Rev Endocr Metab Disord (2016) 17:465–469
DOI 10.1007/s11154-017-9413-4

Editorial: A journey from brain to muscle across the thyroid continent

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Published online: 7 March 2017

One of my long-term interests is the pathogenesis of endocrine tumors [1]. During my tenure at the National Institutes of Health (NIH), I had the privilege of working with and learning from some of the best, world-renowned investigators. Regarding the thyroid gland, among these physician scientists were Nicholas Sarlis, Monica Skarulis, and Paul Yen [2]. Through collaboration with these top-notch colleagues, I also came across other fantastic physician scientists, many of whom had previously worked at the NIH. One of these "NIH alumni" is Salvatore Benvenga, professor of medicine at the University of Messina in Sicily, Italy, and outstanding guest editor of this issue of *Reviews in Endocrine and Metabolic Disorders*.

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After starting as professor and director of the division of endocrinology at the University of Mississippi Medical Center in Jackson, MS, in March 2006, I quickly realized that there were plenty of opportunities and challenges related to my field, including thyroid disorders. Although Mississippi and Sicily appear very different at first glance, they have some factors in common: both are poor, have an agricultural economy and a volcanic history, and both have "Sicilians", as many Sicilians and southern Italians migrated to Mississippi (https://en.wikipedia.org/wiki/Sicily, https://en.wikipedia.org/wiki/History_of_the_Italians_in_Mississippi). After seeing several patients from various geographical areas throughout Mississippi, I had the impression that there were certain counties with a higher prevalence of thyroid disorders including cancer, mainly the Mississippi Delta, Lamar, Covington, and Forrest counties. This stimulated my thought process on possible pathogenetic factors including genetic (migration background) and environmental triggers. Among environmental etiologies I considered endocrine disrupting chemicals which are frequently used in agricultural states, including the Mississippi Delta (considering also the accumulation of various substances in the MS river flowing from North to South), and radiation exposure [3, 4] (https://en.wikipedia.org/wiki/Nuclear_Waste_Policy_Act). Iodine-129 (half-life of approx. 17 million years) is of particular concern during nuclear waste disposal. Caesium-137 in lakes and soil has been very worrisome after the Chernobyl disaster in 1986, as long-term exposure to even small dosages causes cancer. The half-life of caesium-137, a beta- and gamma-emitter, is about 30 years. The World Health Organization has published a health risk assessment from the nuclear accident after the 2011 Great East Japan Earthquake and Tsunami [5].

In Sicily, the volcanic province of Catania has the highest incidence of thyroid cancer, and there seems to be an association between Hashimoto's thyroiditis and papillary thyroid

cancer [6, 7]. Inasmuch trace elements such as vanadium, selenium, zinc, cadmium, sulphur thiocyanate, and iodine, all associated with volcanic activity, are pathogenetically related to thyroid tumorigenesis, is under investigation [8].

According to state cancer profiles, the incidence of thyroid cancer in MS is rising [Fig. 1 (https://statecancerprofiles.cancer.gov/recenttrend/index.php?0&28&0&9599&001&999&00&0&0&0&1#results)].

Trends and patterns of disparities in cancer mortality among US counties from 1980 to 2014 were recently reported, with overall cancer mortality in the United States declining [9]. Utilizing population-based modeling of de-identified death records from the National Center for Health Statistics, the authors found substantial variations among counties and concluded that these data are important when considering strategies for prevention, access to care, and appropriate treatment. As the authors acknowledge, limitations of such analyses of major registries include errors in data entry. Interestingly, age-standardized mortality rates from thyroid cancer were highest in counties bordering Mexico, throughout New Mexico, parts of Arizona near New Mexico, and major parts of California (eFigure 14 in ref. [9]).

