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CLAREMONT McKENNA COLLEGE

COMPLEXITIES IN THE DIAGNOSIS & TREATMENT OF THYROID CANCER: DISCUSSIONS, OBSERVATIONS, RESEARCH AND PUBLIC POLICY

SUBMITTED TO

PROFESSOR FREDERICK LYNCH

AND

DEAN GREGORY HESS

BY

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FOR

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"Intensive surveillance has improved the ability to detect small-volume tumor recurrence with a sensitivity that surpasses current understanding of the clinical implications of detecting clinically occult residual or recurrent disease."

Nathan Johnson and Mitchell Tublin referring to differentiated thyroid cancer

"The combination of data, statistical methodology and motivation seems a potent anesthetic for skepticism."

Sander Greenland referring to treatment recommendations based on epidemiological studies

"It has been hypothesized that increased detection of low-risk disease can lead to overestimation of treatment efficacy and a subsequent increase in use of therapy."

Megan Haymart referring to thyroid cancer treatment

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I would like to acknowledge a large number of people who helped me delve into such an obscure, yet important, subject. I would like to thank Dr. Sharon Elliot and the other researchers in her lab at the University of Miami Miller School of Medicine. They were an absolute pleasure to work with and did their best to both teach me about their research and introduce me to the world of endocrinology research. I would also like to thank Dr. John Lew for allowing me to observe his thyroidectomies and teaching me about endocrine oncology. He taught me a love of surgery that is an inspiration. I would like to thank the Endocrine Society for providing me with the funding to make my experience possible. I would like to thank my reader Frederick Lynch for his encouragement and support throughout the writing process. Last, but not least, I would like to thank my father for his unwavering insight and elucidations. His love and support, not only in the writing of this thesis, but also throughout my life have been unceasing.

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Introduction

Last year I won the Maurice Raben Summer Fellowship Award from the Endocrine Society to do research in thyroid cancer. Thyroid cancer, the most common and prevalent of all endocrine malignancies, accounts for more than 95% of endocrine-related cancers. An estimated 56,000 people will be diagnosed with thyroid cancer this year.[1] With an annual increased incidence of about 5.5% and 6.6% in men and women respectively, it is, and for the last three decades has been, the fastest growing cancer in the United States.[2] Between 1979 and 2009, for example, age-adjusted incidence per 100,000 has increased from 4.48 to 14.25.[3] There is significant geographical variation in reported incidence in other countries, although some differences also are presumably due to differences in the scope and accuracy of other countries' reporting systems. In most countries, annual age-adjusted incidence per 100,000 persons has varied between 0.9 to 2.6 in men and 2.0 to 5.9 in women over the past several decades with additional variation based on race, ethnicity and age.[4]

Differentiated thyroid cancer (DTC), consisting of papillary and follicular thyroid cancer, constitutes approximately 90% of all thyroid malignancies.[5] The increase in cases is almost entirely attributable to an increase in papillary thyroid cancer (PTC). The total

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[1] "Thyroid Cancer Treatment (PDQ®)" National Cancer Institute, http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page1#Reference1.1 (accessed 4/20/2012).

[2] American Cancer Society, *Cancer Facts & Figures 2012* (Atlanta: Georgia, 2012), http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2012 (accessed 4/21/2012).

[3] National Cancer Institute, "Cancer of the Thyroid - SEER Stat Fact Sheets" http://seer.cancer.gov/statfacts/html/thyro.html (accessed 4/21/2012).

[4] Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy,* eds. Biersack, H.J. and Grunwald, F. (Berlin Springer-Verlag 2d ed. 2005) 6.

[5] American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer and others, "Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer" *Thyroid* (2009) 19:1167-1214.

number of PTC cases in the United States increased by more than 300% from 1973-74 to 2003-04.[6] A significant portion of the PTC cases in turn consists of papillary thyroid microcarcinomas (PTMC) measuring 1 cm or smaller which for example, increased by 441% between 1983 and 2006.[7] There is no generally accepted explanation for these startling rates of increase.

The number of persons diagnosed with thyroid cancer is expected to continue to increase. It is estimated that approximately 13-67% of people will have thyroid nodules during their life of which approximately 5% will be malignant regardless of size.[8] The standard treatment, a thyroidectomy frequently followed by radioactive 131 iodine treatment and a lifetime of thyroid replacement therapy, accordingly would seem to be a likely future event for an increasing percentage of the population.

Despite the magnitude of the increase, there has been minimal or no increase in age-adjusted mortality rates depending on the particular time periods selected. In the United States, age-adjusted mortality for all ages, both sexes, in 1979 was 0.5276 as compared to 0.5213 in 2009.[9] Between 1975 and 1988, there was a negative 2.2 annual percentage change and between 1988 and 2009, a positive .8 annual percentage change in age-adjusted mortality in the United States.[10] It is estimated that approximately 1780 people in the United States will die from thyroid cancer this year. Although the majority of these cases involve DTC, simply because they are the overwhelming percentage of cases, it also includes many who were diagnosed with the other more rare and serious

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[6] Guo-Pei Yu, James Chun-Lun, *et al*. "Thyroid Cancer Incidence and Survival in the National Cancer Institute SEER Race Ethnicity Groups" *Thyroid* (2010) 20:468.

[7] Yu, Xiao-Min, Yin Wan, Rebecca Sippel and Herbert Chen, "Should All Papillary Thyroid Microcarcinomas be Aggressively Treated?" *Annals of Surg* (2011) 254:653.

[8] M. J. Yeung and J. W. Serpell, "Management of the Solitary Thyroid Nodule" *Oncologist* (2008) 13:105.

[9] National Cancer Institute, *Cancer of the Thyroid - SEER Stat Fact Sheets*

[10] National Cancer Institute, *Cancer of the Thyroid - SEER Stat Fact Sheets*

forms of thyroid cancer.[11] Survival rates for younger patients (< age 40-45) after a thyroidectomy for PTC, the most common form of DTC, are variously reported as 95-99%.[12] Thyroid cancer is a benign diagnosis for most, but not all, DTC patients.

Women have a significantly higher incidence of thyroid cancer than men and account for a larger percentage of the increased incidence. Thyroid cancer ranks as one of the top 6 types of cancer in women, but does not enter the top 15 in men.[13] However, in males it presents in more aggressive and lethal forms. This epidemiological peculiarity, though baffling, may yield some of the most potent and exciting clues into how sex-specific hormones such as estrogen affect not only the growth of thyroid cancer but also all cancers. Population disparities in incidence and outcome have been responsible for significant medical revolutions. It is possible that progress in understanding this cancer will provide a new understanding of human physiology.

There is no generally accepted explanation for the sexual disparity. The female-to-male ratio in DTC is about 3:1 with significant variation at different ages. At puberty the female-to-male ratio may be as high as 14:1 with declining ratios as age increases.[14] Interestingly, in children under age ten there is no difference in incidence between girls and boys and the higher female incidence decreases after menopause.[15] There also is no sex difference in incidence in clinically irrelevant papillary microcarcinoma ≤1 cm found

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[11] *Thyroid Cancer Treatment (PDQ®)*

[12] Rebecca L. Brown, "Thyroid Cancer: Burden of Illness and Management of Disease" *Cancer* (2011) 2:194.

[13] L. Enewold *et al*., "Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005" *Cancer Epidemiology, Biomarkers & Prevention* (2009) 18:784-791.

[14] Farahati, J., P. Bucsky, T. Parlowsky, U. Mader, and C. Reiners. "Characteristics of Differentiated Thyroid Carcinoma in Children and Adolescents with Respect to Age, Gender, and Histology," *Cancer* (1997) 80:2156-2162.

[15] D. M. Morris *et al*., "Localized Well-Differentiated Thyroid Carcinoma: Survival Analysis of Prognostic Factors and (131)I Therapy" *Annals of Surgical Oncology* (1998) 5:329-337.; L. E. Sanders and B. Cady, "Differentiated Thyroid Cancer: Reexamination of Risk Groups and Outcome of Treatment" *Archives of Surgery* (1998) 133:419-425.

in autopsy studies of persons who died from causes unrelated to thyroid disease, which presumably means that some sex-linked factor causes the microcarcinoma to be more likely to become clinically relevant in females.[16] In fact, estrogen receptor (ER) action has been shown to regulate cell growth and apoptosis by participating in mitochondrial homeostasis in papillary thyroid cancer cell lines.[17]

My research was directed at cellular function that may help to explain the higher rate of female incidence. Communication between the cell nucleus and the mitochondria (retrograde signaling) is believed to control estrogen-induced signaling involved in the apoptosis, proliferation, and differentiation of both normal and malignant cells.[18] In thyroid cancer cells, E_2 mediated extracellular signaling may regulate tumor cell growth and apoptosis.[19] Rapidly dividing cancer cells are known to produce significant amounts of intracellular reactive oxygen species (ROS), which appears to promote accelerated cell cycle activity in neoplastic cells.[20] As the largest producer of ROS, mitochondria may participate in the development and progression of cancers. ROS (mitochondrial and extramitochondrial derived) are implicated in the regulation of signal transduction pathways leading to control of gene expression and post-translational modification of proteins.[21] Therefore, understanding ROS-induced mitochondrial signaling and

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[16] Drucker, William D. and Richard J. Robbins, "Papillary Microcarcinoma of the Thyroid," in *Practical Management of Thyroid Cancer: A Multidisciplinary Approach* eds. Mazzaferri, Ernest L., *et al*. (London Springer-Verlag 2006) 371-73.

[17] Q. Zeng *et al*, "The Contributions of Oestrogen Receptor Isoforms to the Development of Papillary and Anaplastic Thyroid Carcinomas" *Pathology* (2008) 214:429-432; Q. Felty and D. Roy, "Estrogen, Mitochondria, and Growth of Cancer and Non-Cancer Cells" *Carcinogenesis* (2005) 4:1.

[18] Ibid.

[19] Zeng *et al*., "The Contributions of Oestrogen Receptor Isoforms to the Development of Papillary and Anaplastic Thyroid Carcinomas" *Pathology* 214:429-433.

[20] Felty and Roy, "Estrogen, Mitochondria, and Growth of Cancer and Non-Cancer Cells," *Carcinogenesis*, (2005) 4:1.

[21] R. G. Allen and M. Tresini, "Oxidative Stress and Gene Regulation" *Free Radical Biology & Medicine* (2000) 28:463-499; C. K. Sen, "Antioxidant and Redox Regulation of Cellular Signaling: Introduction" *Medicine and Science in Sports and Exercise* (2001) 33:368-370.

mitochondrial regulation of ER expression may provide new insight into thyroid cancer progression and metastasis.

Thyroid cancer cell research is complicated by the recent discovery that a substantial amount of research has been conducted with contaminated or redundant cell lines. One recent study found that up to 36% of the thyroid cancer cells being used for research were misidentified as thyroid cancer cells or were contaminated by other cancer cells. Another major study found only 20 of 40 common cell lines to be correctly identified.[22] The degree to which this misidentification has distorted reported research results is unknown.

My research was conducted under the direction of (the truly wonderful) Dr. Sharon Elliot at the University of Miami Miller School of Medicine Department of Surgery Endocrinology Lab. I spent my winter break period in the lab conducting an extensive review of the literature, learning the methods and techniques that I would need over the summer and gaining an introduction to the lab.

We set up an experiment to derive and propagate thyroid cancer cell lines from fresh surgical specimens and then remove the nucleus from the cancer cells with actinomycin D under conditions that preclude recovery of treated cells. The next step was to remove mitochondrial DNA from control cells using a two-week treatment with ethylene bromide. This would allow us to fuse the cells using 45% polyethylene glycol (12). The intention was to create cells that contained mitochondrial DNA (mtDNA) of cancer cells and a nucleus from control cells. Prior to the development of the cybrids, the mtDNA of each cell line would be sequenced to determine the unique polymorphisms

[22] R. E. Schweppe *et al*., "Deoxyribonucleic Acid Profiling Analysis of 40 Human Thyroid Cancer Cell Lines Reveals Cross-Contamination Resulting in Cell Line Redundancy and Misidentification" *Clinical Endocrinology & Metabolism* (2008) 93:4331.

present in the mtDNA. This fingerprint could be used to ensure that the cybrids contain only the mtDNA from the cancer cells. Respiration and ROS content can then be determined before and after cybrid production. ER expression can be determined by real time PCR and western analysis and invasion assays. This research with some variation is now ongoing with results that are not ready for publication.

Obtaining genuine cancerous thyroid cell lines obviously is critical for all thyroid cancer research. Dr. Elliot's laboratory at the University of Miami is particularly well situated to address this issue because of its proximity to the surgical suites where the patients' thyroids are removed. Dr. Elliot's lab harvests the cell lines directly from the thyroid cancer patients at Jackson Memorial, the University of Miami's teaching hospital. Dr. John Lew, an endocrine oncology surgeon at the University of Miami Medical School and one of Dr. Elliot's colleagues, also invited me to shadow thyroid surgeries in order to learn more about biopsies and creation of cell lines.

My interest in the thyroid is personal. I began having unexplained symptoms when I was a teenager. An eventual diagnosis of hypothyroidism, perhaps caused by a virus, was made only after considerable delay. I was an athlete engaged in intensive physical training and exhaustion resulting from pathology was not the most obvious diagnosis. It was striking, however, how vague the guidelines were on symptoms, blood tests and monitoring the inception, continuation and diminution of treatment. Also striking has been how many other people I meet on a daily basis who also suffer from thyroid conditions.

