



# RISK FACTORS OF THYROID GLAND MALIGNANCY

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## ABSTRACT

**Introduction:** Thyroid gland malignancy is the fifth most common endocrine malignancy in women, which is classified into differentiated and undifferentiated carcinoma. Risk factors of thyroid gland malignancy consist of individual, family history and exposure to irradiation.

**Purpose:** to discuss risk factors of thyroid gland malignancy. **Literature Review:** Genetic risk factors are the most strongly associated with malignancy, but the mechanisms are still unknown. External risk factors include exposure to ionizing radiation with a total dose of 20 Gy, under- or over-consumption of iodine, diabetes, women, exogenous estrogen exposure, smoking, alcohol, and excess body weight. Processing of red meat at high temperatures, excessive consumption of protein and carbohydrates, pollutants such as pesticides and industrial chemicals, lack of physical activity, history of benign thyroid tumors and goitre can increase the risk of thyroid malignancy.

**Conclusion:** Malignancy of the thyroid gland accounts for 1-2% of all malignancies and has a high mortality rate. Review and early detection are needed regarding the risk of thyroid malignancy to improve prognosis and reduce complications in patients.

**Keywords:** risk factor, malignancy, thyroid gland.

## INTRODUCTION

Thyroid malignancy is the most prevalent endocrine malignancy. Thyroid malignancy accounts for nearly 1-2% of all diagnosed malignancies annually in the United States.<sup>1,2</sup>

In the last two decades, there is a significant rise in the incidence of malignancy of the thyroid gland worldwide. According to the American Cancer Society, the annual estimate for thyroid gland malignancy has increased from 18,400 new cases in 2000 to 56,000 new cases in 2017. Similar trends are being reported in Europe and elsewhere in the world. The number of deaths associated with thyroid malignancy has not changed much over this period, with an estimated 2,000 deaths annually in the United States in recent years.<sup>3</sup>

Thyroid gland malignancies are grouped into 2 main groups, namely differentiated and undifferentiated carcinoma. Various risk factors are related to thyroid gland malignancy, both from individuals and in relation to family history and exposure to radiation.<sup>4</sup> This literature will discuss risk factor of the thyroid gland malignancy.

## LITERATURE REVIEW

### Definition

Thyroid gland malignancy is one of the most prevalent endocrine malignancies in the world and grouped into 2 main groups, namely differentiated carcinoma that consists of papillary, follicular and medullary and undifferentiated (anaplastic) carcinoma. The incidence of thyroid malignancy has elevated rapidly over the past two decades.<sup>1</sup>

### Epidemiology

Thyroid gland malignancy is the fifth most prevalent malignancy in women. Thyroid malignancy accounts for nearly 1-2% of all diagnosed malignancies each year in the United States. Thyroid malignancy is also the most common malignancy in those with a family history of thyroid disease.<sup>1</sup>

In the last two decades, there is a marked rise in the occurrence of malignancy of the thyroid gland worldwide. According to the American Cancer Society, the annual estimate for malignancy of the thyroid gland has increased from 18,400 new cases in 2000 to 56,000 new cases in 2017. Similar trends are being reported in Europe and elsewhere in the world.<sup>1,3</sup>

Thyroid gland malignancy also has the highest annual mortality rate in comparison with other endocrine malignancies.<sup>1</sup> Despite since 1970, the incidence of thyroid malignancy has increased rapidly, the mortality rate has tended to be stable or even decreased in several countries.<sup>1</sup> Thyroid malignancy mortality is estimated at 0.3 % of all malignancy deaths in 2016. The 5-year survival rate of thyroid malignancy is 98.1%.<sup>2</sup>

### Type of Thyroid Gland Malignancy

Malignancy of the thyroid gland is grouped based on the histological appearance and course of the disease, divided into 3 types, namely differentiated carcinoma (papillary carcinoma and follicular carcinoma), anaplastic carcinoma, and rare types of thyroid malignancy (medullary thyroid carcinoma). The latest classification of thyroid malignancy is divided into 2, namely, follicular type and neuroendocrine cell C.<sup>2</sup>

### Risk Factor of Thyroid Malignancy

#### Genetic

Genetic factors are believed to be one of the strongest risk factors associated with various types of malignancy. Most thyroid malignancies are sporadic, and at least 5% of all patients

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Table 1. Differences

Subtype	Prevalence	Prognosis	Differentiation	Characteristics
<b>Papillary</b>	80-85%	Good: up to stage II 5 year survival: 100%	Well-differentiated	Tumor cells form finger-like or papillary structures
<b>Follicular</b>	10-15%	Good: up to stage II 5 year survival: 100%	Well-differentiated	Tumor cells have the same follicles as normal thyroid follicles
<b>Medullary</b>	2-4%	Good: up to stage II 5 year survival: 98%	Bediferensiasi baik	The tumor originates from the para-follicular C cells of the thyroid gland which produce calcitonin and secrete the peptide into the bloodstream. The tumor is unable to concentrate with radioiodine, does not secrete thyroglobulin, and is unresponsive to TSH levels
<b>Anaplastic</b>	1-2%	Very poor 5 year survival: 100%	Undifferentiated, characterized by epithelial to mesenchymal cell transition	The tumor cells do not resemble normal thyroid cells or form follicles. Unresponsive to radioactive iodine, serum TSH level.

