studies when evaluating trends in thyroid cancer incidence. This study thus examined thyroid cancer incidence rates by demographic and tumor characteristics based on 48,403 patients with thyroid cancer diagnosed from 1980 through 2005.

For a long-term trend analysis of thyroid cancer incidence rates in white patients, regardless of Hispanic ethnicity, and black patients, the years of diagnosis in the SEER-9 database were grouped into seven calendar-year categories: 1980–1983, 1984–1987, 1988–1991, 1992–1995, 1996–1999, 2000–2002, and 2003–2005. For a shorter-term analysis of whites stratified by Hispanic ethnicity and APIs, only the last four calendar-year categories, 1992–1995 to 2003–20005 were used. Tumor size has been recorded since 1983 in the SEER database, before which this was unavailable in 23% of thyroid tumors. Tumor stage was stratified into three groups: localized, regional, or distant disease at the time of diagnosis. All incidence rates were age-adjusted to the year 2000 U.S. population and expressed as rates per 100,000 person-years.

RESULTS BY HISTOLOGY By far the most common form of thyroid cancer among all sex and race/ethnic groups was papillary thyroid cancer (65 to 88%), followed by follicular cancer (9 to 23%); the rates were twofold to threefold greater in women (Figure 1). The incidence rates tended to be higher among white than among black patients and among white non-Hispanics than among white Hispanics or APIs. From 1980–1983 to 2003–2005, the incidence rates of papillary cancer tripled among white and black women ($P<0.001$) and doubled among white and black men ($P<0.001$). From 1992–1995 to 2003–2005, the incidence rates of papillary thyroid cancer increased among every sex and race/ethnic group, ranging from 23% ($P = 0.07$) among API men to 104% ($P<0.01$) among black women (Figure

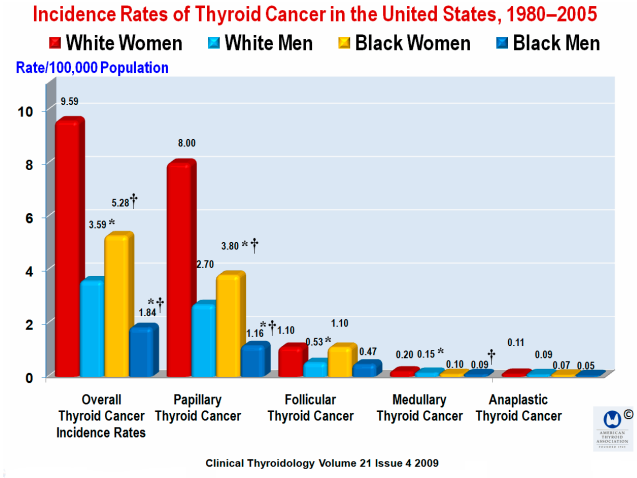

Figure 1. The incidence rates of thyroid cancer in the United States adjusted to the 2000 population and stratified according to tumor histology. Data are derived from the SEER-9 registries from 1980 through 2005.*$P<0.01$ as compared with same-race women. †$P<0.05$ as compared with same-sex white patients. This figure is derived from Table 1 in Enewold et al.

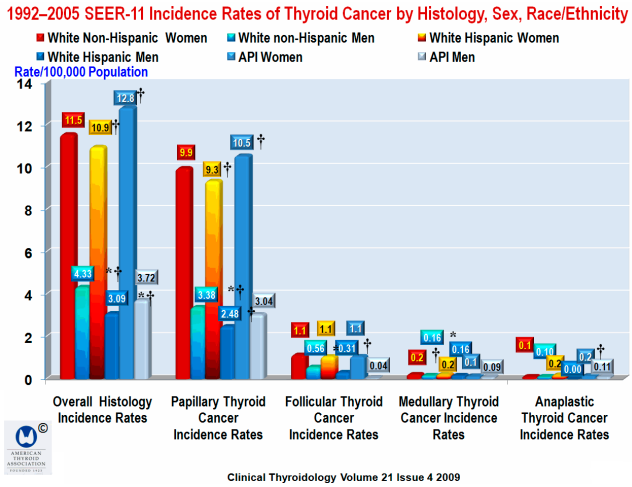

Figure 2. The incidence rates of thyroid cancer by sex and race/ethnicity, and histology, 1992-2005 in SEER-11 registries (this is SEER-13 registries excluding the Alaska Natives and rural Georgia registries).*P<0.01 as compared with same-sex/ethnicity for women. †P<0.05 as compared with same-sex white non-Hispanic patients. This figure is derived from Table 2 in Enewold et al.

