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INCIDENCE, MORTALITY, AND RISK FACTORS OF THYROID CANCER IN THE WORLD: A REVIEW

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Abstract – *Objective:* *Thyroid cancer is the most common endocrine disorder. This study aimed to investigate the incidence, mortality and risk factors for thyroid cancer in the world.*

Materials and Methods: *A through literature search strategy was conducted for all English language literature published before December 2017. The search was conducted using the electronic databases PubMed, Scopus, and Web of Sciences. The search strategy included the keywords 'thyroid cancer', 'epidemiology', 'incidence', 'mortality', 'risk factor, and 'world'. The search method was adjusted according to different requirements for each database.*

Results: *The standardized incidence of the cancer was 4 in both sexes and 1.9 and 6.1 out of 100,000 in men and women, respectively, in the world. The standardized mortality rate of the cancer was 0.5 in both sexes and 0.4 and 0.6 per 100,000 in men and women, respectively, in the world. The major risk factors for thyroid cancer include radiation, smoking, alcohol and nutrition elements.*

Conclusions: *The incidence of thyroid cancer varies considerably according to the geographical area. This study may provide considerable evidence for thyroid cancer as well as major and minor risk factors. This may be helpful in identifying subsets of the population who are more at risk of developing thyroid cancer. Effective preventive actions, such as less exposure to radiation, health education, nutritional intervention, and screening programs, are needed especially in high-risk areas of the world.*

KEYWORDS: *Thyroid cancer, Incidence, Mortality, Risk factors, World.*

INTRODUCTION

Thyroid cancer could be considered as the most common endocrine disorder worldwide. The incidence and prevalence of the cancer has increased in the world over the past few decades. This trend is seen on all continents except Africa region (probably due to the inadequacy of the appropriate research studies)[1,2]. The disease also has the highest annual mortality rate compared to all other endocrine cancers[3]. It is responsible for 1-2% of all cancers around the world[4,5] and is one of the most common cancers in the young population. Also, it is worth fully to note that the incidence rate is increasing especially among women, children, and young adults[5,6]. Since the 1970s, its incidence has climbed dramatically, but its mortality remained stable or has declined in most parts of the world[5,7].

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Malignancy rate varies throughout the world[8]. This cancer is the seventh common cancer among women, the ninth common one among European female and the fifth most prominent malignancy among US women[9-11]. Half of a million of people are recently living with thyroid cancer in the United States. Among all of them, it has the fastest rising incidence in the United States. At present, the most common are leukemia, pancreatic and liver cancer[9]. The rising trend of this cancer is probably due to access to medical care and detection of less invasive cases at an early stage, as well as genetic factors and environmental effects[1,7]. The reason for staying steady and reducing its mortality is probably due to improved management and treatment of the disease. It is associated with high survival rate[7]. Several studies have been conducted on the incidence, mortality, and causes of this cancer in the world. There is no comprehensive study on risk factors and its occurrence. Therefore, this study aimed to investigate the incidence, mortality and risk factors for thyroid cancer in the world.

MATERIALS AND METHODS

A rapid literature search strategy was conducted for all English language literature published before December 2017. The search was conducted using the electronic databases PubMed, Scopus and Web of Sciences. The search strategy included the keywords 'thyroid cancer', 'epidemiology', 'incidence', 'mortality', 'risk factor, and 'world'. The search strategy was adjusted according to different requirements for each database. Studies related to incidence, mortality and risk factors for thyroid cancer were entered in to the review.