Until recently, most of the medical community attributed the increased incidence in thyroid cancer to increased diagnostic capabilities resulting from advances in

technology rather than an actual increase in prevalence based on data showing that 87% of the increase was attributable to tumors measuring less than 2 cm., the absence of any significant improvement in therapy which might explain the unchanged mortality rates and the absence of any clear evidence of a risk factor responsible for the increased incidence.[23] Recent evidence suggests that this reasoning is not fully accurate.[24] A subsequent comprehensive study of this issue, which examined 48,403 thyroid cancer patient records, concluded that at least 50% of the increase could not be explained solely by increased diagnostic capabilities.[25] Most endocrinologists now acknowledge that more research needs to be done for a more complete understanding of the increase.[26]

Improved ultrasound and fine needle biopsy technology enables doctors to more easily find smaller tumors that older technology would overlook in all types of cancer. However, studies show an increase in thyroid tumors of all sizes and types across all communities. This contradicts the belief that the increase is solely the result of smaller tumors now being detected with better technology but leaves open the determination of precisely how much of the increased incidence is clinically significant.[27] The next phase of research now is beginning to focus on other factors such as environmental, dietary, and

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[23] Davies, Louise and H. G. Welch, "Increasing Incidence of Thyroid Cancer in the United States, 1973-2002" *JAMA* (2006) 295:2164-2167.

[24] Enewold *et al*., "Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005" *Epidemiology, Biomarkers and Prevention* (2009) 18:784-791; Yu, Guo-Pei, *et al*. "Thyroid Cancer Incidence and Survival in the National Cancer Institute SEER Race Ethnicity Groups" *Thyroid* (2010) 20:470-473; Amy Y. Chen, Ahmedin Jemal and Elizabeth M. Ward, "Increasing Incidence of Differentiated Thyroid Cancer in the United States, 1988-2005" *Cancer* (2009) 115:3807.

[25] Enewold *et al*., "Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005" *Epidemiology, Biomarkers and Prevention* (2009) 18:784-91.

[26] Shari Rudavsky, "Medical Researchers Unsure Why Thyroid Cancer Cases on the Rise – USATODAY.com " http://www.usatoday.com/news/health/story/health/story/2012-01-15/Doctors-unsure-why-thyroid-cancer-cases-on-the-rise/52582694/1 (accessed 4/20/2012)..

[27] Chen, Jemal and Ward, "*Increasing Incidence of Differentiated Thyroid Cancer in the United States, 1988-2005" Cancer* (2009) 115:3807.

genetic causes that may explain some portion of the increasing incidence in thyroid cancer.

Despite the pressing issues raised by its growth rate, thyroid cancer is one of the least studied and least funded cancers in the United States.[28] Although there is almost no reliable data on its economic impact, its prevalence makes it likely that it is becoming one of the more expensive diseases in our health care system. There remains much to be questioned, much less understood, in the realm of thyroid cancer. This thesis is a presentation of what is known, about thyroid cancer with the intent of fostering more research, awareness, and education on the subject.

[28] "Cancer Research Funding," National Cancer Institute, http://www.cancer.gov/cancertopics/factsheet/NCI/research-funding (accessed 4/18/2012).

Chapter 1: The Facts: An Introduction to the Thyroid and Thyroid Cancer

The thyroid is tucked away inside the lower part of the neck wrapped around the trachea. It is a butterfly-shaped organ with two lobes connected by a narrow bridge called the isthmus. It weighs about 20 grams and is approximately the size of a quarter. Three main arteries, the superior thyroid artery, inferior thyroid artery, and the thyroideaima, supply about 5 mL of blood per gram of tissue to the thyroid, twice as much as what is supplied to each kidney.

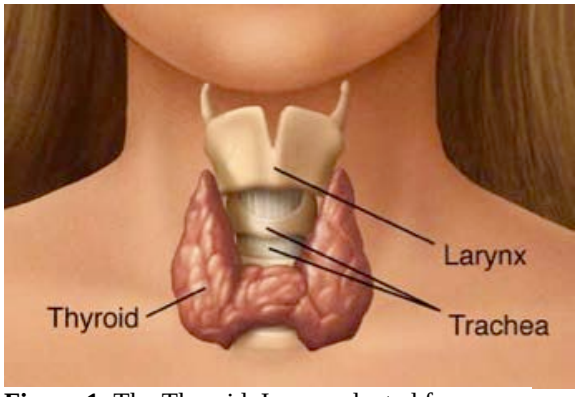

Figure 1: The Thyroid. Image adapted from: The Mayo Clinic. "Thyroid Cancer." http://www.mayoclinic.com/health/thyroid-cancer/DS00492 (accessed 4/02/2012).

Thyroid function is essential for every cell in the human body. It is responsible for regulating appropriate amounts of the pituitary gland's secretion of thyrotrophin (known as Thyroid Stimulating Hormone or TSH) to carry out bodily functions including the synthesis and storage of hormones that regulate metabolism, heart rate, body temperature, and tissue growth. The thyroid secretes three hormones, triiodothyronine (or T3, indicating 3 iodine atoms), thyroxine or tetraiodothyronine (or T4, indicating 4 iodine atoms), and calcitonin (CT). The synthesis of T3 and T4 are dependent on dietary iodine and are regulated by TSH. The hormones are controlled via thyrotrophin releasing hormone (TRH) from a negative feedback pathway beginning in the anterior pituitary gland whose thyrotroph cells produce TSH. The precise roles of T3 and T4 once released into the bloodstream by the thyroid are poorly understood.

Thyroid dysfunction is implicated in a number of diseases including, but not limited to, hyperthyroidism, hypothyroidism, Grave's disease, Hashimoto's thyroiditis, and goiter. There is a rich history of thyroid disease in medicine. There are reports as early as 2700 B.C. of the treatment of enlarged thyroids using burnt seaweed and sponges in Chinese medicine whose efficacy was due to the iodine contained within. In 961, Abul Kasim, a court physician in Codoba, described the first thyroidectomy and thyroid biopsy for goiter. Thomas Wharton, who drew the original surgical sketches of thyroidectomy procedures, named the thyroid in 1656 after the Greek word for shield "thyreos," based on the shape of the near-by thyroid cartilage.[29] In 1909, Theodor Kocher won the Nobel Prize in Medicine for his research on the thyroid and complications following thyroidectomies. His work resulted in a reduction in thyroidectomy mortality from 14% in 1884 to .18% in 1898.[30]

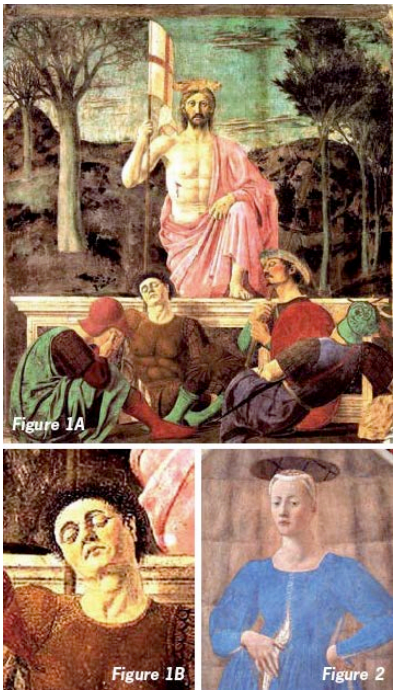

Figure 1: "La Resurrezione" (Figure 1A) and "La Madonna del Parto" by Piero Della Francesca. Each painting identifies goiter from iodine deficiency in Borgo San Sepolcro, the village where Della Francesca was born. Image adapted from International Council for the Control of Iodine Deficiency Disorders. "IDD Newsletter" no. 39 (Feb 2011): 1-20

The discovery of the role of iodine in goiter was the first recognized discovery of the association between the environment and human health and the first discovery of the importance of a trace element to human health. It is one of the most significant public

[29] Sawin, Clark T., "The Heritage of the Thyroid," in *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text* (8th ed.), ed. Lewis E. Braverman and Robert D. Utiger (Philadelphia: Lippincott Williams & Wilkins 2000) 3.
[30] Ibid; "American Thyroid Association Thyroid Timeline" American Thyroid Association, http://www.thyroid.org/professionals/education/timeline.html (accessed 4/18/2012).

health discoveries of modern epidemiology.[31] Health problems resulting from iodine deficiency, collectively referred to as iodine deficiency disorders, or IDDs, can cause mental retardation, growth and development impairment in children including hearing and speech impediments, and miscarriages, still births, and other complications in pregnant women. Congenital hypothyroidism resulting from iodine deficiency (hypothyroidism at birth) is the single most common cause for preventable mental retardation and even mild deficiencies may be associated with low intelligence in children.[32]

Approximately 2.2 billion people (38%) in the world live in iodine-deficient areas.[33] According to the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), "iodine deficiency was once considered a minor problem, causing goiter [sic], an unsightly but seemingly benign cosmetic blemish. However, it is now known that the effects on the developing brain are much more deadly, and constitute a threat to the social and economic development of many countries."[34] Only small amounts (100–150 μg) of iodine are required daily to prevent any complications, making iodine deficiency disorders one of the most easily preventable illnesses in public health.[35]

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[31] C. C. Johnson, F. M. Fordyce and A. G. Stewart, *Environmental Controls in Iodine Deficiency Disorders- Project Summary Report* (Nottingham, UK: British Geological Survey, 2003) (accessed 4/18/2012).
[32] "Thyroid.Org: Iodine Deficiency" http://www.thyroid.org/patients/patient_brochures/iodine_deficiency.html (accessed 4/9/2012); International Council for the Control of Iodine Deficiency Disorders, "IDD Newsletter" 39, Feb 2011 (2011): 1-20 (accessed 4/21/2012).
[33] Johnson, Fordyce and Stewart, *Environmental Controls in Iodine Deficiency Disorders- Project Summary Report*, 2.
[34] *Ibid*.
[35] *Ibid*.

Thyroid conditions are collectively referred to as thyroid disease. It is estimated that about 1 in 10 Americans suffer from abnormal TSH levels.[36] The most common functional disorder is hypothyroidism which results from the production of insufficient amounts of thyroid hormones. Prevalence of overt hypothyroidism is estimated to be approximately 1-2% in women and 0.1% in men. Subclinical hypothyroidism (elevated TSH but otherwise normal T4 values), which progress to overt hypothyroidism in 5-18% of patients per year, occurs in 4-10% of the United States population.[37] Women have a significantly higher prevalence of thyroid disease than men.[38] This is important because, after radiation, the most significant risk factor for thyroid cancer is benign thyroid disease and goiter.[39]

Thyroid disease, including thyroid cancer, leads to a remarkable number of thyroidectomies. A recent study surveyed the largest database of hospital admissions and found that 59,478 patients (74.8% female, 30.8% malignant neoplasm) were admitted and underwent thyroidectomies in 2009. The authors noted that it is believed that nearly 50% of thyroidectomies are performed on an out-patient basis and thus are not included in those statistics.[40] It is likely that these numbers have increased since 2009.

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[36] Carnaris GJ, Manowitz NR, Mayor G Ridgway EC. "The Colorado Thyroid Disease Prevalence Study" *Arch Intern Med* (2000) 160:526-534.
[37] McDermott, Michael T. and E. Chester Ridgway, "Diagnosis and Treatment of Hypothyroidism," in *Medical Management of Thyroid Disease.* David S. Cooper ed. (New York Marcel Dekker, Inc. 2001) 136.
[38] Wang, Clifford and Lawrence M. Crapo, "The Epidemiology of Thyroid Disease and Implications for Screening" Epidemiology and Clinical decision Making (1997) 26:189-218.
[39] Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy*, Biersack, H.J. and Grunwald, F. (eds). (Berlin Springer-Verlag (2d ed.) (2005) 20; Figge, James J., "Epidemiology of Thyroid Cancer" in L. Wartofsky and Douglas Van Nostrand, *Thyroid Cancer: A Comprehensive Guide to Clinical Management*, 9.
[40] Vashishta, Rishi, *et al*., "Thyroidectomy Outcomes: A National Perspective" *Otol. Head Neck Surgery July 2012.*

Thyroid disease, as well as thyroid cancer, is inexplicably increasing annually resulting in depression, exhaustion, and temperature, metabolic, and appetite irregularities among an estimated 70 million Americans. Like thyroid cancer, it now is believed that the increase in thyroid disease is attributed to more than just increased diagnosis and detection of preexisting pathology. The mystery behind the increase of thyroid conditions has become one of the confounding current medical puzzles.

Despite its enormous importance and long history, relatively little is known about the thyroid and its physiology. There is continuing controversy over the reference range for "normal" TSH serum levels. Although the results differ among groups of patients, many tests of thyroid function have little diagnostic value because there is too much overlap between individual patients.[41] In sample populations, iodine deficiencies are diagnosed based on the median urinary iodine concentration (UIC), the amount of iodine excreted in urine. A diagnosis of iodine sufficiency in a population, because it is based on median measurements, does not determine whether there is a subgroup who suffers from a deficiency or the size of the subgroup and the degree of their deficiency. The populations used are normally school-age children because of the relative simplicity of obtaining their urine samples and there is limited data on high-risk groups such as pregnant women and women generally.[42] Similarly, hypothyroidism, the condition resulting from an underactive thyroid that produces insufficient thyroid hormones, does not have characteristic symptoms. There are no symptoms always present and many

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[41] Smallridge, Robert C., "Metabolic, Physiologic and Clinical Indexes of Thyroid Function," in *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text* (8th ed.), ed. Lewis E. Braverman and Robert D. Utiger (Philadelphia: Lippincott Williams & Wilkins 2000) 393, 398.