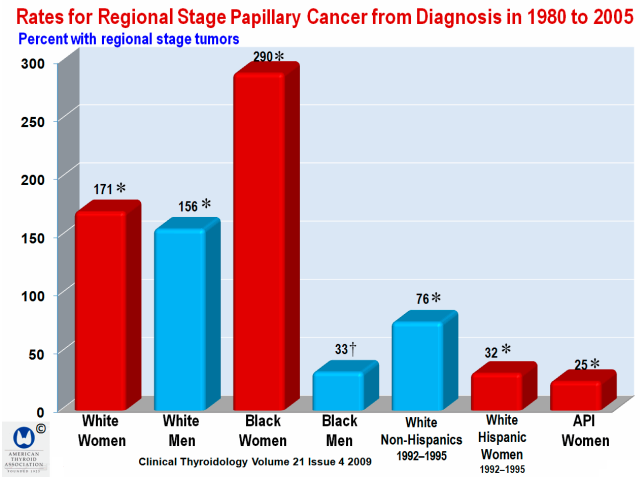

Figure 4. The rates for regional staged papillary thyroid cancer are shown over a >20-year period from 1980 to 2005. P<0.01 for rising incidence rates, except for regional tumors among black men (P>0.40). Papillary cancer distant stage rates more than doubled among whites and among Asian Pacific Islanders (APIs) from 1980 to 1983. Regional tumor rates were stable among white Hispanic and APIs.

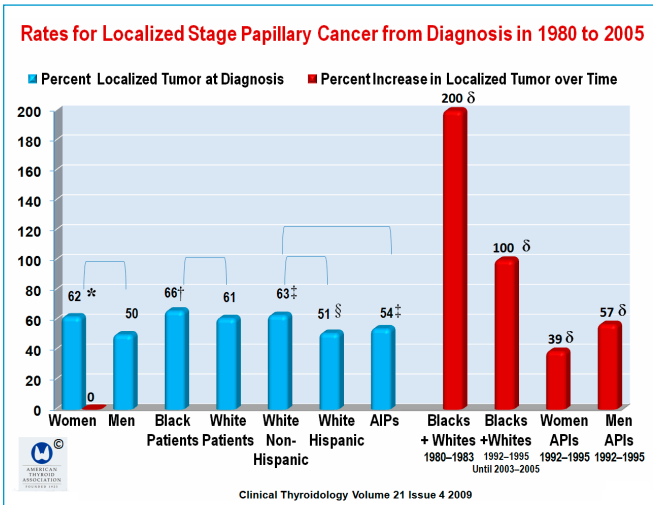

Figure 3. Incidence rates for localized papillary thyroid cancers. *P<0.01 for women versus men. †P<0.01 for black versus white patients. ‡P<0.01 for white non-Hispanics versus white Hispanics. §P<0.01 for white non-Hispanics versus Asian Pacific Islanders (API). δP<0.01 for percent increase in localized tumor over the times noted in the horizontal axis.