RESULTS

The Incidence and Mortality of Thyroid Cancer in the World

Thyroid cancer has undergone an increasing change in global geographic areas over the past decades[1]. Based on the GLOBOCAN study in 2012, the standardized incidence of the cancer was 4 in both sexes and 1.9 and 6.1 out of 100,000 in men and women, respectively. The highest standardized incidence of thyroid cancer in this study was in North America (3.6%), South America (3.8%), Australia and New Zealand (3.8%), America (3.7%) and Oceania (3.4%), respectively. The highest standardized incidence of thyroid cancer in this study was revealed among men in North America (20%), Micronesia/Polynesia (13.3%), America (12.1), Australia, New Zealand (11.8%) and Oceania (11.3%), respectively. The standardized mortality rate of the cancer was 0.5 in both sexes and 0.4 and 0.6 per 100,000 in men and women, respectively, in the world. The highest standardized mortality rate for males was seen in Melanesia (1.5%), Micronesia/Polynesia (0.9%), East Africa (0.8%), Southeast Asia (0.8%), and North Africa and West Asia (0.7) per 100,000, respectively. Also in women, the highest standardized mortality rate was observed in Melanesia (5.7%), East Africa (1.8%), North Africa (1.8%), West Asia (1.7%) and South-East Asia (1.6%)[12]. The incidence of thyroid cancer has increased in many countries in the world in the last few decades in Sweden[13], Switzerland[14], England[15], Italy[8], and France[16]. A study in the United States by Hershman et al[17] indicated that the incidence of thyroid cancer increased from 4.56 per 100,000 person-year between 1974 and 1977 to 14.41 during 2010 to 2013[17]. In a study in South India, the incidence of thyroid carcinoma was 6.6 per 100,000 in 2006, 10 per 100,000 in 2009, 13.2 per 100,000 in 2012. It shows an increase of 93% in the incidence of this cancer[2]. The reasons for an increase in thyroid cancer can be due to an increase in the detection of small cancers in the pre-clinical phase and large tumors have also increased over the year. The increased incidence of thyroid cancer can be due to more sensitive diagnostic methods, and a real increase in thyroid cancer due to exposure to radiation and due to other undetected carcinogens[1].

The incidence of thyroid cancer is generally higher in women than in men and has been increasing in recent decades. The increased trend of incidence in both sexes was similar[18]. A study done by Raposo et al[7] in Portugal showed that the incidence of thyroid cancer in Portuguese women is higher than global estimates and Europe. Deaths in Portugal have declined for women, with the largest decline seen in the north, but it has risen in men, with the largest increase in the South. Another research in Scotland showed that thyroid cancer was 3 times in men more likely than women[19]. According to a study in Korea between 1999 and 2014, the incidence of thyroid cancer ranged from 6.3 in 1999 to 43.3 in 2014 in both genders. The mortality rate was fixed at 0.4 during these years (20). Another study in Korea in 2017 showed that the cancer was 6th cancer in men (5.3% of all cancers) and 2th in women (17% of all cancers). In terms of mortality, it was not in the first 10 cancers. In 2017, the age-standardized incidence in Korea was 32.8% per 100,000 in both sexes, 17.4% per 100,000 in men and 50.8% per 100,000 in women. Standardized mortality rates in 2017 in Korea were 0.3 per 100,000 in both sexes, 0.2 per 100,000 in men and 0.4 per 100,000 in women[21]. One of the reasons that could explain sexual differences is time change in reproductive factors among young women[22]. Other researches[3] have shown that the incidence of thyroid cancer in the geographical

regions such as Hawaii is highest and in areas such as Poland is the lowest. The mean age of women and men decreased significantly during diagnosis. Age at death has increased significantly and the diagnosed patients are younger and die at a higher age[11]. A study in New Caledonia, in South Pacific, showed that most cancers occurred in the age group of 54-45 and 54-55 years[23]. A study in Brazil showed that 70% of thyroid cancer deaths occurred in Brazil in the elderly, regardless of sex. In young adults, mortality was low, and there was no difference between men and women[24]. A study in the United States by Enewold et al[25] showed that the cancer had an increase of almost 100 percent among non-Hispanic whites and black women. Merely 20% to 50% of cancer cases were found among Hispanic whites, Asians, Black men, and Pacific Islanders. This marked growth is largely due to much medical care and improved diagnosis[25]. According to WHO data on 5 continents in 2014, male deaths declined in all major countries and the percentage of annual change in the last decade was about 32.22%. In the United States, deaths declined among men until the mid-1980s, and then increased again. Similarly, female mortality has declined in most countries, and the percentage of annual change in the last decade was 25.22%. Neglecting UK, in the United States and Australia deaths among women declined until the late 1980s and increased thereafter. Based on these data in 2008-2012, age standardized mortality rate in most countries was between 0.2 and 0.4 per 100,000 in men, and between 0.2 and 0.6 per 100,000 in women. Reducing thyroid cancer mortality can be attributed to both changes in exposure to risk factors, and changes in diagnosis and treatment of the disease[26]. Overall, thyroid cancer deaths worldwide are low and have declined in most countries[27].