[42] International Council for the Control of Iodine Deficiency Disorders, *IDD Newsletter* (Feb. 2012) 40:1 (accessed 4/21/2012).

symptoms are common to other disease. The resulting lack of understanding and clarity complicates any analysis of thyroid issues in public health.

Thyroid Cancer

For how little is known about the thyroid, even less is known about thyroid cancer. It is the most common and prevalent of all endocrine malignancies and accounts for more than 95% of endocrine-related cancers. There are four types of thyroid cancer which are grouped based on their cell morphology (referred to as histology) as follows: papillary, follicular, medullary, and anaplastic. Hurthle cell cancer, a form of follicular cancer, is frequently listed as a fifth type because it has a distinctive appearance and is less responsive to standard therapy.[43]

Research in cellular function in thyroid cancer is therefore critical for understanding the mechanism and providing new drugs and therapy options. It not only assists cancer research but it has also helped developed drugs for other illnesses. As it turns out, however, much of our understanding of thyroid biology has been confounded by misinformation. Many of the cells that have been used in the last 25 years in thyroid cancer research have been shown to be either redundant or from another organ besides the thyroid. Recent studies suggest that up to 36% of cells being used for thyroid cancer research fall under this category. One of the most comprehensive studies analyzing 40 thyroid cell lines found only 50% accuracy in identification, 20 of the cell lines were

[43] Brown *et al*., "Thyroid Cancer: Burden of Illness and Management of Disease" *Cancer* (2011) 2: 193.

either redundant or misidentified. One cell line, A-375, was found to originate from melanoma. The cell line has been used since 1973 on multiple studies in thyroid cancer.[44]

Papillary cell carcinoma, is by far the most prevalent, and most treatable, of the thyroid cancers, comprising about 80% of diagnosed cases each year and cure rates approaching 97-99% for younger patients (< age 40-45).[45] It is found primarily in females younger than 45. Follicular thyroid cancer comprises about 15% of thyroid cancer cases and is the most difficult to diagnose. Together papillary and follicular carcinomas are referred to as well-differentiated or differentiated thyroid cancer (DTC), meaning that they physically resemble normal thyroid cells. They grow slowly and are generally non-lethal even in cases of relapse. While advanced papillary metastases center around the neck, follicular cancer can spread further afield into the body such as the lungs and brain. Cure rates for follicular cancer can vary from 40-99% depending on whether it has become metastatic.[46]

There are other variants in DTC. It is common for follicular cancer cells to be intermixed with papillary cancer cells which does not seem to alter prognosis. Other less common variants include “tall,” “columnar” and “insular” cells which are believed to be more aggressive with a poorer prognosis. These variants include between 3-16% of papillary cancer cells with columnar at 1-7% which is particularly confounding for statistical analysis because it seems to be the only form of PTC that is more prevalent in

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[44] R. E. Schweppe *et al.*, "Deoxyribonucleic Acid Profiling Analysis of 40 Human Thyroid Cancer Cell Lines Reveals Cross-Contamination Resulting in Cell Line Redundancy and Misidentification" *Clinical Endocrinology & Metabolism* (2008) 93:4331.
[45] Wartofsky, Leonard, “Staging of Thyroid Cancer” in, *Thyroid Cancer: A Comprehensive Guide to Clinical Management*, ed. L. Wartofsky and Douglas Van Nostrand (New York Springer 2005) 87.
[46] Reina Yao *et al*., "Gender Differences in Thyroid Cancer: A Critical Review," *Expert Review of Endocrinology & Metabolism* (2011) 6:215.

men.[47] The staging systems to predict risk, however, include all of these potentially distinctive cancers within the general papillary staging profile.[48] Similarly, there is a growing amount of literature identifying common tumor genes with increasing evidence of predictive value for more aggressive tumors that are not differentiated by staging systems.[49]

Medullary thyroid cancer comprises about 5% of thyroid cancer cases. It occurs in "C" cells, or parafollicular cells, which are neuroendocrine cells that regulate calcium levels in the body. They are not classified according to differentiation (or appearance) because they are not thyroid cells. Instead they are categorized by origin as either sporadic (non-hereditary), multiple endocrine neoplasia (MEN) 2A or 2B associated (a genetic disease associated with hormone gland tumors), or familial (inherited). The 10-year survival rate is variously reported at 50-80%, representing about 13% of thyroid cancer mortality.[50]

Anaplastic thyroid cancer (also called undifferentiated for its stark contrast to normal thyroid cells) is the most rare and deadly form of thyroid cancer. It accounts for

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[47] Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy*, eds. Biersack, H.J. and Grunwald, F. (Berlin Springer-Verlag 2d ed. 2005)Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy*, Biersack, H.J. and Grunwald, F.; Kloos, Richard T. and Ernest Mazzaferri, "Thyroid Carcinoma" in *Medical Management of Thyroid Disease, ed.* David Cooper (New York Marcel Dekker, Inc. 2001) 238-39.

[48] Wartofsky, Leonard, "Staging of Thyroid Cancer" in *Thyroid Cancer: A Comprehensive Guide to Clinical Management*, 90.

[49] Sipos, J.A. and Ernest L. Mazzaferri, "Thyroid Cancer Epidemiology and Prognostic Variables," *Clinical Oncology* (2010) 22:399-400.

[50] Pinchera, Aldo and Rossella Elisei, "Medullary Thyroid Cancer: Diagnosis and Management" in *Practical Management* 255; B. Panigrahi, *et al*., "Medullary Thyroid Cancer: Are Practice Patterns in the United States Discordant from American Thyroid Association Guidelines?" *Annals of Surgical Oncology* (2010) 7:1490-98.

only about 2% of thyroid cases but 14-50% of mortality from thyroid cancer.[51] Interestingly, most patients are 65 or older when they are diagnosed. Because of its fast rate of growth and location in the neck, it constricts airflow and causes difficulty breathing. Patients generally live less than 3-5 months after diagnosis. Some percentage of anaplastic thyroid cancer is the result of slow transformation of DTC tumors. This possibility has been cited as a reason for aggressive treatment of DTC.[52] The introduction of dietary iodine is believed to reduce anaplastic cancer and, unlike other thyroid cancers, anaplastic thyroid cancer incidence is decreasing worldwide.[53]

The majority of DTC patients show no symptoms, although some people show a lump or swelling in the neck originating in the lymph nodes or complain of trouble breathing or swallowing. It is common for doctors to attribute these symptoms to causes other than cancer before making the thyroid cancer diagnosis. The first indication of thyroid cancer is a nodule, or a tumor, growing in the thyroid tissue. In some cases pressing or palpating around the neck will reveal a nodule. Doctors will visualize nodules using a CT scan, MRI, radioactive iodine scan, or, most frequently, an ultrasound exam. Most cases of thyroid cancer in the United States are found during non-related diagnostic procedures or after the disease has considerably progressed.[54] A common example of this is visualization of nodules during a CT or MRI for spinal cord injuries following a car accident. Finally, a fine-needle aspiration biopsy (FNAB) or surgical biopsy of the

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[51] G. Nagaiah *et al*.,"Anaplastic Thyroid Cancer: A Review of Epidemiology, Pathogenesis, and Treatment" *Oncology* 2011:542358.

[52] Mazzaferri, Ernest L., "Thyroid Cancer" in *Early Diagnosis and Treatment of Endocrine Disorders*, ed. Robert S. Bar (Totawa, New Jersey: Humana Press 2003) 4.

[53] Ibid; R. Gorges in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy* 18-19.

[54] Davies, Louise, Michelle Ouellette, et al., The Increasing Incidence of Small Thyroid Cases: Where are the Cases Coming From?" *Laryngoscope* (2010) 120:2446-51.

thyroid is performed and cells are collected to determine if the tumor is benign.[55] In the case of familial forms of medullary thyroid cancer, a simple DNA blood test for the RET gene can be used for diagnosis.

Once diagnosed, doctors determine the staging, or the extent to which the cancer has progressed, to decide treatment protocol. Staging is also used to determine prognosis. Disease classified as stage 1 or 2 are "low risk" while stage 3 or 4 are "high risk," with a higher chance of residual disease after treatment, recurrence or death. The overwhelming number of patients are diagnosed with stage 1 or 2 thyroid cancer because of the low rate of mortality. Most papillary thyroid cancer patients, for example, will have a 25-year survival rate of about 97% after treatment.[56] Despite the reassuring scientific tone of this summary, reality when applied to actual patients is more complex.

Determination of staging can be elusive and unreliable. It is extremely difficult to determine the history of the patients' thyroid cancer from how it presents upon diagnosis. Tumors can vary drastically from patient to patient, with some metastasizing regionally or distantly for no apparent reason. Some people die quickly from aggressive tumors that in others remain dormant for years. In terms of absolute numbers, there are many more deaths among low-risk DTC patients than high-risk patients because there are so many more patients with low-risk staging given the generally benign outcomes.[57] Fundamentally, staging must be viewed as an initial evaluation with recognition that it does not incorporate any subsequent events to update the evaluation.

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[55] *Ibid.*
[56] Wartofsky, Leonard, "Staging of Thyroid Cancer" in *Thyroid Cancer: A Comprehensive Guide to Clinical Management*, 87.
[57] Villaret, Douglas B. and Ernest L. Mazzaferri, "Initial Thyroid Surgery for Patients with Differentiated Thyroid Carcinoma" in *Practical Management of Thyroid Cancer* 138.

In thyroid cancer, staging is determined by the various known determinants of outcome including histologic tumor type, tumor size, growth pattern, the presence of metastases, patient's history, predicted duration of cancer, age and gender. Differentiated thyroid cancer patients are usually categorized further into high- and low-risk groups by a number of scoring systems developed by a number of different clinics around the country. There are at least fifteen different staging systems, a number which shows that none have demonstrated any significant superiority.[58] Some of the most commonly used ones are the AMES (Age, Metastases, Extent, and Size), TNM (Tumor, Node, and Metastases (developed by the American Joint Commission on Cancer and the American Thyroid Association)), the AGES (Age, Histologic Grade, Extent, Tumor Size), MACIS (Metastases, Age, Completeness of resection, Invasion, Size of tumor) and the Memorial Sloan-Kettering Cancer Center systems. The European Consensus does not use any of these systems and instead simply categorizes levels of risk i.e. "very low" or "high" through defined risk factors. The systems classify based on the primary factors of patient age, tumor size, and extent of the tumor with additional factors according to preference. For example, low-risk individuals in the AMES system show papillary or follicular thyroid cancer with no evidence of metastases, are less than 40 years if male or less than 50 years if female, the tumor is smaller than 5 cm and shows no signs of extrathyroidal invasion (for papillary) or major vascular or capsular invasion (for follicular). Everyone else is considered high risk including medullary and anaplastic thyroid cancer patients.[59] A study by Sanders and Cady using 1019 patients treated between 1940 and 1990 with a

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[58] Bilmoria, Karl Y. *et al*., "Extent of Surgery Affects Survival of Papillary Thyroid Cancer" *Annals of Surg* (2007) 246:378.

[59] Wartofsky, Leonard, "Staging of Thyroid Cancer" in *Thyroid Cancer: A Comprehensive Guide to Clinical Management* 88.

median follow-up of 13 years to investigate the validity of the AMES criteria showed that high-risk individuals have a mortality rate of about 50% with a recurrence rate of 31%, while low-risk individuals have a mortality rate of about 4%, with a recurrence rate of 5%.[60]

There have not been any prospective, randomized treatment or prevention trials, to determine optimal treatment in thyroid cancer because they are inherently long and expensive and survival rates from total thyroidectomy are exceptional.[61] Surgery is the uniform treatment option for thyroid cancer for differentiated thyroid cancer based solely on retrospective studies.[62] Patients with advanced thyroid cancer will undergo a total thyroidectomy in which the entire thyroid is removed, followed by postoperative 131 iodine (^{131}I) therapy to diagnose and treat metastases and thyroid hormone suppression therapy.[63] Most low-risk patients also will undergo a total thyroidectomy and thyroid hormone suppression therapy and many will also receive ^{131}I therapy. Patients with small tumors sometimes undergo lobectomies, in which only one lobe or wing of the thyroid is removed, sometimes along with the isthmus.

In DTC, both the extent of the surgery and, for small tumors <1cm, whether to perform surgery are controversial decisions that in practice seem to generally depend on the individual surgeon and patient.[64] There has been a growing trend among surgeons to

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[60] Sanders, Laura E. and B. Cady, "Differentiated Thyroid Cancer: Reexamination of Risk Groups and Outcome of Treatment" *Archives of Surgery* (1998) 133:419.
[61] Brown, *et al.*, "*Thyroid Cancer: Burden of Illness and Management of Disease*," *Cancer* (2011) 2:194.
[62] Ibid.
[63] Ibid; American Cancer Society, *Cancer Facts & Figures 2012* (Atlanta: 2012), http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2012 (accessed 4/21/2012).
[64] Hundahl, Scott and Irvin D. Fleming, Amy M. Fremgen and Herman R. Menck, "A National Cancer Data Base Report on 53,856 Cases of Thyroid Carcinoma Treated in the U.S., 1985-1995" *Cancer* (1998) 83:2645-46; R. Udelsman, E. Lakatos and P. Ladenson, "Optimal Surgery for Papillary Thyroid

advocate for total thyroidectomy. Before the 1980's, twice as many partial thyroidectomies as total thyroidectomies were performed. Between 1979-2004, the trend reversed as surgeons performed increasing numbers of total thyroidectomies. In most retrospective studies, total thyroidectomy has been shown to improve disease-free survival and reduce recurrence rates. Some argue that total thyroidectomies are unnecessarily invasive for some categories of patients.[65]

In order to provide appropriate care based on current knowledge, there has been an attempt to standardize care to enhance the treatment of thyroid cancer. The American Thyroid Association (ATA) originally developed treatment guidelines in 1996. British Thyroid Association, Royal College of Surgeons, National Comprehensive Cancer Network, American Association of Clinical Endocrinologists, and the American Head and Neck Society have also published guidelines for clinical management of thyroid tumors. The ATA subsequently convened a task force of leading experts who produced the ATA Guidelines in 2006. The Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer Guidelines (2009 Guidelines) were reissued in 2009 to reflect changes in medical practice and new evidence.[66] The 2009 Guidelines have been endorsed by the Endocrine Society and other leading professional organizations and are the current standards.