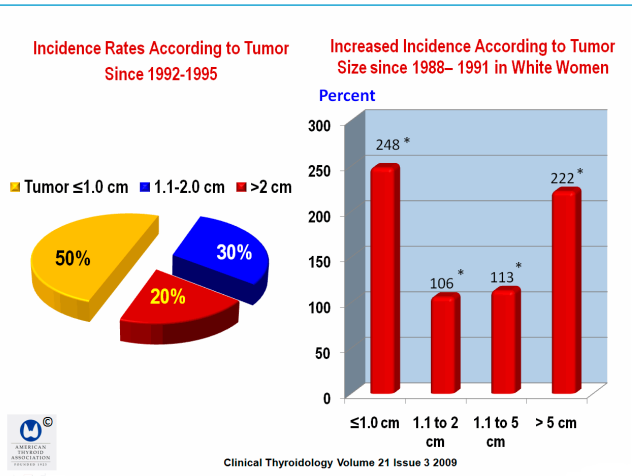

Figure 5. The increased incidence rates according to tumor size since 1988–1991 are for white women with papillary thyroid cancer. P*<0.01 for all four size groups. Rates among white men and black women were similar. During the years of study, the rates for most tumor sizes also increased among white Hispanics, Asian Pacific Islanders and black men. About 50% of the overall increase in papillary cancers since 1992–1995 was due to the increasing rates of cancers ≤1.0 cm, 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm.

2). Because papillary cancer was increasing more rapidly than all other forms of thyroid cancer, it was the most common form of thyroid cancer, thus permitting stratification by other patient and tumor variables as well histology alone. Follicular cancer rates were more variable, increasing only moderately among API men and to 104% (P<0.01) among black women.

RESULTS BY TUMOR STAGE Although the incidence rates for papillary cancer increased for tumors of all stages, it increased most regularly for localized tumors among all racial/ethnic groups. The rate of localized tumors was greater among women than among men (62% vs. 50%) and among black than among white patients (66% vs. 61%), and among white non-Hispanics (63%) as compared with white Hispanics (51%) or APIs (54%) (P<0.01 for all) (Figure 3). The most common tumor stage at the time of diagnosis was thus localized for all racial/ethnic groups, except for white Hispanic and API men, among whom regional stage was most frequent. The rates of localized tumor among white and black patients increased approximately 200% (range, 186 to 232%) since 1980–1983 and 100% (range, 97 to 155%) from 1992–1995 to 2003–2005. Since 1992–1995, the incidence rates of localized papillary cancer among APIs increased 39% in

women and 57% in men (all P<0.01) (Figure 3). During the more than 20-year period from 1980–1983 to 2003–2005, regional tumor rates increased 171% and 156% among white women and men, respectively, and 290% and 33% among black women and men, respectively (Figure 4). Since 1992–1995, regional tumor rates increased 49% to 76% among white patients and non-Hispanics, 32% among white Hispanic women, and 25% among API women and were stable among white Hispanic and API men (Figure 4). Distant stage tumor rates more than doubled among white patients since 1980–1983, increasing >130% since 1980–1983

RESULTS BY TUMOR SIZE Although the incidence rates for tumors of all sizes increased, the increases were most rapid for the smaller tumors (Figure 5). Since 1988–1991, the earliest years that tumor size was adequately recorded, the tumor rates among white women increased 248% for tumors ≤1 cm, 106% for tumors 1.1 to 2 cm, 113% for tumors 1.1 to 5 cm, and 222% for tumors >5 cm (all P<0.01). (Figure 5) The tumor size increases among white men and black women were similar. The rates for most tumor sizes also increased among white Hispanics, APIs, and black men during this period. Approximately 50% of the overall increase in papillary thyroid cancer since 1992–1995 was the result of increasing rates of very small cancers (≤1.1 to 2 cm) and 20% among tumors >2 cm. The size-specific increases in tumor incidence among white men and black women were similar. During the period studied, the rates for most tumor sizes also increased among white Hispanics, APIs, and black men. From 1992 to 1995, approximately half of the increase in papillary thyroid cancers was due to increasing rates of very small cancers (≤1.0 cm), 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm (Figure 5).

RESULTS BY AGE-SPECIFIC TIME TRENDS The age-specific time trends in papillary thyroid cancers were consistently apparent across all age, sex, and race/ethnic groups, except for the youngest (<20 years) and oldest (≥80 years) patients, who comprised only 2% and 3%, respectively, of each race/ethnic group. Among women, the highest incidence rates occurred among those who were 40 to 59 years of age, but the steepest increases in tumor incidence were observed among those of 60 through 79 years. However, both the highest age-specific time trends for papillary cancer and the largest increases over time tended to be among older men.