With regard to prevention, various types of radiation exposure are known to cause cumulative DNA damage and mutant cell development. In this regard, one should consider the Waste Isolation Pilot Plant, a geological repository licensed to permanently dispose of transuranic radioactive waste (https://en.wikipedia.org/wiki/Waste_Isolation_Pilot_Plant). The plant is located 26 miles east of Carlsbad, New Mexico, in the Delaware Basin, a 600-m deep salt basin. Before construction of this plant, a similar site in Lyons, Kansas, had been abandoned in 1973, as it was considered unusable due to unmapped oil and gas wells located in the area and because of local and regional opposition. In 1999, the first waste was shipped to the plant in New Mexico from Los Alamos National Laboratory, a major nuclear weapons research and development facility north of Albuquerque. In 2014, various mishaps occurred, including the release of trace amounts of airborne radiation consisting of americium and plutonium particles above ground, half a mile from the facility. Similarly, issues occurred at the Hanford Nuclear Site in Washington State, storing high-level nuclear waste for more than 40 years (177 storage tanks holding 53 million gallons of nuclear waste), with incidents including tanks that leaked radioactive contaminants into the ground at depths ranging from 60 to 250 feet, causing the site to be considered dangerously polluted and certainly unsafe [10]. High numbers of cancer cases including thyroid cancer have been reported near St. Louis, Missouri, near Coldwater Creek, where contamination with radioactive waste from the US nuclear weapons program (processing of uranium) occurred