Treatment guidelines, however, do not necessarily induce compliance among surgeons. In a study on medullary thyroid cancer treatment in 2010, Panigrahi *et al*.

Carcinoma" *World Journal of Surgery* (1996) 20:88; N. J. Sarlis and L. Gourgiotis, "Unresolved Issues, Dilemmas and Points of Interest in Thyroid Cancer: A Current Perspective" *Hormones* (2004) 3:149-170.

[65] Samuel Beenken *et al*.,, "Extent of Surgery for Intermediate-Risk Well-Differentiated Thyroid Cancer" *American Journal of Surgery* (2000) 179:51.

[66] American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer and others, "Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer" *Thyroid* (2009) 19:1167.

found that practice patterns in the United States did not follow ATA guidelines.[67] The authors found that 41% of surgical patients did not receive appropriate surgery. Surgeons chose to operate less aggressively on patients with known distant metastases and prescribe more EBRT therapy. Patient age >65 and female sex were statistically significant predictors of treatment in noncompliance with the guidelines. Patients receiving treatment that did not correlate with recommendations exhibited worse outcomes.

In another comprehensive study testing whether radioactive iodine treatment followed some discernable rationale, Haymart *et al*. found that there was an increase in radioactive iodine treatment from 40 to 56% of all patients between 1990 and 2008. The treatment provided patients frequently was not correlated with patient and tumor characteristics, but instead, to a significant extent, was based on unexplained variance among hospitals.[68] There was substantial variation in the prescribed radioactive iodine practice patterns among surgeons with only 21.1% of the variation correlated with patient and tumor characteristics. The study found that hospitals with high volumes of thyroid cancer prescribe higher levels of radioactive iodine and that younger age and absence of co-morbidity was associated with a higher probability of receiving radioactive iodine. Female sex, African American race, and the absence of private/government insurance were associated with significantly less likelihood of receiving radioactive iodine. There were both significant instances of overtreatment with the associated risks of serious side effects which include other solid malignancies, leukemia and strong correlations with

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[67] B. Panigrahi, *et al*., "Medullary Thyroid Cancer: Are Practice Patterns in the United States Discordant from American Thyroid Association Guidelines?" *Annals of Surgical Oncology* (2010) 7:1490-98.

[68] Haymart, M. R., M. Banerjee, A. K. Stewart, R. J. Koenig, J. D. Birkmeyer, and J. J. Griggs. "Use of Radioactive Iodine for Thyroid Cancer" *JAMA* (2011) 306:721-728.

bone, soft tissue colorectal and salivary gland cancers and the loss of teeth and undertreatment which results in increased mortality and complications from unchecked thyroid cancer.[69]

There are six major reasons why more extensive surgery has become the norm (and is recommended in the Guidelines). Malignancy is found in both lobes in about 30-85% of cases, which eliminates the option of lobectomy. About 4.7-24% of patients have recurrent cancer, which has higher mortality rates. A total thyroidectomy obviously eliminates the possibility of recurrent thyroid cancer (but not other types of recurrence) unless remnants were left from the surgery. (The variation in percentage is based on the range found in different studies and provides further evidence of the poor understanding of the disease process.) Most studies have shown that in tumors greater than 1.5 cm total thyroidectomy has better outcomes. The efficacy of ^{131}I post-operative treatment improves with total thyroidectomy. Serum thyroglobulin can be used with total thyroidectomy to determine presence of metastases. Finally, follow-up surgery if required by a recurrence has an increased rate of complications.[70]

Notwithstanding these apparently substantial grounds, other studies continue to question whether thyroidectomies are necessary for less advanced cases when a lobedectomy, or even observation without surgery, could be sufficient. Proponents of lobectomies cite that less than 5% of recurrences are found in the thyroid making thyroidectomies seem heavy-handed.[71] There is also an increased risk of complications

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[69] Ibid.
[70] Udelsman, Lakatos and Ladenson, *Optimal Surgery for Papillary Thyroid Carcinoma*, World J Surg (1996) 20:88-93.
[71] R. L. Rossi *et al*., "Malignancies of the Thyroid Gland: The Lahey Clinic Experience" *The Surgical Clinics of North America* (1985) 65:211-230.

with total thyroidectomy and it does not remove lymph node metastases. More importantly, many tumors that are found incidentally do not appear to be a danger to patients. It is quite possible that many patients are being wrongly treated.[72]

The controversy focuses on low-risk papillary carcinomas which constitute a significant portion of the increased diagnosis of thyroid cancer. There is evidence from studies by both Davies and Ito indicating that surgery might not be immediately necessary for some of these carcinomas and that at least some DTC patients accordingly could choose observation over immediate surgery. Davies conducted a retrospective study of 35,663 persons diagnosed with localized papillary carcinomas (any size but without metastases or extraglandular extension) between 1973 to 2005 which compared those who had surgery with the 440 patients (1.2%) who did not. The 20-year cancer specific survival rate (comparing those who died from papillary thyroid cancer) for the treated group was 99% as compared to 97% for those who did not receive immediate treatment.[73]

A similar study published at approximately the same time used the 1992-2002 subset of the same database and compared mortality rates without the cancer-specific limitation of 7678 treated patients with the 47 who did not have surgery.[74] The nonsurgically treated patients were older and had more advanced tumors. In this analysis, the one- and five-year survival rates for the surgically versus nonsurgically treated patients were 99% and 98% compared to 90.8% and 83.1%. The authors speculated that

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[72] Noguchi, Shiro, *et al*., "Papillary Microcarcinoma" *World J Surg* (2008) 32:747-753; Udelsman, Lakatos and Ladenson, *Optimal Surgery for Papillary Thyroid Carcinoma*, World J Surg (1996) 88-93.

[73] Davies, Louise and H. Gilbert Welch, "Thyroid Cancer Survival in the United States: Observational Data from 1973 to 2005" *Arch Otolar Head Neck Surg* 136 (2010) 136:440-44.

[74] Sanabria, Alvaro, *et al*., Prognosis of patients with thyroid cancer who do not undergo surgical treatment: a SEER database analysis" *Clin Transl Oncol* (2011) 13:692-96.

the survival differences may have been heavily influenced by co-morbidity (deaths from other illnesses) which is not described in the SEER database. Contrary to Davies, however, the authors still found these differences sufficient to prove the desirability of surgery.

A study by Ito *et al*. tracked 732 papillary thyroid cancer patients. Patients with microcarcinomas (< 1 cm) without other risk factors were offered observation and 162 chose to forgo surgery. Patients who developed various risk factors such as tumor growth or extension outside the thyroid received surgery subsequently while observation continued for the remainder. The authors found that 70% of the patients' tumors either did not change in size or shrunk during an 8-year observation period and metastasis only occurred in 1.2% of cases indicating that surgical treatment was not necessary for most of the cases.[75] A study by Moosa and Mazzaferri found that the much briefer delay in surgery until after birth had no adverse effects for pregnant women.[76]

Ito *et al*. has continued to address the consequence of delaying surgery in low-risk patients. The follow-up study compared 1055 patients who had surgery with 340 who chose observation.[77] Surgery was done if the tumor was adjacent to the trachea or laryngeal nerve, if there was nodal metastases or evidence that the tumor was aggressive. Observation was done by ultrasound 1-2 times per year and surgery was recommended if there was tumor enlargement greater than 3 mm (2 mm was believed to be possible observer variation), nodal metastases and when requested by the patient. There was

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[75] Y. Ito *et al*, "An Observation Trial without Surgical Treatment in Patients with Papillary Microcarcinoma of the Thyroid" *Thyroid* (2003) 13:381-387.

[76] M. Moosa and E. L. Mazzaferri, "Outcome of Differentiated Thyroid Cancer Diagnosed in Pregnant Women" *Clinical Endocrinology and Metabolism* (1997) 82:2862-2866.

[77] Ito *et al*., "An Observational Trial for Papillary Microcarcinoma in Japanese Patients" *World J. Surg.* (2010) 34:28-35.

enlargement after 10 years in 15.9%. Of the 340, 109 (31%) ultimately had surgery. This surgical group included patients who did not develop increased risk factors and excluded some who refused surgery despite developing risk factors. In comparing the two groups, there was no evidence that the delay in surgery had any adverse results. Ito's studies have been widely cited. There does not appear to be any indication in the literature, however, that appropriate patients should be advised of these results when considering whether to have surgery.

High-risk patients, particularly medullary and anaplastic, are less responsive to standard surgical and radiation treatment. Thyroidectomy has shown little benefit to these patients with metastatic thyroid cancer and doctors generally prescribe chemotherapy or radiation therapy with poor results.[78] Stage III and IV patients are initially prescribed total thyroidectomy and administered higher concentrations of radioactive iodine post-operatively.[79] Like low-risk thyroid cancer treatment, high-risk treatment is accompanied by thyroid hormone suppression therapy to keep TSH levels low. Because TSH stimulates thyroid growth, high-risk patients have more aggressive TSH suppression. Radioactive iodine supplementation, serum thyroglobulin assays, and TSH suppression have shown efficacy in decreasing recurrence rates and cancer-related mortality in high-risk patients though its efficacy in low-risk patients has not been established.[80] External beam radiation (EBRT) is sometimes used as an adjunct to therapy but it has yet to be proven successful in curing patients. Patients require lifetime monitoring after therapy

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[78] Brown, "Thyroid Cancer: Burden of Illness and Management of Disease" *Cancer* (2011) 2:193.
[79] Beenken *et al*., "Extent of Surgery for Intermediate-Risk Well-Differentiated Thyroid Cancer" *Am J Surg* (2000) 179:51-56.
[80] Brown, Thyroid Cancer: Burden of Illness and Management of Disease, *Cancer* (2011) 2:193.

because recurrence may occur years or decades later. Despite these efforts, anaplastic thyroid cancer in particular is essentially untreatable using currently available options.

Studies analyzing the prevalence of thyroid cancer in patients containing cancer-like nodules who are referred to surgery find approximately 45-55% malignancies in surgeries performed in teaching hospitals and highly specialized facilities.[81] Much lower rates have also been reported. Stojadinovic *et al.*, for example, reports 61% misdiagnosis on ultrasound and fine needle aspiration biopsy (FNAB) with 70-80% of surgeries finding no malignancy.[82] While FNAB guided by ultrasound is both the most cost-effective and accurate diagnostic tool with very high levels of accuracy when malignant or benign diagnoses are made, there remains a significant percentage of nodules found to be suspicious or indeterminate. The extent to which these nodules when biopsied after surgery turn out to be benign determines to a great degree the percentage of surgeries which then appear unnecessary. The high level of misdiagnosis apparently is caused by the lack of clear distinctions in nodule image between benign and malignant nodules. Also critical are the experience and competence of the cytologist and radiologist and the selection process employed by the referring physician.[83]

It should be noted, however, that many of the imaging studies become suspect soon after publication because of the rate of change in imaging technology. The newest

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[81] Lew, J. I., R. A. Snyder, Y.M. Sanchez and C.C. Solorzano, "Fine Needle Aspiration of the Thyroid: Correlation with Final Histopathology in a Surgical Series of 797 Patients" *Am Coll Surg* (2011) 213:188-94; Yassa, Leila, *et al.*, Long Term Assessment of a Multidisciplinary Approach to Thyroid Nodule Evaluation" *Cancer* (2007) 111:508-516.

[82] Stojadinovic, A. *et al*, "Development of a Clinical Decision Model for Thyroid Nodules" *BMC Surg* (2009) 9:12.

[83] Choi, Seon Hyeong et al, "Interobserver and Intraobserver Variations in Ultrasound Assessment of Thyroid Nodules" *Thyroid* 20:167-172; Kim, Sung Hun, *et al*., "Observer Variability and the Performance Between Faculties and Residents: US Criteria for Benign and Malignant Thyroid Nodules" *Korean J Radiol* (2010)11:149-155; Lew, J. I., *et al*., "Fine Needle Aspiration of the Thyroid: Correlation with Final Histopathology in a Surgical Series of 797 Patients" *Am Coll Surg* (2011) 213:188-94.

technology, ultrasound elastography, which is based on the difference in stiffness in tumor walls compared to soft tissue, appears promising but has yet to be tested on a large-scale basis.[84] The University of Miami and other institutions also have very recently implemented changes in the FNAB analysis classification system (the Bethesda system) which also are intended to reduce the number of unnecessary thyroidectomies.[85]

Epidemiological studies on thyroid cancer patients yield possible risk factors for thyroid cancer. Ionizing radiation exposure is the only established causative risk factor for thyroid cancer. Before the advent of antibiotics, radiation therapy was commonly used as a treatment for a variety of medical issues such as acne and enlarged tonsils, thymus, or lymph nodes in the neck. Between 1920 and 1960, when its effects became noticeable, over 100 million Americans were exposed to radiation therapy. Exposure to nuclear energy fallout or too much low-dose radiation such as those found in X-rays and CT scans offers similar risk for thyroid cancer.