CONCLUSION Increased medical surveillance and the use of more sensitive diagnostic procedures do not completely explain the observed increases in papillary thyroid cancer rates, leaving other possible explanations for the observed increase in papillary thyroid cancer over the past three decades.

COMMENTARY

The incidence of thyroid cancer in the United States has been increasing steadily over the past three decades. Why this has occurred has become a matter of debate. Davies and Welch (1) recently investigated the size distribution of papillary thyroid cancers in approximately 2,400 thyroid cancer cases in the SEER-9 registry from the years 1988 to 2002, 88% of which were papillary thyroid cancers. They found a 2.4-fold increase (P<0.001 for trend) in the incidence of thyroid cancer, which was virtually completely due to an increase in papillary cancer that increased by 5 per 100,000 persons, from 2.7 to 7.7, thus representing a nearly 3-fold increase in the incidence (P<0.001 for trend). However, there was no significant change in the incidence of follicular, medullary, and anaplastic thyroid cancer (P>0.2 for trend). The bulk of the increased was from the detection of small cancers: 49% (95% confidence interval, 47 to 51) were from cancers 1 cm or less and 87% from tumors 2 cm or less. Papillary thyroid cancer mortality was found to be stable between 1973 and 2002, with approximately 0.5 deaths per 100,000. The authors concluded that the increasing incidence of thyroid cancer is predominantly due to the increased detection of small papillary cancers, which, combined with the flat mortality rates, suggests that this is an artifact produced by a reservoir of subclinical disease, not a true occurrence of thyroid cancer. The authors opined that knowing the underlying cause of the increasing incidence is important because if this is a true occurrence of disease, then efforts should be made to address its cause and aid those at greatest risk of the disease, but if it is based simply on increased diagnostic scrutiny, then the challenge to the health care community is how to identify patients who truly warrant therapy.

In another study, Kent et al. (2) used the Ontario Cancer Registry to investigate the relation between incidence rates and tumor size, age, and sex, and also found a significantly higher number of differentiated thyroid cancer, from 403 cases in 1990 to 990 in 2001—a 146% increase in 12 years, or 13% per year. In all, papillary thyroid cancer comprised approximately 95% of the cases. An analysis that grouped tumor size into small (≤2 cm), medium (2 to 4 cm), and large (>4 cm) found a significant increase in the incidence rate for the small-tumor group (P = 0.001) and the large-tumor group (P = 0.023), but not the medium-sized-tumor group. The overall incidence rates were significantly lower among men (22.1%) as compared with women (77.4%), but there was no significant difference when tumor size was compared among men and women or among patients 45 years of age or younger. Both studies concluded that the more frequent use of medical imaging has led to an increased detection rate of small, subclinical tumors, which accounts for the high incidence of papillary thyroid cancer. Of note, both studies were done without reference to patient race/ethnic demographics, which are important because thyroid cancer incidence rates vary by sex and race/ethnicity, which are factors that also influence access to and utilization of health care. One would thus expect reduced incidence rates in men, especially Hispanics and blacks, and higher rates in APIs with a known high incidence of thyroid cancer.

Enewold et al. began with the hypothesis that if the increase in thyroid cancer incidence was all due to improved disease detection, then one would expect more rapid increases in small, early-stage tumors than large late-stage tumors, and as a result, the incidence rates for large late-stage tumors should decline and

the rates of tumors with all other histologies should increase, except for anaplastic thyroid cancer. However, the Enewold study found trends in disease incidence that did not completely support this hypothesis. There were consistent increases in the incidence rates for papillary cancer only. Although the greatest increases were observed among smaller, early-stage papillary thyroid cancers, there were no declines in larger, more advanced tumors, while tumors of all sizes increased over time. For example, the incidence rates of the smallest tumors (≤1 cm) increased 248%, and in those with the largest tumors (>5 cm), it increased 222%. Moreover, the incidence rates for all tumor stages at the time of diagnosis increased among white women.

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References

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2. Kent WD, Hall SF, Isotalo PA, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ 2007;177:1357-61.