RISK FACTORS F OR THYROID CANCER

The factors related to thyroid cancer are listed in Table 1.

RADIATION

Exposure to ionizing radiation, especially in childhood, is the most estimated risk factor for thyroid cancer. Therefore, one of the ways to reduce thyroid cancer is avoiding ionization radiation[28]. Studies[29-31] have shown that radiation therapy in the past on the head and neck is a risk factor for thyroid cancer; the lower the age of radiation, the higher the risk of thyroid cancer is seen. A dose-response relationship

TABLE 1. Factor related to thyroid cancer.

Factor	*Modifiable*	*Unmodifiable*	*Preventive*	*Risk factor*
Sex (female)		*		*
Age		*		*
Radiation	*			*
Smoking	*		*	
Alcohol	*		*	
Weight	*			*
Height		*		*
Coffee	*		*	
Iodine deficiency	*			*
Consumption of vegetables	*		*	
Seafood	*		*	
Protein	*			*
Nitrate	*			*
Goiter	*			*
Nodules and tumors	*			*
Family history of thyroid cancer		*		*
Number of live births	*			*
Pregnancy number	*			*
Contraceptive pill or				
Hormone replacement therapy	*			*
Artificial menopause	*			*
Irregular menstruation	*			*
Acromegaly	*			*

has been reported in exposure during childhood. For a dose of Grayl, the risk of thyroid cancer is approximately 7 times and a linear dose-risk relationship has been observed for at least Gray 2. The risk of thyroid cancer attributed to radiation was 3 times higher than in areas with iodine deficiency[32,33]. Ron et al[29] found that the mean age between exposure and cancer diagnosis was 35 years (ranged from 6 to 58 years old). They revealed that exposure below the 10 years old caused the highest risk of thyroid cancer than other group of ages and the risk has significantly decreased with increasing the age of exposure.

SMOKING

In many studies, the protective role of cigarette smoking has been approved[34-36]. In a study on comparing people who have never smoked and those who are already smoking, the relative risk for women was 0.71 and for men 0.77. This evidence shows the protective effect of cigarettes against thyroid cancer. This risk reduction has been seen in all age groups. This protective effect may be due to various mechanisms including effects on hormonal stimuli and on the estrogen mechanism[37]. A study by Kitahara et al[38] in 2012 showed that the severity of smoking, duration and pack-year was associated with a lower risk of thyroid cancer[38]. In the cohort study conducted by Navarro Silvera in 2005, in the United States, there was no association between smoking factors such as commencement and duration of smoking, the number of cigarette per day pack-year, and changes in thyroid cancer[39]. If the effect of smoking is reliable, the anti-estrogenic properties of tobacco smoke and the reduction of thyroid stimulating hormones (TSH) might be biological mechanisms[35]. Although most case-control studies of thyroid cancer and smoking have revealed a reciprocal and protective relationship between cigarette smoking and thyroid cancer, less cohort studies have been consistent with this evidence. These differences may reflect the greater likelihood of confounding in most prospective studies, which is highly likely to encounter less information about the risk factors for thyroid cancer[36].