As was previously discussed, after radiation, the most significant risk factor is benign thyroid disease and goiter particularly among women.[86] There does not seem to be any literature that attempts to directly correlate the increase in thyroid disease with the increase in PMTC in women. There is some support for dietary (other than iodine-

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[84] Luo *et al*., "Screening of Thyroid Nodules by Ultrasound Elastography using Diastolic Strain Variation" *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Conference* 1 (2009): 4420-4423.

[85] Lew, J. I., *et al*., "Fine Needle Aspiration of the Thyroid: Correlation with Final Histopathology in a Surgical Series of 797 Patients" *Am Coll Surg* (2011) 213:193.

[86] Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy*, ed. Biersack, H.J. and Grunwald, F. (Berlin Springer-Verlag (2d ed.) (2005) 20; Figge, James J., "Epidemiology of Thyroid Cancer" in *Thyroid Cancer: A Comprehensive Guide to Clinical Management*, ed. L. Wartofsky and Douglas Van Nostrand, 9.

related) risk factors but again no significant studies that have related specific dietary changes to increased incidence of thyroid cancer.[87]

Epidemiological studies on thyroid cancer yield some additional information on factors that are common across patients. Family history of thyroid cancer is the most generic known risk factor. Approximately 5% of papillary thyroid cancer patients and 25% of medullary thyroid cancer patients have a family member who has also been diagnosed with thyroid cancer.[88] Age is another for more aggressive thyroid cancers with a poorer prognosis.

Dietary iodine is a controversial risk factor for thyroid cancer. It is well established that iodine deficiency negatively affects thyroid function. Iodine's association with thyroid cancer, however, is not clear. National Institute of Health research found that a diet deficient in iodine might increase the risk of follicular thyroid cancer. It also showed that over consumption of iodine increases a person's risk for papillary thyroid cancer. Other research seems to show that iodine supplementation in iodine-deficient areas increases the incidence of DTC but lowers the incidence of anaplastic thyroid cancer with no overall change in mortality rates.[89] Iodine supplementation is therefore worthy of consideration as a therapy for thyroid cancer prevention to the extent that papillary thyroid cancer becomes more treatable or perhaps should be provided to men to the extent research shows benefit due to their diminished vulnerability for papillary cancer.

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[87] Chen, Amy Y. *et al.* "Increased Incidence of Differentiated Thyroid Cancer in the United States, 1988-2005" *Cancer* (2009) 115:3801.
[88] C. Wang and L. M. Crapo, "The Epidemiology of Thyroid Disease and Implications for Screening" *Endocrinology and Metabolism Clinics of North America* (1997) 26:189-218.
[89] Gorges, R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy, ed.* Biersack, H.J. and Grunwald, F., 19-20.

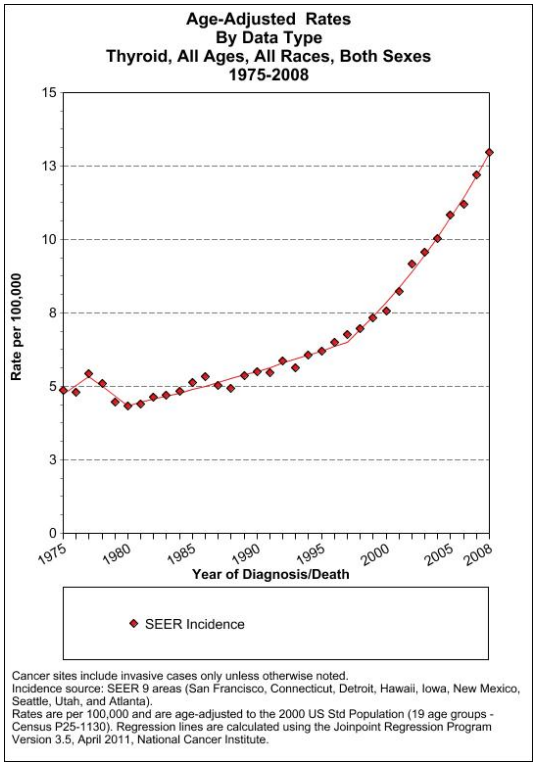
Much of the current research on exposure to radioactive iodine has been associated with the nuclear energy industry because of radionuclides such as *I*-131 and *I*-129 that are released after nuclear accidents. Chernobyl has been a particular focus of investigation.[90] *I*-131 is filtered quickly through the body, but *I*-129 has a half-life of 16 million years and concentrates in the thyroid where it is thought to cause cancer. More research is required to fully explore this issue.

[90] Williams D, "Radiation carcinogenesis: Lessons From Chernobyl" *Oncogene* (2009) 27:9-18.

Chapter 2: Growing Incidence and Prevalence of Thyroid Cancer

Since 1973, the incidence of thyroid cancer has increased faster than any other endocrine malignancy and faster than any other cancer in women. The incidence has almost tripled in the United States since 1973 according to the National Cancer Institute's SEER data.[91] Papillary thyroid cancer has comprised the largest proportion of the increase (see Figure 2). However, mortality remains stable despite the increased incidence.

The prevailing theory explaining a substantial portion of the increase is the improved ability to diagnose due to advancements in detection technology particularly in ultrasound and fine needle biopsy. A landmark report in 2006 by Davies and Welch investigated the trends in thyroid cancer between 1973-2002 and concluded



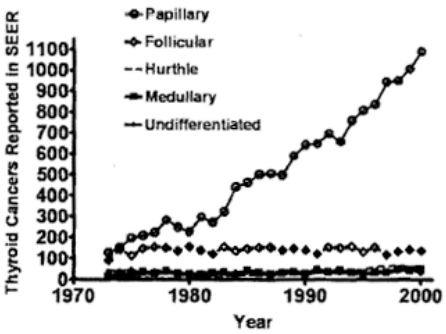


Fig 2. Trends in thyroid cancer histology (SEER).

Figure 1: Age-Adjusted Incidence of Thyroid Cancer. Figure 2: Incidence of thyroid cancer by histology. Images and data derived from National Cancer Institute." SEER Fast Stats " Survelliance Epidemiology and End Results. http://seer.cancer.gov/faststats/selections.php?#Output (accessed 4/04/2012).

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[91] I. Mitchell *et al*., "Trends in Thyroid Cancer Demographics and Surgical Therapy in the United States" *Surgery* (2007) 142:823-8; L. Davies and H. G. Welch, "Increasing Incidence of Thyroid Cancer in the United States, 1973-2002" *JAMA* (2006) 295:2164-2167.

that the increased incidence rate should be attributed to "overdiagnosis."[92] The study found that 87% of the cases accounting for the increase were tumors smaller than 2 centimeters, with 49% smaller than 1 centimeter. Additionally, the authors said there was no evidence to prove that therapy for cancers has improved such that it would account for the stability of mortality rate. Proponents of this theory also cite the increase in the number of cases referred to endocrinologists in which the patient's thyroid tumor was found accidentally during imaging procedures taken for another reason.[93]

Several studies subsequently concluded that the authors were partially mistaken. The increase did, in actuality, include some tumors of larger size and advanced stages, even those larger than 5 centimeters.[94] A more recent study in *Cancer* that investigated trends in differentiated thyroid cancer between 1988-2005, for example, determined that increased detection could not be the only underlying cause for the increased incidence of larger cancers. The authors advocated for research to identify environmental, dietary, and genetic risk factors responsible for the increase.[95] Although debate continues as to the extent of the real increase in incidence, it is clear that a significant part of the increase is only the diagnosis of what previously had been subclinical disease.

As was previously discussed, therapeutic radiation treatments are a known risk factor. Its use on over 100 million Americans between 1920 and 1960 could account for

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[92] Ibid; Carmen Phillips, "NCI Cancer Bulletin Special Report: Thyroid Cancer's Rising Incidence: Reality Or Illusion?" National Cancer Institute, http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2008/021908/page5 (accessed 4/21/2012).
[93] Ibid. L. Davies and H. G. Welch, "Increasing Incidence of Thyroid Cancer in the United States, 1973-2002" *JAMA* (2006) 295:2164-2167.
[94] X. M. Yu *et al*., "Should all Papillary Thyroid Microcarcinomas be Aggressively Treated? an Analysis of 18,445 Cases" *Annals of Surgery* (2011) 254:653-660.; L. Enewold *et a*l., "Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005" *Cancer Epidemiology, Biomarkers & Prevention* (2009) 18:784-791.
[95] Amy Y. Chen, Ahmedin Jemal and Elizabeth M. Ward, "Increasing Incidence of Differentiated Thyroid Cancer in the United States, 1988-2005" *Cancer* (2009) 115:3801.

some of the increase although the belief that radiation-induced thyroid cancer usually occurs within 5-20 years of exposure does not explain the continued increases after the 1980's.[96]

Low-dose radiation remains an integral property of diagnostic imaging procedures. Procedures on children such as dental X-rays and increased use of CT scans in pediatric care could also account for some of the increase in cancer due to ionizing radiation. Children are known to be particularly vulnerable to thyroid cancer following radiation exposure.[97]

There has also been an increase in the number of people near nuclear testing sites or nuclear accidents exposed to ionizing radiation, which may contribute to diagnosed cases. Belarus, Russia, and Ukraine are experiencing a significant increase in thyroid cases as a direct result of the Chernobyl nuclear accident. Studies in the United States of nuclear testing areas such as in Nevada, Tennessee, Ohio, Kentucky, Colorado, South Carolina, New Mexico, Idaho, New York, Texas, California, and Washington States also report not only an increase in thyroid cancer incidence but general autoimmune thyroid disease incidence as

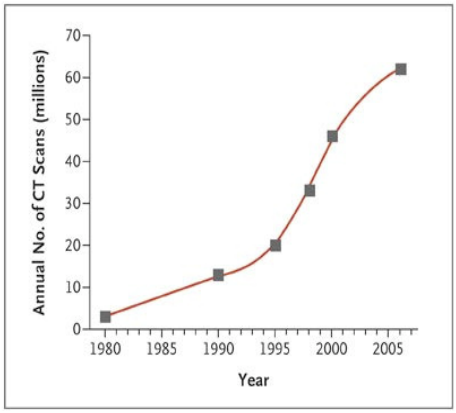

Figure 2: Estimated Number of CT Scans Performed Annually in the United States. The most recent estimate of 62 million CT scans in 2006 is from an IMV CT Market Summary Report.3 Brenner, David J. and Eric J. Hall. "Computed Tomography — an Increasing Source of Radiation Exposure." *N Eng J Med* (2007) 357: 2277-2284.

[96] McDougall, I. Ross. *Thyroid Cancer in Clinical Practice* (*London* Springer-Verlag, 2007) 7.
[97] Enewold *et al*., *Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005*, (2009) 18:784-791.

well.[98]

Recent evidence suggests that CT scans are the most dangerous current source of therapeutic radiation. Over 70 million people are diagnosed using CT scans per year, including thyroid cancer patients. CT scan use higher radiation doses than most imaging technology such as X-rays or MRIs and these doses are within a range that could increase cancer risk.[99] In a National Cancer Institute Bulletin, Dr. David Brenner, of the Center of Radiological Research at Columbia said, "Given the relatively short latency period for radiation-induced thyroid cancer…it is quite possible that CT is influencing current thyroid cancer rates in the United States in young people." Current studies are looking into the risk.

There has also been an increase in exposure to toxic substances that are known to inhibit thyroid function but have yet to be associated with thyroid cancer. Perchlorate, a naturally occurring and manmade chemical used in rockets, missiles and other explosives, and fluoride are abundant in food and water supplies and are both known to interfere in iodine uptake in the thyroid. Polybrominated diphenyl ethers (PBDE) have also been linked to thyroid disorders. They are commonly used as a flame retardant in consumer goods in everything from clothing to electronics, including children's products. Teflon, too has been found to affect thyroid function.[100] Smoking is also a potential risk factor for thyroid problems, though it has not been explicitly linked to thyroid cancer. Cigarettes contain an anti-thyroid agent called thiocyanate. Soy consumption is also a

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[98] McDougall, I. Ross. *Thyroid Cancer in Clinical Practice* (*London* Springer-Verlag, 2007) 3-10; Sara Rosenthal, *The Thyroid Cancer Book* (Canada: Trafford Publishing, 2002), 25.

[99] D. J. Brenner and E. J. Hall, "Computed Tomography--an Increasing Source of Radiation Exposure" *New England Journal of Medicine* (2007) 357:2277-2284.

[100] Yu, X. M., Y. Wan, R. S. Sippel, and H. Chen. "Should all Papillary Thyroid Microcarcinomas be Aggressively Treated? An Analysis of 18,445 Cases" *Annals of Surgery* (2011) 254:653.

potential risk factor because soy has been shown to mimic the effects of estrogen in the body thereby triggering problems with hormonal regulation, a significant feature of the thyroid. There is speculation that the increase may be due to wireless radiation in cell phones based on studies with rats.[101]

Some doctors are attributing increases in thyroid cancer and thyroid malignancies overall in the United States to iodine deficiency. Iodine deficiency is not common in the United States since the addition of iodine into table salt. However, data from the National Health and Nutrition Examination Surveys (NHANES) since the 1970s showed that the rate of iodine deficiency in the United States has since quadrupled, directly correlating with the increased thyroid cancer rate data seen in National Cancer Institute surveys. The first NHANES survey showed only 2.6% of Americans between 1971-1973 demonstrated iodine deficiencies. Between 1988-1994 the figure increased to 11.7%. The study found a notable increase of iodine-deficient pregnant women (from 1% in 1974 to 7% in 1994), which is particularly alarming not only for the thyroid health of the baby but for mental health as well. It is possible that the recommendations for decreased salt intake for hypertension were responsible for the decreased intake.[102] The ICCIDD speculates that decrease also may be attributed to an increased diet of processed and fast foods, which commonly do not use iodized salt.[103]

Diagnosing iodine deficiency in patients can be difficult. Although bodily iodine can be easily measured through urine samples, a cut-off value for iodine deficiency has

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[101] Ibid.