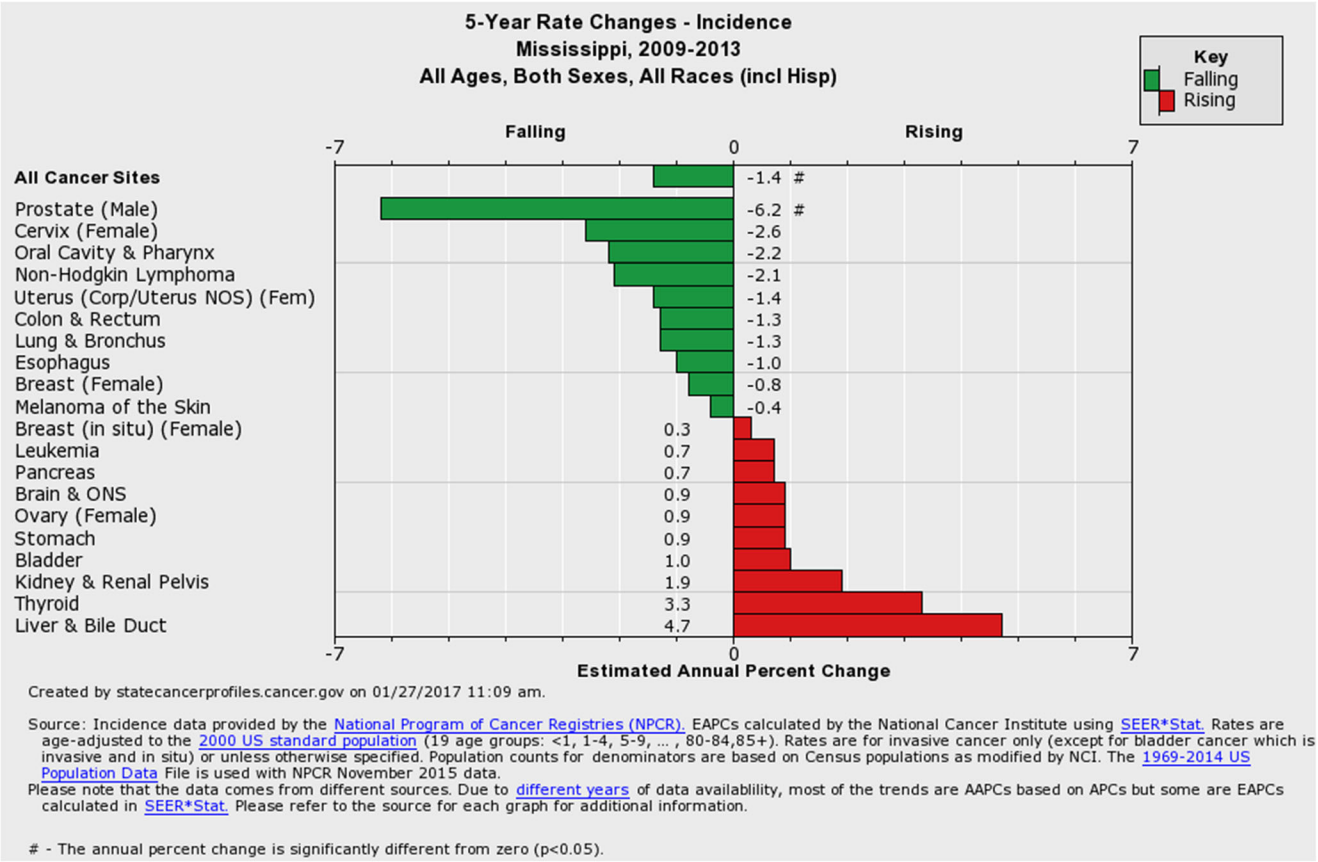

Fig. 1 Five-year Cancer Rate Changes - Incidence

(http://www.cbsnews.com/news/cdc-investigating-possible-cancer-cluster-near-st-louis/, http://www.wsj.com/articles/radioactive-hot-spot-prompts-researchers-concerns-1461874573). In Cameron, Arizona, there are radioactive uranium mines (http://www.nytimes.com/2012/04/01/us/uranium-mines-dot-navajo-land-neglected-and-still-perilous.html). In Germany, the Morsleben radioactive waste repository and the Schacht Asse II salt mine had been suspended in 1998, and the stability of the salt domes deteriorated to a state in which collapse could occur (https://en.wikipedia.org/wiki/Morsleben_radioactive_waste_repository). In the United States, in 2010, the Department of Energy withdrew plans to develop the Yucca Mountain nuclear waste repository in Nevada. In the past, the government had considered volcanic tuff formations at its Nevada nuclear test site, and several salt formations in Utah, Texas, Louisiana, and Mississippi.