ALCOHOL

Different studies[28,29,36] have shown the protective effect of alcohol in thyroid cancer[35,38], while some others have not revealed this relationship. A research was shown those who have never consumed alcohol or occasionally consumed alcohol have odds ratio of 1 and those who have taken more than or equal to 4 times a week have odds ratio of 0.7. It indicates the protective effect of alcohol against thyroid cancer34. Those who consume alcohol may alter the risk of thyroid cancer by altering sex steroid hormones[38]. Reducing the risk of thyroid cancer may be due to decreased thyroid cell proliferation due to the modified THS response to the THS release hormone, which has always been reported among alcohol user[35]. Some studies reported findings on alcohol consumption through questionnaires and self reporting. This may lead to a variety of non-differential classification of individuals from actual exposure levels[38].

WEIGHT AND HEIGHT

Studies[28,29,40-42] have shown a positive relationship between weight and height, and the risk of thyroid cancer. McTieman et al[43] conducted a study in the United States and concluded that women who had a weigh of 60 kg or more were 25 times more likely to be at risk for thyroid cancer than those with 52 kg or less. The result of another study conducted by Kitahara et al[44] in the United States in 2011 depicted that in every 5 kg hazard ratio (HR) it climbed to 1.6 and 2 in women and men, respectively. In this study, a positive significant correlation was found between the young adults (18-20 years old) with the risk of thyroid carcinoma (every 5 kg HR = 1.8)[44]. In a case-control study done by Goodman et al[45] in Hawaii, a stable dose-response relationship was found between the late-adulthood weight and the risk of thyroid cancer in men and women. A 5 and 2 fold increase in risk in men in women was found for people with the highest quintile in compared to the lowest in the late adulthood. Height was significantly associated with an increase in thyroid cancer in men, but not in women population. In this study, the effect of weight gain on the increased risk of thyroid cancer in postmenopausal women was stronger than that of women before menopause. A significant positive interference was observed between the use of fertility drugs and weight at early puberty and the risk of thyroid cancer in adult women. A significant odds ratio (larger than median) was also found in this study for women overweight in early adulthood, who experienced an abortion or stillbirth in early pregnancy. In a study conducted by Meinhold et al[36] in 2009 in the United States, obesity did not relate to thyroid cancer and was not a risk factor for it. In a case-control study conducted by Guignard et al[35] in 2007, especially in men, a positive correlation was found between obesity and thyroid cancer. An explanation for the undesirable effect of weight on the risk of thyroid cancer may be related to the endocrine disorder. This may be associated with body weight and thyroid cancer[46].

In researches where weight and height are filled by a questionnaire, it has been shown that individuals and especially women tend to report their height higher and their weight lower than that of real one. In such studies, actual values and valid sizes of weight and height are not obtained. So, the relationship between weight gain and thyroid cancer may be biased, meaning that one reason for the difference in studies about weight and height with thyroid cancer is self-report incorrectly[40].

NUTRITION FACTORS

Coffee

One of the factors associated with thyroid cancer is coffee consumption. According to findings from various studies, the use of coffee per day is associated with a reduction in the risk of thyroid cancer[34]. Several studies[28] have not shown the relationship between coffee consumption and thyroid cancer. A mechanism in which coffee consumption may play a protective role against the development of benign or malignant thyroid neoplasms can be due to the caffeine-stimulating effect on the production of intracellular AMP, which is known to be a growth cell inhibitor[34]. One possible reason for the difference in the results between numerous studies may be the exposure measurement method. A case in point intake of coffee, some studies have reported long-term consumption and some others considered frequency of consumption[47].

Iodine

Iodine deficiency may cause benign illness and excessive intake affects thyroid function. These are likely to affect thyroid cancer rate[28]. In a study by Hom-Ross et al[30], an increase in iodine intake in low-risk women, probably due to the use of multivitamins, was associated with a reduction in the risk of thyroid cancer. Iodine deficiency, directly and indirectly, affects thyroid function by decreasing thyroid hormone levels, thereby increasing TSH secretion. It can be a potential cause for increased thyroid cancer risk, as well as increased care and improvement in the quality of diagnostic tools is probably another reason to identify more thyroid cancer than before[48,49].