[102] International Council for the Control of Iodine Deficiency Disorders, "IDD Newsletter Nov 1999" International Council for Control of Iodine Deficiency Disorders, http://www.iccidd.org/media/IDD Newsletter/1991-2006/nov1999.htm#a5 (accessed 4/17/2012).

[103] International Council for the Control of Iodine Deficiency Disorders, "IDD Newsletter" (Feb 2011): 1-20 (accessed 4/21/2012).

never been established. Instead of diagnosing on the basis of each individual, iodine deficiency is diagnosed across populations as a median urinary iodine concentration less than 50 μg/L in the population of interest. Iodine deficiency is also generally treated as a public health measure across populations by adding iodine to common foods rather than treating individuals.[104] The FDA, however, does not require the listing of iodine as an ingredient in food labels.

[104] "Thyroid.Org: Iodine Deficiency" http://www.thyroid.org/patients/patient_brochures/iodine_deficiency.html (accessed 4/9/2012).

Chapter 3: Gender Distinctions in Thyroid Cancer

It is well established that the incidence of thyroid cancer is significantly higher for females than males.[105] Females account for about 75% of all thyroid patients. The incidence pattern is fairly consistent across all geographical and racial spheres. The ratio between female to male incidence has remained almost constant with the increased overall incidence since 1973, with females higher than males. There is some evidence that female incidence may be even higher for papillary thyroid microcarcinoma. The National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) database for 1988 to 2007 contains 18,445 papillary thyroid microcarcinoma patients of which females were 82.7%.[106] The largest follow up study in the literature showed a 8.9 to 1 female/male ratio for Japanese patients.[107]

The marked variation between male and female disease incidence has led to speculation on whether gender is a possible epidemiologic risk factor. The AMES risk categorization system discussed earlier explicitly relies on gender as a critical variable.[108] Further analysis has shown that the gender distinctions differ among types of thyroid cancer and the patient age. Differentiated thyroid cancer is about 3:1 female dominated, anaplastic thyroid carcinoma is 2:1 female dominated, and medullary (which does not develop from follicular cells like the other cancers) is equal incidence among genders.[109] Faratati *et al.* found that, at puberty, the female-to-male incidence ratio was as high as

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[105] Rebecca L. Brown, "Thyroid Cancer: Burden of Illness and Management of Disease" *Cancer* (2011) 2:193.

[106] Yu, Xiaoo-Min, *et al*., Should All Papillary Thyroid Microcarcinomas be Aggressively Treated?" *Annals of Surg* (2011) 254:654.

[107] Noguchi, Shiro, *et al.*, Papillary Microcarcinoma" *World J Surg* (2008) 32:747-753.

[108] Reina Yao *et al*, "Gender Differences in Thyroid Cancer: A Critical Review" *Expert Review of Endocrinology & Metabolism* (2011) 6:216.

[109] Ibid 6:215

14:1 in DTC and then declines with age. Incidence rates in females peaks between 45-49, just before menopause when disease prognosis is also at its worst.[110] The peak age for males is between 65-69.[111]

Although females have an increased incidence of thyroid cancer, males demonstrate a poorer prognosis after diagnosis. The presence of large (greater than 5 cm) tumors doubles in males.[112] Their tumors are also more likely to metastasize, both regionally and distally.[113] Unsurprisingly, Mitchell et al. found that males were more likely to have advanced stage tumors at diagnosis. These factors, combined with the increased age at which men develop thyroid cancer, contribute to higher mortality rates among males (7.1%) compared to women (3.5%).[114]

Not only is the mortality rate higher in males, but numerous studies have also provided evidence to show that gender is a significant independent predictor of mortality, even when stratified by age and stage of diagnosis.[115] SEER data suggest males have a higher rate of reappearance of cancer after therapy even though females undergo less aggressive therapy.[116]

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[110] Ibid; L. E. Sanders and B. Cady, "Differentiated Thyroid Cancer: Reexamination of Risk Groups and Outcome of Treatment" *Archives of Surgery* (1998) 133:419-425; J. Farahati *et al*., "Characteristics of Differentiated Thyroid Carcinoma in Children and Adolescents with Respect to Age, Gender, and Histology" *Cancer* (1997) 80:2156-2162.

[111] Yao *et al*., "Gender Differences in Thyroid Cancer: A Critical Review" *Expert Review of Endocrinology & Metabolism* (2011) 6:----------.

[112] Ibid.

[113] I. Mitchell *et al*.,"Trends in Thyroid Cancer Demographics and Surgical Therapy in the United States" *Surgery* (2007) 142:823-8; Edgar Frazell, David Schottenfeld and Robert Hutter, "The Prognosis and Insurability of Thyroid Cancer Patients," CA: A Cancer Journal for Clinicians, http://onlinelibrary.wiley.com/doi/10.3322/canjclin.20.5.270/pdf (accessed 3/16/2012).

[114] Mitchell *et al*., Trends in Thyroid Cancer Demographics and Surgical Therapy in the United States, *Surgery* (2007) 142:823-8.

[115] Yao *et al*., "Gender Differences in Thyroid Cancer: A Critical Review" *Expert Review of Endocrinology & Metabolism* (2011) 6:

[116] Ibid.

The reasons behind the discrepancy are poorly understood. The studies are inconsistent and controversial, but there are a number of prevailing theories. The four major theories proposed to account for the difference among genders in incidence levels are disproportionate screening, gender-specific behavior differences, variations in tumor biology, and biological sex differences.

Because women are nine times more likely to develop non-cancerous thyroid conditions than men, doctors are more likely to prescribe surgical procedures or diagnostic imaging that would result in the discovery of a tumor.[117] This also means that women have a greater tendency to be screened for thyroid conditions overall. In fact, the American College of Physician Guidelines include running blood tests to check for thyroid stimulating hormone levels for women over 50, while men rarely have their thyroid examined during routine medical visits.

Social behavioral differences among men and women in medical settings could also account for some of the difference in incidence. Women across all socioeconomic and racial groups are more likely to actively participate in their healthcare treatment then men. They utilize doctors and medical services to a greater extent and are more likely to engage with their doctors during visits, attend follow-up appointments, and listen to medical advice. Doctors unconsciously have a tendency to order more tests for active patients. A side-result of this is that women are much more likely to undergo diagnostic testing (making it more likely for women to receive a diagnosis of cancer). This could partially account for why males are more likely to be diagnosed later in life.[118] Although

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[117] Ibid.

[118] Yao *et al*., "Gender Differences in Thyroid Cancer: A Critical Review" *Expert Review of Endocrinology & Metabolism* (2011) 6: 217.

these social and cultural hypotheses may have some degree of validity, it seems unlikely that they could account for all of the discrepancy. It is more probable that at least some of the discrepancy is founded on biological differences.

Autopsy studies generally do not show any difference in male/female prevalence[119] It has been postulated that the lack of male/female discrepancy in autopsy results is due to the difference in onset in which females have fast-growing nodules while males have slow-growing and eventually larger, and more easily visualized nodules.[120] This hypothesis has not been tested.

An interesting alternative hypothesis also focuses on the many small, clinically irrelevant thyroid tumors that are only seen on autopsy studies, but never affect quality of life or mortality rates. Large autopsy studies demonstrate a high prevalence of incidental discovery of clinically unapparent tumors, especially in iodine-deficient areas with a high prevalence of nodular goiter.[121] Some studies suggest that up to 50% of the population contain these tumors.[122] Furthermore, it also seems that the determined frequencies in autopsies depend on the thickness and completeness of slices microscopically examined. The more closely the gland is studied, the more frequently such lesions are found. This has led some to suggest that the presence of these microcarcinomas may be "normal." Since some of these microtumors, do become clinically significant, and do so at a 3 to 1 female/male ratio, it is argued that there must be a biological basis for the transformation.

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[119] Y. Yamamoto *et al*., "Occult Papillary Carcinoma of the Thyroid. A Study of 408 Autopsy Cases" *Cancer* (1990) 65:1179.

[120] H. Biersack and F. Grunwald (eds), *Thyroid Cancer: Current Concepts in Diagnosis and Therapy*.

[121] Ibid 6.

[122] Ibid 4.

Some propose that normal thyroid tissue varies among sexes with female tissue more susceptible to the formation of tumors (tumorigenesis).[123] Sex-specific hormones are known to play a role in disease, but there is little understanding of their role in normal thyroid function. A study used injections of estrogen and testosterone to show that the thyroid cell growth among female and male rats differed in association with sex-specific hormones.[124] Further research is required to confirm this hypothesis.

The most plausible theory for the cause of the gender distinctions, however, is the idea that female sex hormones, primarily estrogen, play a role in the pathology of thyroid cancer. As a result, estrogen has become a major target for new therapy research in thyroid cancer. Its primary evidentiary support is the decrease in incidence for females after menopause. Elevated TSH levels are associated with increased thyroid cell growth. TSH in women is known to elevate during parts of the menstrual cycle, during pregnancy, during treatment with hormone replacement therapy, and with birth control.[125] As discussed in the introduction, mitochondria may be implicated in these biological pathways.

There is no conclusive information on the link between estrogen and the development of thyroid cancer. Estrogen receptor status, however, has been shown to differ according to the type of thyroid cancer though estrogen receptor expression in cell

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[123] *Ibid*.

[124] S. K. Banu, P. Govindarajulu and M. M. Aruldhas, "Testosterone and Estradiol Differentially Regulate TSH-Induced Thyrocyte Proliferation in Immature and Adult Rats" *Steroids* (2002) 67:573-579.

[125] Yao *et al*., "Gender Differences in Thyroid Cancer: A Critical Review" *Expert Review of Endocrinology & Metabolism* (2011) 6: 216.

growth is not yet understood. As such, there is no definitive molecular element to explain the molecular basis of gender differences in thyroid cancer.[126]

Studies on the influence of menopausal status have provided inconsistent evidence. The majority of studies have found that menopause does not have statistically significant correlation with thyroid cancer but that artificially induced menopause through surgery has an overwhelming association with thyroid cancer.[127] Interestingly, women who had undergone only a partial oophorectomy (removal of ovaries), allowing some estrogen production had a decreased and nonsignificant risk for thyroid cancer. However, women who were given hormone replacement therapy following their surgery continued to show the same risk.[128] Yao *et al.* hypothesize that the increased cancer risk in surgical menopause is due to the "sudden drop in estrogen levels with oophorectomy compared with the more drawn-out changes seen with natural menopause."[129] Surprisingly, hormone replacement therapy, though found to deliver an increased risk in a number of different cancers, has no significant association with the development of thyroid cancer.[130]

Understanding the role of gender in thyroid cancer prevalence is important before any steps can be taken to treat it. Estrogen function seems to be the most promising theory. However, it is clear that our understanding remains limited and further research is necessary before we can be certain about the cause of the discrepancy.

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[126] R. Rahbari, L. Zhang and E. Kebebew, "Thyroid Cancer Gender Disparity" *Future Oncology* (2010) 6:1771-1779.
[127] F. Levi *et al*., "Female Thyroid Cancer: The Role of Reproductive and Hormonal Factors in Switzerland" *Oncology* (1993) 50:309-315.
[128] Ibid: 217.
[129] Ibid: 217.
[130] Ibid: 217.

Chapter 4: Thyroid Cancer as a Women's Issue

The ultimate cause for all cancers remains mysterious. As has been frequently noted, we do know that it is not caused by an insufficiency in surgical technique or a lack of sufficiently advanced pharmaceuticals. While limited progress has been made in curing cancer, public perception of cancer has changed dramatically in the last 50 years. There are now dedicated grants and institutions for the war on cancer and cancers that once held stigma for patients have become rallying points for people across the country, raising millions in funds for research and therapy. More importantly, changes in public perception have provided the impetus needed for public policy changes and awareness of the economic and political considerations necessary for successful approaches to treatment and medical advances in cancer.

Thyroid cancer has not experienced the same level of public awareness and medical success that other cancers have seen. This perhaps can be attributed to its relatively small incidence rate, comprising only 1% of all cancer incidence internationally and almost 2% in the United States. Attention is rarely given to diseases of low mortality that are not accompanied by a dramatically decreased quality of life. Thyroid cancer has neither a high mortality nor dramatically decreased quality of life and many who die do so fairly late in life. The median age of death from thyroid patients between 2005-2009 was 73 years old.[131] The prevailing belief that the increase was attributed to improved diagnostic capability rather than actual incidence also may have discouraged additional attention.

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[131] National Cancer Institute, "Cancer of the Thyroid - SEER Stat Fact Sheets" http://seer.cancer.gov/statfacts/html/thyro.html (accessed 4/21/2012).