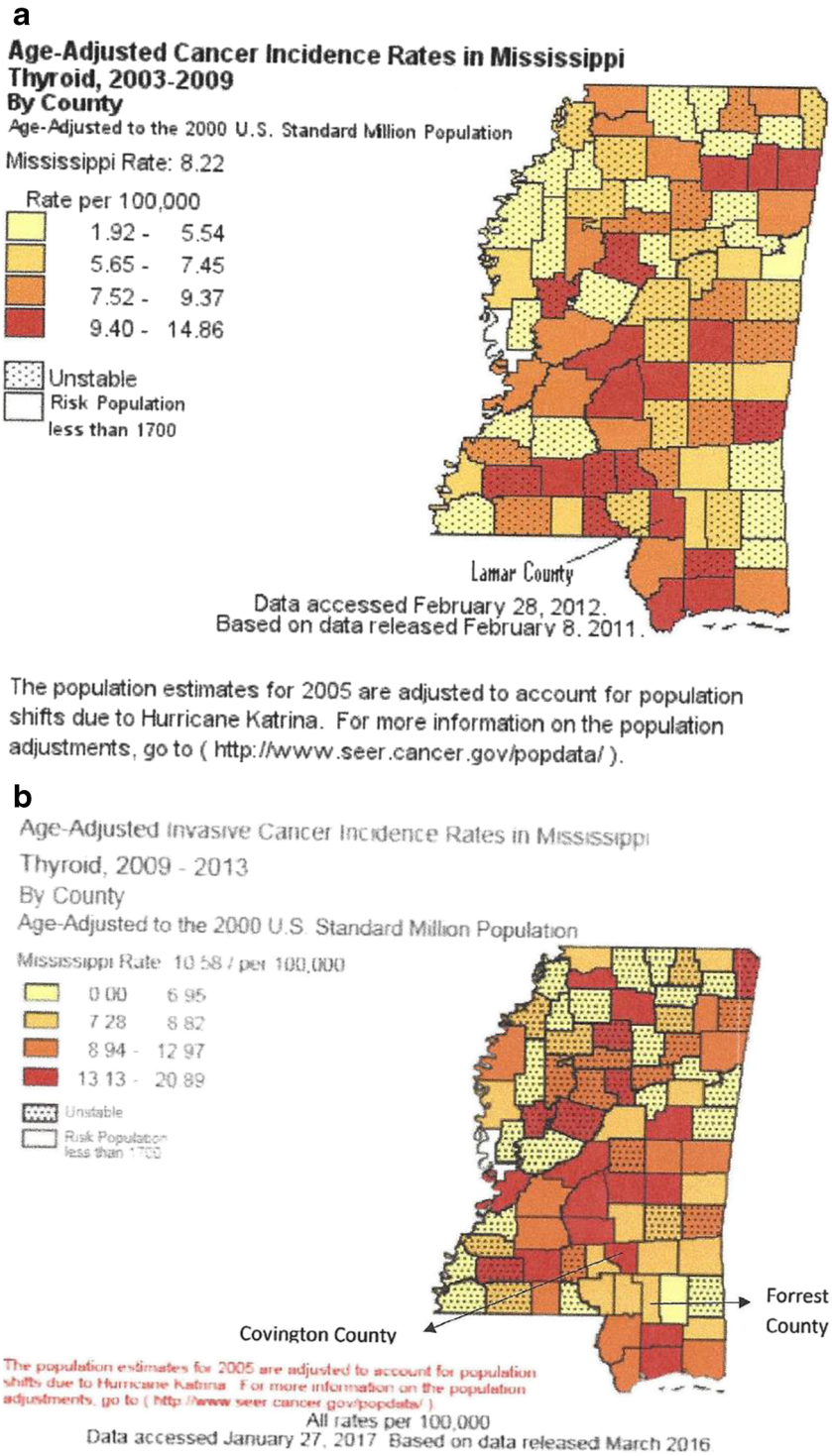

Fig. 2 **a** Age-adjusted invasive cancer incidence rates in Mississippi, Thyroid 2003–2009. **b**. Age-adjusted invasive cancer incidence rates in Mississippi, Thyroid 2009–2013

In Mississippi, the Tatum Salt Dome was the site of nuclear weapons testing in the 1960s as part of Project Dribble (http://mshistorynow.mdah.state.ms.us/articles/293/nuclear-blasts-in-mississippi, https://en.wikipedia.org/wiki/Salmon_Site) [11]. The Salmon event, which took place in 1964, involved the detonation of a 5.3-kiloton device at a depth of 2700 feet. The Sterling event occurred in 1966, involving the detonation of a 380-ton device suspended in the cavity left by the previous test. Due to resident health concerns, around the year 2000, the government built a pipeline to transport outside water to those living near the Tatum Salt Dome. According to the Mississippi Cancer Registry, which is available since 2003 and unfortunately not complete, there appears to be a higher incidence of thyroid cancer in Lamar County, the site of the Tatum Salt Dome (Fig. 2a and b, with thanks to Debra Christie and Deirdre Rogers, Mississippi Cancer Registry).

Preliminary data reveal that many people affected by thyroid cancer resided in the counties of Lamar, Covington, and Forrest, and were born between 1954 and 1973, followed by those born between 1934 and 1953. It is unclear how much migration occurred from county to county. On the other hand, children age 5 and younger of the Belarus region at the time of the Chernobyl disaster fallout in 1986 were at high risk of developing locally aggressive papillary thyroid cancer, frequently involving cervical lymph nodes. Chernobyl-exposed individuals were often found to have positive antithyroid thyroid peroxidase antibodies without increased incidence of Hashimoto's thyroiditis [12, 13]. Based on data regarding Japanese atomic bomb survivors, the risk of thyroid cancer for those exposed to radiation after age 20 years is low [14]. Inconsistent with the Chernobyl and Japanese study are the results of atmospheric nuclear bomb tests conducted in Nevada in the 1950s, which found a lack of a dose response for those exposed at ages 1 to 15 years [15]. After the accident at the Fukushima Dai-ichi Nuclear Power Plant in 2011, long-term environmental monitoring is necessary, as shown in the Kawauchi Village and in areas within a 20- to 30-km radius of this power plant [16]. A survey involving 1351 residents who lived near six former US Department of Energy nuclear weapon sites found that the greatest concerns included threats to the drinking water, transportation accidents, and worker exposure [17].

Interestingly, RET/PTC and other chromosomal rearrangements in papillary thyroid cancers often occur in patients with radiation exposure, as shown in post-Chernobyl tumors [18–20]. Less commonly seen are BRAF (15%) and RAS (8%) point mutations [18]. In this guest issue, Ieni and colleagues [21] review the micropapillary/hobnail variant of papillary thyroid carcinoma from various cohorts including northern and southern Italy, Korea, Mexico, and North America, and report that some of these cancers harbored the BRAF V600E variant, and one cancer was positive for the RET/PTC1 rearrangement.

Apart from aspects of thyroid cancer, this guest issue of *Reviews in Endocrine and Metabolic Disorders* offers many other interesting articles related to thyroidology from authors around the globe. All this has been made possible by the fantastic guest editorship of Professore Salvatore Benvenga, and I cannot say enough, mille, mille grazie, caro amico Sal!

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest related to this article.

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