Consumption of Vegetables

One study revealed that people who consumed high levels of greenery showed a 20% reduction in thyroid cancer risk[28]. Consumption of herbs containing goitrogen can likely lead to a reduction in total thyroid cancer due to the nature of cruciferous[28,29]. In a casecontrol study conducted by Memon et al[50] in 2002 among Kuwaiti, there was no clear relationship between thyroid cancer and cruciferous vegetable products[50]. Cruciferous vegetables including cabbage, broccoli, Brussels sprouts and cauliflower, contain various types of compounds such as flavonoids, phenols and isothiocyanates, in addition to goitrogen. They are known to prevent thyroid cancer in the animal model studies[51,52]. Inhibition of the formation of carcinogenesis, as well as damage to macromolecules and modulation of immune function, are the mechanisms that help to prevent cancer and that can be found by vegetables. It is not clear how these elements are acting on carcinogens of thyroid cancer[28].

Seafood

In a case-control study conducted in the United States by Mack et al[47], it was revealed that the high consumption of shellfish in childhood reduced the risk of thyroid cancer (OR = 0.2 for at least several times a week). Also, among papillary thyroid cancers (82% of cases), the high intake of marine fish by adults has declined the risk. It was also shown that the risk of cancer has decreased with the consumption of certain herbs, wine and tea, and among papillary samples risk has increased with prolonged use of multivitamin[47]. One of the reasons why many marine foods reduce thyroid cancer is the presence of iodine factors in these foods[47].

Macronutrients

In a case-control study conducted by Franceschi et al[53], it has been shown that starchy foods and various sources of fat and animal protein have a direct relationship with thyroid cancer. The high consumption of other foods including foods rich in iodine, such as fish, green vegetables and fruits, has had a significant protective effect. A case-control study done by Marcello et al[54] in Brazil in 2012 revealed that the consumption of excess protein and carbohydrates was associated with an increased risk of thyroid cancer, and, on the contrary, the absorption of fiber and lipids, and physical activity reduced this risk[54]. The mechanism by which the thyroid cancer is created by protein is not known but it is suggested that high levels of nitrosamine in some meat products may increase the risk of thyroid cancer[55]. Others have suggested that the relationship between animal protein and the risk of cancer may be due to the effect of regulating the growth factor I (IGF-1) activity, such as insulin, that has been shown to be a cancer enhancer. Animal protein and especially dietary protein may increase IGF-1 accumulation[56].

Nitrate

The risk of thyroid cancer increases with a growth in the average nitrate level in public water products and with a prolonged consumption of water with nitrate above 5 mg/l. Also high intake of nitrate in the diet arises the risk of thyroid cancer[57]. The hypothe-

sized mechanism for nitrate is that it inhibits iodine absorption due to sodium-iodine bonding on the surface of the thyroid follicles. Nitrate levels in the drinking water are associated with increased thyroid volume, elevated TSH levels and other symptoms of subclinical thyroid disorders[58,59].

A History of Benign Thyroid Disease

One of the most prominent risk factors for thyroid cancer is the history of benign tumor thyroid and goiter cancer. Various studies[34,50,60,61] have confirmed these findings. In a case-control study by Mack et al[31] in the United States, it was shown that there was a significant relationship between benign thyroid disease (including thyroid enlargement in adolescents, goiter, nodules and tumors) and thyroid cancer. Another study conducted by Meinhold et al[36] in United States in 2009 showed that despite the low thyroid carcinoma in men, whom with a history of benign disease were highly likely to risk for thyroid cancer (HR = 6.45). Although a history of thyroid nodules is known as a threat to thyroid cancer types, there is a higher risk for follicular type than papillary thyroid carcinoma[61]. Thyroid tumors produced by iodine deficiency block the production of thyroid hormone with effect on THS directly or with chemical goitrogen. In addition, the suppression of THS release by the use of thyroxin is often an effective treatment for thyroid cancer. So, it makes sense that some common risk factors for creating additional TSH or imbalance in its secretion play a crucial role in the development of benign tumors and thyroid cancer[62,63]. Recall bias and medical care bias are among other factors can distort the results of studies. Detection of nodules and thyroid cancer could be determined earlier in people with more medical care[29].