However, with the number of studies now demonstrating an actual increase, together with the massive increase in the number of patients, it is peculiar that thyroid cancer has not elicited more attention, if not for its prevalence among women, then simply because it is a type of cancer. The absolute numbers of people living with thyroid cancer is large enough for thyroid cancer to warrant becoming a political force. The National Cancer Institute's SEER data state that "On January 1, 2009, in the United States there were approximately 496,901 men and women alive who had a history of cancer of the thyroid -- 108,920 men and 387,981 women."[132]

The struggle for visibility in thyroid cancer is reflected in its failure to become a women's issue despite its existence as a growing problem for young women. Approximately 10% of the DTC cases affecting women during their reproductive years, occur during pregnancy or within a year of childbirth.[133] Although twice as many women are diagnosed with thyroid cancer as ovarian cancer each year in the United States, it has yet to be classified as a woman's cancer by the National Cancer Institute.[134]

Because of the lack of awareness and distinguishable symptoms, doctors often overlook signs that indicate a thyroid cancer diagnosis. Most symptoms resemble "female" problems associated with menstruation and menopause. These include fatigue, nausea, skin and hair hypopigmentation, and general discomfort. These symptoms frequently are disregarded as feelings rather than concrete indicators like fever.

Women do not even realize what a diagnosis of thyroid cancer entails. In an article entitled, "Dear Thyroid, Thanks for Nothing, You Jerk," Megan Johnson writes:

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[132] Ibid.
[133] Haq, Masud S. and Clive Harmer, "Non-surgical Management of Thyroid Cancer" in *Practical Management of Thyroid Cancer: A Multidisciplinary Approach* 175.
[134] National Cancer Institute, *Cancer of the Thyroid - SEER Stat Fact Sheets.*

> I couldn't even get *the cancer* other women get. No, my disease doesn't come in pink, isn't globally recognizable and supported, doesn't have multiple multi-million-dollar fundraising organizations attached to it – even the treatments are different. Every time someone learns I have cancer, I have to explain how I didn't have chemo, how my hair didn't fall out, and how I even GAINED weight. No one understands why, now that it's "gone," I still can't stay up late or get fewer than 8-9 hours of sleep without feeling ill.[135]

Johnson, along with countless other thyroid cancer patients, recounts years of struggle through the medical establishment with diagnoses of depression, unexplained weight gain, or goiter, before their doctors arrive at the accurate diagnosis.

Breast cancer, in contrast, has gained momentous attention over the past two decades. Prior to the 1980s, breast cancer was a stigmatized subject, rarely mentioned in public. In the late 1970s, Betty Ford came out as the symbol of breast cancer, advocating its awareness for the first time. More recently, pink ribbons have become synonymous with the campaign for breast cancer awareness. There are countless walks and fundraising events to support breast cancer patients and research. There is no doubt that the publicity has paid off financially: in 2010, the National Cancer Institute spent $631.6 million on breast cancer, 40 times more than that spent on thyroid cancer. Recently, breast cancer became one of the few cancers with a decreasing incidence rate.

Despite the difference in societal perception, the two cancers share similar biological features. Studies have found an increased risk of thyroid cancer in individuals with a history of breast cancer and an increased risk of breast cancer in those individuals

[135] Meggan Ann Johnson, "Dear Thyroid, Thanks for Nothing, You Jerk" (http://dearthyroid.org/dear-thyroid-thanks-for-nothing-you-jerk/, Dear Thyroid™, 2011) (accessed 4/21/2012).

with a history of thyroid cancer.[136] There is increasing concern that the ^{131}I treatment for thyroid cancer is a risk factor for breast cancer.[137] Some, however, believe that breast cancer and thyroid cancer are simply both primarily found in women, that someone who suffers from one form of cancer is more susceptible to other cancers or that women are generally more susceptible to cancer and that no causative factor exists between the two.[138] Both thyroid and breast cancer have been associated with sex steroid receptor mutations and the presence of estrogen receptor and progesterone receptor expression can affect disease prognosis and treatment options. These similarities could provide the link needed to generate a new level of awareness.

Thyroid cancer has failed to produce any advocates or anything concrete for which to advocate. Whereas breast cancer patient advocate groups could fight for insurance coverage of mammograms, thyroid cancer has no rallying point. There is nothing to demonstrate cost-effectiveness of screening for thyroid cancer. No preventative measures have been established to date.[139] As a result, thyroid cancer patients do not have a platform to promote thyroid health. Whereas doctors can annually screen for cervical cancer via pap smear, DTC thyroid cancer has no similarly useful diagnostic tool. There is nothing that is known to prevent thyroid cancer. If thyroid cancer treatment could achieve the same level of urgency as breast cancer, research might identify measures needed for its prevention.

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[136] McDougall, I. Ross. *Thyroid Cancer in Clinical Practice*. London Springer-Verlag, (2007). 73-74.
[137] *Ibid*.
[138] *Ibid*.
[139] American Cancer Society, *Cancer Facts & Figures 2012, 31*.

Current thyroid cancer treatment has some obvious corollaries with the early treatment of breast cancer. The late 1880s saw the development of initial surgeries for breast cancer and the discovery that post-operative cancer recurrence could be attributed to parts of the original tumor that metastases and escaped the knife. In response, Halstead developed his radical mastectomy, cutting out not only breast tissue, but also the pectoralis minor and through the pectoralis major, the muscle responsible for significant movement in the shoulder and hand. As Siddhartha Mukherjee relates in his biography of cancer, "even more breast tissue was removed during the initial operation. Since the margins of extirpation were the problem, then why not extend the margins?"[140] When that failed to cure cancer, surgeons would excavate even deeper into the chest, through the collarbone, and strip out the lymph nodes underneath.[141]

The procedure remained the height of surgery for almost 50 years, forcing women to undergo indiscriminate, disfiguring and gruesome operations without any benefit. Its allure and glamour inspired surgeons across all cancers and increasingly radical surgeries were performed each day. By 1929, an English surgeon wrote "the measure of operability depend[ed] on the question: 'Is the lesion removable?' and not on the question: 'Is the removal of the lesion going to cure to patient?'"[142]

The treatment of thyroid cancer appears to follow the same thought process. In the case of thyroid cancer, the primary lesion is always removable through thyroidectomy. Haymart hypothesizes that increased detection of low-risk disease can lead to overestimation of treatment efficacy and a subsequent increase in use of therapy and it

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[140] Siddhartha Mukherjee, *The Emperor of all Maladies: A Biography of Cancer (*New York Scribner 2010*)*.
[141] *Ibid*.
[142] *Ibid*.

certainly makes sense to remove a malignancy prior to metastasis. The problem is that there may already have been metastasis or it may have been a malignancy that would never have become clinically significant. The continuing difficulty is the lack of change in mortality rates. If 50% of the increased incidence is simply the result of improved diagnosis, what is the basis for believing that its treatment is beneficial to the patient?

The history of the radical mastectomy has showed the importance of research to determine what is clinically significant and this research remains lacking in thyroid cancer. As the main beneficiaries of thyroid cancer awareness and treatment, it is important for women to come forward to advocate for thyroid cancer research to ensure that history does not continue to repeat itself. Thyroid cancer results in a significant and increasing amount of surgery on women. Furthermore, female thyroid cancer disproportionally accounts for the large number of the cases of small tumors which appear to be clinically irrelevant. The ethical issues relating to treating huge numbers of patients simply because it will benefit an unidentifiable much smaller number of patients deserves considerably more attention than it has received in the literature.

Although the literature does not seem to suggest that women are being treated disproportionately due to gender bias, gender bias must be considered due to its high prevalence in the American health care system. Traditionally, research on diseases specific to females receives low priority unless directly related to reproduction.[143] More emphasis needs to be placed on generating female interest groups in thyroid cancer to advocate for more research to determine appropriate treatment for hundreds of thousands of women.

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[143] L. Baider and J. Bengel, "Cancer and the Spouse: Gender-Related Differences in Dealing with Health Care and Illness" *Critical Reviews in oncology/hematology* (2001) 40:115.

Chapter 5: Implications for Health Policy

Thyroid cancer and particularly differentiated thyroid cancer present public policy challenges on several levels. There are the medical/public health problems of identifying the most appropriate care and addressing the burdens of hundreds of thousands of patients who do not have functioning thyroids. Because medical certainty is not likely in the near future, there also are ethical issues concerning how best to communicate choices to low-risk patients that respect patient autonomy. Finally, there are the economic issues presented by the costs of treatment.

As the fastest growing cancer and an illness that affects the lives of hundreds of thousands each year, the impact of these challenges will be magnified in the next decade. A significant part of this impact will be the result of medical decisions based on incomplete data. The 2009 Guidelines, for example, recommend surgery for any malignant nodules larger than 1 centimeter. This fairly arbitrary cut off, if followed, creates a population of patients. A decision to remove smaller nodules expands the pool of patients. Many malignant modules have no clinical significance as measured by mortality. This is shown by the lack of mortality change despite enormous increases in the number of patients treated. Treatment decisions therefore are being made which presumably benefits some subset of patients at the cost of unnecessary treatment to others.

It is possible to begin to imagine the scale of this issue. It is estimated that 10-18 million adults in America have a palpable thyroid nodule, 95% of which are benign.[144] Studies have found that anywhere from 2-60% of the population have small benign thyroid nodules and it appears that many of these will be diagnosed as

[144] A. B. Mariotto *et al*., "Projections of the Cost of Cancer Care in the United States: 2010-2020" *National Cancer Institute* (2011) 103:117-128.

cancer.[145] The potential impact of these kinds of numbers is illuminated by Sarlis and Gourgiotis' summary based on other estimates of the magnitude of malignant thyroid cancer nodules in the United States:

> From the above data, it appears that clinically occult TC [thyroid cancer] has minimal clinical importance. The very same data pose the dilemma of optimal management of incidentally discovered thyroid nodules, given the fact that the size threshold—among experienced examiners—for palpation of thyroid nodules is 1.0-1.5 cm. Most experts advocate fine needle aspiration biopsy (FNAB) of all thyroid nodules larger than 1.0 cm. By applying the above criterion and assuming that ~40-50% of the population harbors inapparent thyroid nodules, as well as that ~30% of these nodules will be greater than 1.0 cm in size, one would then conclude that ~10-12% of the population could be candidates for a diagnostic FNAB. Theoretically, if all the above individuals were biopsied, and with an estimated 5% malignancy rate, up to 0.6%-0.7% of the general population could end up with a diagnosis of TC! This rationale could well create a public health conundrum, considering that the majority (>80%) of the TCs diagnosed in this manner would never become clinically significant during an individual's lifetime.[146]

The impact of current treatment practices is also apparent upon consideration of Yu *et al.'s* summary of the papillary thyroid microcarcinoma patient files in the SEER database for 1988-2007.[147] The 18,445 patients had 10-year and 15-year disease specific survival rates of 99.5 and 99.3 respectively with an overall survival of 94.6 and 90.7. There were 49 deaths from thyroid cancer. If we accept Davies' estimate of a 2% increase in survival from surgery, there are thousands of surgeries required to prevent 1 death. If we accept Ito's finding that 70% of the low risk patients do not require surgery, the conclusion is similar. Davies' estimate of surgical advantage could be increased by an

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[145] L. Davies and H. G. Welch, "Increasing Incidence of Thyroid Cancer in the United States, 1973-2002" *JAMA* (2006) 295:2164-2167; Y. Yamamoto *et al*., "Occult Papillary Carcinoma of the Thyroid. A Study of 408 Autopsy Cases" *Cancer* (1990) 65:1173-1179.

[146] N. J. Sarlis and L. Gourgiotis, "Unresolved Issues, Dilemmas and Points of Interest in Thyroid Cancer: A Current Perspective" *Hormones* (2004) 3:149-170.

[147] Yu *et al*, "Should All Papillary Microcarcinomas be Aggressively Treated?" *Annals of Surgery* (2011) 254:653.

order of magnitude without a substantial change in the issues raised by current treatment practices. Ito is not even challenging current treatment practices but simply suggesting observation as an initial stage for a subset of patients who have been repeatedly shown to have little risk. This attempt to quantify the many thyroid cancer patients who gain limited or no benefit from surgery also does not include those who go through surgery and have negative findings for cancer when the thyroid is examined.

It seems evident that more focus on avoiding unnecessary surgery is required. Recognizing that some papillary cancer patients have potentially aggressive disease which requires treatment, is not grounds for treating patients who do not meet this profile. In reviewing the literature, part of the problem appears to be the use of diagnostic labels that blur the issues. Discussion of "thyroid cancer," for example, is virtually meaningless in many contexts. The different histological variants are simply different diseases with different diagnoses and prognoses. While reference to the subset of DTC is an improvement, there still is too much variation for clinical utility. Given the generally benign outcome of PTC, a long-term study which includes tall cell or columnar papillary cancer within a broader group of PTC patients may change the results in a statistically significant manner. Similarly, assuming for example the reliability of data showing that there is a 2.7 per 100,000 mortality rate for persons >age 65 compared to .1 <age 65, a 27 times difference, studies need to take care to separate out these patient populations based on the various identified risk factors.[148]

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[148] Yu *et al*, "Should All Papillary Microcarcinomas be Aggressively Treated?" *Annals of Surgery* (2011) 254:657.

Another somewhat similar issue is the continued use of older studies to justify overtreatment and to continue past practices. There have been significant advances in measuring tumor size and in the ability to visualize and monitor nodules technologically and significant expansion in clinical experience resulting from the dramatically increased patient volumes, which make many studies obsolete. It is not particularly clear, for example, why the current practice of measuring a tumor by its longest diameter is more meaningful than measuring volume. Recent developments in genetics are resulting in new subsets of patients whose clinical experience may vary from broader less specific patient cohorts. If we are going to assume that any substantial portion of the increased incidence is real, the assumption that a prospective study is too expensive will probably not survive the changed economics created by hundreds of thousands of thyroid cancer and thyroidectomy patients.