Factors Related to Fertility and Hormones and Other Factors

Findings from studies[64] have shown that abortion and multiparty may increase the risk of thyroid cancer merely in women who have had thyroid cancer before the age of 35 years. The utilizing of spironolactone, vitamin D supplements and familial history of thyroid cancer revealed a relationship with the risk of thyroid cancer[29]. A case-control case study was conducted in Norway and Sweden and revealed that there is a significant relationship between thyroid cancer and the number of live births, the number of pregnancies, the incomplete pregnancy history, and the use of fertility pills or alternative hormone replacement therapy. The first delivery (before age 20 or less than 5 years after menstruation) was considerably associated with an increased risk of thyroid cancer. Among women with a history of artificial menopause, the risk of thyroid cancer is higher than those with normal menopause[65]. Mack et al[31] shown that irregular menstruation increases the risk of thyroid cancer. TSH is a suspected thyroid cancer stimulant that increases during puberty and fertility, meaning that this increase during these courses may help the thyroid cancer etiology[29]. Patients with acromegaly are at higher risk for thyroid cancer and should therefore be screened regularly through endoscopy and thyroid hormone testing[66,67]. Acromegaly has a thyroid-induced goitrogenic effect, stimulated by THS and IGF-1[68]. The palpable thyroid nodules are most commonly seen in acromegaly patients and the risk of malignancy is higher in acromegaly patients with thyroid nodules[69].

SUMMARY

The purpose of this review study was to determine the incidence and mortality rate of thyroid cancer in the world and its related factors. The incidence of thyroid cancer varies considerably according to the geographical area. The highest standardized incidence in males per 100,000 was found in North America (6.3), South Europe (3.8), Australia and New Zealand (3.8), America (3.7), and Oceania (3.4). The highest standardized mortality rates were observed in men per 100,000 in Melanesia (1.5), Micronesia/Polynesia (0.9), East Africa (0.8) and Oceania (3.4%), South East Asia (0.8), North Africa and West Asia (0.7). One of the risk factors for thyroid cancer is radiation. Exposure to ionizing radiation, especially in childhood, is the most estimated risk factor for thyroid cancer. In many studies, the protective role of cigarettes and alcohol has been shown. This protective effect of cigarettes may be due to various mechanisms including effects on hormonal stimuli and on the estrogen mechanism. Reducing alcohol-related risk may be due to decreased thyroid cell proliferation due to the modified THS response to the THS release hormone. Height and weight have shown a positive relationship with the risk of thyroid cancer. An undesirable effect of weight on the risk of thyroid cancer may be related to the endocrine disorder. Nutritional factors are other factors that are associated with thyroid cancer. Consumption of coffee and herbs containing goitrogen as well as consumption of many seafood have shown an inverse association with thyroid cancer. Iodine deficiency, fat and protein intake, and carbohydrate, nitrate consumption have a direct correlation with thyroid cancer. One of the reasons why consuming a lot of seafood is reducing thyroid cancer is the presence of iodine in these foods. One of the most prominent risk factors for thyroid cancer is the history of benign tumor thyroid and goiter cancer, meaning that Thyroid tumors produced by iodine deficient di-

ets block the production of thyroid hormone effects on THS directly or with chemical guitrians. Other features associated with thyroid cancer are factors related to fertility and hormones such elements as Abortion, familial history of thyroid cancer, number of births, number of pregnancies and the use of birth control pills or replacement therapy with hormone, and irregular menstruation, are associated with increased risk of thyroid cancer. THS is a suspected thyroid cancer stimulant that climbed during puberty and fertility. This during these courses may help to realize the thyroid cancer etiology.

CONCLUSIONS

The incidence of thyroid cancer varies considerably according to the geographical area. This study may provide considerable evidence of major and minor risk factors for thyroid cancer. This may be helpful in identifying subsets of the population who are more at risk of developing thyroid cancer. Effective preventive actions, such as less exposure to radiation, health education, nutritional intervention, and screening programs, are needed especially in high-risk areas of the world.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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