The need to start focusing on eliminating unnecessary care also is based on economics. The American health care system is exorbitantly expensive. In 2007, Americans spent more than $2.3 trillion and more than 16% of GDP on health care.[149] In 2005 the cost was $5,267 per capita on health care per year, almost two and half times the industrialized world's median of $2,193.[150] Both figures are more than those of any other developed country in the world. Current projections anticipate increases to almost $4.5 trillion and a 19.3% share of GNP by the end of the decade.[151] The cost of health care

[149] Drew Altman, "Health Reform, What's Next?" (2010).
[150] Malcolm Gladwell, "The Moral-Hazard Myth," *New Yorker* (08/29, 2005) 81:44-49.
[151] Altman, *Health Reform, What's Next?*

increases about 12.5% annually, contributing substantially to the growing number of Americans without health insurance.[152]

Quantifying the financial burden of cancer specifically is difficult. Conservative estimates for medical expenditures for cancer in 2010 are $124.6 billion. The highest costs are associated with breast cancer ($16.5 billion), then colorectal cancer ($14 billion), lymphoma ($12 billion), lung cancer ($12 billion) and prostate cancer ($12 billion). The costs are projected to reach $158 billion in 2010 dollars by 2020, assuming that cancer incidence and survival rates and costs remain the same.[153] The rising cost of innovative procedures in cancer diagnosis, pharmaceuticals and other treatment, and follow-up care makes these assumptions unrealistic, however, and a more accurate projection, according to the National Cancer Institute would be at least $207 billion. Future health care resource allocation will therefore need to become more focused and efficient to remain affordable.

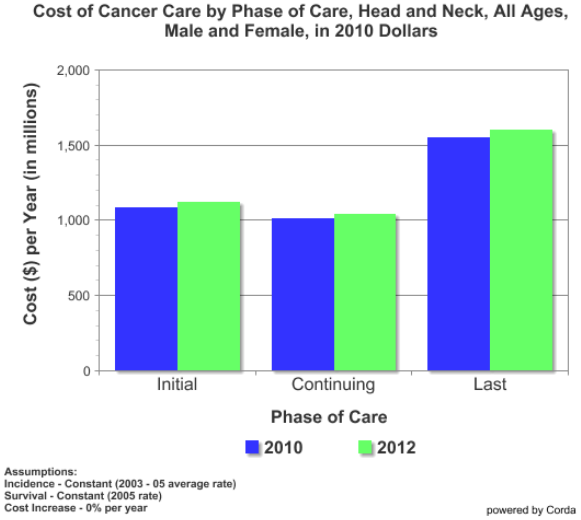

Figure 1: Cost of Cancer in 2010 as determined by the National Cancer Institute. Cost is divided into 3 categories: Initial Treatment, Continuing Care, and End of Life (Last) Care. Image generated from National Cancer Institute. "SEER Fast Stats" Survelliance Epidemiology and End Results. http://seer.cancer.gov/faststats/selections.php?#Output (accessed 4/22/2012, 2012).

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[152] Ceci Connolly, "Medicine; A Few Diseases Fuel Healthcare's Rising Cost; Citing 15 Major Illnesses, a Study Says Proactive, Affordable Treatments can Help Stem the Tide." *Los Angeles Times* Sep 6, 2004, http://proquest.umi.com/pqdweb?did=688481411&Fmt=7&clientId=42799&RQT=309&VName=PQD.

[153] National Cancer Institute, "Cancer Costs Projected to Reach at Least $158 Billion in 2020," http://www.cancer.gov/newscenter/pressreleases/2011/CostCancer2020 (accessed 4/18/2012); Mariotto *et al*., *Projections of the Cost of Cancer Care in the United States: 2010-2020*, National *Cancer Institute* (2011) 103:117-128.

The total cost associated with treating thyroid cancer is even more difficult to determine. There does not appear to be any published data regarding total costs of non-metastatic thyroid cancer or management of long-term care for thyroid cancer.[154] There also does not appear to be any published data on the costs of treating patients for potential thyroid cancer. Some idea of the scale of this latter issue is shown by estimates that there will be approximately 250,000-300,000 thyroid fine needle aspiration biopsies in 2012 of which an estimated 70% will be benign.[155] There has been some limited research demonstrating the unsurprising conclusion that avoiding unnecessary radioactive iodine treatment would achieve cost savings and it is obvious that avoiding unnecessary treatment itself would yield enormous cost savings.[156]

The National Cancer Institute estimates health care costs associated with total neck and head cancer will amount to approximately $3.5 billion in 2012 (figure 1). Two of the assumptions on which this estimate is based, that incidence will remain constant based on 2003-05 average rate and that costs will not increase, appear to be mistaken. Some perspective on the actual scale of increase in thyroid cancer alone is shown by the estimated 18,400 cases diagnosed in 2000, the 25,700 in 2005, 37,000 in 2009 and the estimated 56,000 in 2012. As discussed below, the 2012 costs of metastatic thyroid cancer alone may exceed $3.5 billion. Thyroid cancer represents the overwhelming percentage of head and neck cancers and it accordingly may be assumed that current costs substantially exceed the $3.5 billion estimate.

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[154] Rebecca L. Brown, "Thyroid Cancer: Burden of Illness and Management of Disease" *Cancer* (2011) 2:193.

[155] S. Luo *et al*., "Screening of Thyroid Nodules by Ultrasound Elastography using Diastolic Strain Variation " *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Conference* 1 (2009): 4420-4423.

[156] P. Z. Pace-Asciak *et al*., "Cost Savings of Patients with a MACIS Score Lower than 6 when Radioactive Iodine is Not Given" *Archives of Otolaryngology--Head & Neck Surgery* 133 (2007): 870-873.

Metastatic thyroid cancer expenditures have received some attention in policymaking among thyroid cancer cases perhaps due to the much higher death rates. Studies indicate that 1-4% of DTC patients will present with metastatic cancer and another 5-23% will have a reoccurrence of metastatic cancer after surgery with survival rates below 50% after 10 years. A study using a US health insurance database, which covered over 14 million lives, determined the per patient costs of metastatic thyroid cancer between 2003 and 2005 to be $60,196 during the first year and $35,189 during the second year of follow-up. The retrospective longitudinal cohort study followed 183 patients with newly metastatic thyroid cancer.[157] Inpatient care was the main driver of the total healthcare expenditure, and represented 43% of all costs. Radiation therapy was used in 23%, ^{131}I therapy in 19%, thyroid surgery in 13%, and chemotherapy in 11% of patients.

There were 2823 people diagnosed with metastatic thyroid cancer in 2011.[158] If there were no increases in costs from the 2003-05 figures and no increase in patients from 2011, this represents a $2.8 billion expense assuming approximately similar numbers were in follow-up care. If the 12.5% estimated average annual increase in health care costs is applicable here, then actual costs after the seven years from 2005 will be more than double the estimate.[159]

It also seems likely that this study significantly understates current costs. For example, it did not consider the extremely high costs of newer targeted agents, drugs

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[157] A. Berger *et al*., "Healthcare (HC) Utilization and Costs in Patients (Pts) with Newly Diagnosed Metastatic Thyroid Cancer (mTC)." *Clinical Oncology 2007 ASCO Annual Meeting Proceedings Part I* 25, no. 18S (2007) (accessed 4/21/2012).

[158] National Cancer Institute, "Cancer of the Thyroid - SEER Stat Fact Sheets" http://seer.cancer.gov/statfacts/html/thyro.html (accessed 4/21/2012).

[159] Connolly, *Medicine; A Few Diseases Fuel Healthcare's Rising Cost; Citing 15 Major Illnesses, a Study Says Proactive, Affordable Treatments can Help Stem the Tide* F.3.

expressly designed to address specific pathways in differentiated thyroid cancer. The National Institute for Health and Clinical Excellence (NICE) in Great Britain has considered this issue for the same drugs in relation to other types of cancer. NICE, which is required to determine the cost effectiveness of new medications in comparison to the older treatment, has determined as to several targeted agents that they are not cost effective. Unless the relevant pharmaceutical company chooses to dramatically decrease drug costs, it seems likely that similar determinations will be made as to their use in thyroid cancer.[160]

It is also apparent that the decision whether to invest public health resources in thyroid cancer care will have to be made using very limited information. Biersack and Grunwald, for example, state that in the United States only about 60% of diagnosed thyroid cancer cases are reported to the National Cancer Institute.[161] More importantly, because overall prognosis for DTC is so good, the epidemiological research necessary to make diagnostic and therapeutic decisions requires analyses of very large cohorts over extended periods of time.[162] The lengthy amount of time between disease onset and symptoms with subsequent limited mortality makes it hard to detect beneficial practices or who would have done well regardless of treatment. Over the course of lengthy studies, it also is likely that there will be significant changes in treatment and there may be changes in environmental, cultural or other factors that themselves will have an impact on interpretation of results. The studies then will fail to provide information on the current protocol, and will likely fail to accurately determine causation resulting from

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[160] Brown, "Thyroid Cancer: Burden of Illness and Management of Disease" Cancer (2011) 2:197-198.
[161] Gorges R., "The Changing Epidemiology of Thyroid Cancer" in *Thyroid Cancer: Current Concepts in Diagnosis and Therapy* ed Biersack, H.J. and Grunwald, F. (2005) 1.
[162] *Ibid.* at 2. Villaret and Mazzaferri in Mazzaferri, *Practical Management* 135.

the impact from changes in technology. Considerations like national representativeness of the population sample, method of diagnosis, and determination of the long-term survival rates will further complicate the reliability of epidemiological studies.[163]

The screening conundrum in thyroid cancer has some obvious parallels with the current controversy with mammography policy in breast cancer and PSA testing policy in prostate cancer. Both have been used in the general population despite a lack of conclusive clinical-trial evidence that they save lives, and as the tests are becoming more available there is concern that they themselves are causing damage. Studies estimate that about half of men and women who are screened annually will receive a false-positive. In a study in Detroit of 1,087 people who were tested for prostate, ovarian, colorectal and lung cancer, 43% had false-positives for cancer.

There is a significant financial and emotional toll on the cancer patients and their families for cancer diagnosis as well as false-positives. According to the Wall Street Journal:

> "The assumption has been that as long as a person eventually find out that first test was wrong [or does not indicate certain death], any distress is transitory and minor – and that the cost of additional testing is worthwhile for the peace of mind it brings. Instead, several studies reveal that the impact of false positives can be serious and persist far longer than expected…A study in the American Journal of Medicine found that a significant proportion of men who had an elevated PSA test [for prostate cancer] followed by a benign biopsy result still felt negative psychological effects from the experience six weeks later…And the medical costs of unnecessary additional testing can be considerable. In a study published [in 2004] researchers found that men and women who had false-positive screening

[163] Gary Taubes, "Do We Really Know What Makes Us Healthy?" *New York Times Magazine* (09/16, 2007): 52, http://search.ebscohost.com/login.aspx?direct=true&db=aph&AN=28697580&site=ehost-live.

results averaged more than $1,000 each in follow-up care in the year following the test."[164]

The same study found that 25% of the men who were in the group that had a benign biopsy said that they had additional biopsies because their doctors wanted to make sure that the first one truly was benign.[165]

However, while in mammography and PSA testing the major issue is the financial and emotional expense of screening disease with significant mortality but uncertain benefit, in thyroid cancer, the major issue is that there are so many people who present with nodules known to be clinically insignificant that it is uncertain whether any treatment is appropriate. As was discussed above, there are significant side effects to thyroidectomies and radioactive iodine treatment. If increased screening results in increased treatment, there will be a small portion of patients who may benefit, but there appears to be an even larger portion who, in addition to being screened for no reason, may be being harmed for no reason.

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[164] Marcus, Amy Dockser, "The Hidden Toll of Cancer Testing," *The Wall Street Journal* Dec 28, 2004.
[165] M. McNaughton-Collins *et al*., "Psychological Effects of a Suspicious Prostate Cancer Screening Test Followed by a Benign Biopsy Result" *The American Journal of Medicine* (2004) 117:719-725.

Conclusion

The issues discussed in the previous chapters demonstrate the limits of our current knowledge in thyroid cancer. We have yet to understand the factors that influence cancer outcomes, especially in thyroid cancer, and have difficulty evaluating, much less implementing the best outcome for each thyroid cancer patient. The diagnosis and incidence of thyroid cancer is increasing at such an alarming rate as to warrant increased research. The National Cancer Institute's SEER data shows that there were approximately 500,000 living Americans who had a history of thyroid cancer in 2009.[166] This 0.5 million patient population will increase dramatically without changes in our current approach to thyroid cancer issues. Thorough investigation is needed to stop treatment of those cancers that lack clinical significance.

Patient education is a neglected aspect of thyroid treatment. Public awareness in thyroid cancer is limited. It is common knowledge that too much sun exposure may cause skin cancer and smoking dramatically increases the risk of lung cancer. Relatively few people in the general population, however, know anything about risk factors for thyroid cancer or even the location of the thyroid in their body.

It also is quite possible that the increase in papillary thyroid cancer, and the corresponding increase in overall thyroid disease that is not due to improved technology, is an indication of some environmental contamination. Instead of disregarding thyroid cancer because of its low mortality, the medical community should consider the possibility that it is a canary in a public health mine. Women in particular need to demand greater attention of this issue.

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[166] National Cancer Institute, *Cancer of the Thyroid - SEER Stat Fact Sheets.*

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