adenomatous polyposis should be screened at 15 years of age.<sup>4,16</sup>

### Radiation

One of the most calculated risk factors associated with the incidence of thyroid malignancy is ionizing radiation exposure, especially on children. A history of radiation exposure is known to account for about 9% of all cases of thyroid malignancy. Exposure to radioiodine can be obtained from the environment or from medical intervention such as Computed Tomography scans and radiation therapy to the head and neck. The younger the age exposed to radiation, associated with increased risk of developing thyroid malignancy in the future. The dose used during therapy is also closely related to the incidence of thyroid malignancy. The total radiation dose of 20 Gy is closely related to the risk of thyroid malignancy.<sup>4</sup>

### Iodine Consumption

Iodine is an important component in the synthesis of thyroid hormones. Consumption of excessive or insufficient iodine for a long period of time can affect thyroid function, potentially resulting in benign or malignant thyroid disease, including the risk of thyroid malignancy.<sup>4,17</sup> Based on the research of Hom-Ross et al, increased consumption of iodine in low-risk women, and consumption of multi-vitamins, is linked to a reduced risk of thyroid malignancy. Iodine deficiency affects thyroid gland function by reducing thyroid hormone levels, thereby increasing TSH secretion. This condition has the potential to result in an increased risk of malignancy.<sup>1</sup>

### Diabetes

The rise in the incidence of thyroid malignancy in past decades has coincided with diabetes, although the mechanism is not known with certainty.<sup>17</sup> In a metaanalysis studies it was found that women with diabetes mellitus have an increased risk of malignancy that is higher in those with diabetes.<sup>17</sup>

Insulin resistance activates the insulin and insulin-like growth factor-1 (IGF-1) pathways, which are important in cell proliferation and apoptosis. Chronic increase in circulating insulin levels can affect the risk of thyroid malignancy through overexpression of insulin receptors by cancer cells.<sup>17</sup>

### Female Sex and Estrogen

The prevalence of thyroid malignancies is more common in women, with a frequency of 2 to 4 times higher than in men.<sup>18</sup> This is related to estrogen levels in women. Estrogen is believed to be a risk factor in more than ¾ cases of thyroid malignancy in women. Exposure to exogenous estrogens is also increasing as a consequences of several medical and environmental therapies, including oral contraceptives, hormone replacement therapy, and consumption of meat that injected with growth hormones. Estrogen plays a role in increasing cell proliferation, migration, and invasion of thyroid malignancies. The mechanism for promoting cell growth is through estrogen receptor (ER) membrane binding. ER $\alpha$  activation induces the development of thyroid malignancy, while ER $\beta$  type acts to inhibit thyroid malignancy.<sup>19</sup>

### Smoking

Several studies have shown that smoking is related with the risk of thyroid malignancy. In several studies, it was found that smoking has the potential to affect the risk of thyroid malignancy by affecting TSH levels, serum thyroid antibodies, and sex steroid hormone levels.<sup>17</sup>

### Alcohol

The statement that alcohol consumption can increase TSH levels, which regulate the growth and function of the thyroid

gland which further increase the risk of thyroid malignancy is still a hypothesis. The results of several previous studies have not been consistent due to different types of alcoholic drinking. Further research is still needed to analyze the association between alcohol consumption and thyroid malignancy.

### Overweight

There is a relationship between body weight and the risk of thyroid malignancy. Based on research by McTieman et al. in the United States, it was reported that women weighing more than or equal to 60 kg had a 25 times higher risk of suffering from thyroid malignancy than women weighing less than or equal to 52 kg. Another research by Kitahara et al. in 2011 in the United States reported that every additional 5 kg increased the hazard ratio of 1.6 in women and 2 in men.<sup>1</sup>

### Food Factor

#### a. Coffee

Coffee consumption is one of the factors associated with thyroid malignancy. Based on the results of several studies, daily coffee consumption is linked with a reduced risk of thyroid malignancy. Other research stated that there is no relationship between coffee consumption and thyroid malignancy. The protective mechanism of coffee in preventing the development of thyroid lesions may be related to the stimulatory effect of caffeine in producing intracellular AMP, which is known as cell growth inhibition.<sup>1</sup>

#### b. Fruits and vegetables

High consumption of fruits and vegetables helps prevent malignancy.<sup>20</sup> High consumption of green vegetables shows a reduced risk of thyroid malignancy by up to 20%. Vegetables contain goitrogens which can reduce the incidence of thyroid malignancy. Apart from containing goitrogens, these vegetables contain flavonoids, phenols and isothiocyanates which are known to prevent thyroid cancer.<sup>1</sup>

#### c. Seafood

Research by Mack et al. in the United States reported that intake of shellfish in large quantities (several times a week) in earlyhood is related with a decreased risk of thyroid malignancy. In some cases of papillary thyroid carcinoma, high consumption of marine fish in adults also reduces the risk of malignancy. In marine fish found the presence of iodine, which functions to reduce the risk of thyroid malignancy.<sup>1</sup>

#### d. Red meat

Processing red meat at high temperatures produces carcinogenic complex such as N-nitroso compound, heterocyclic-amines (HCA), polycyclic-aromatic hydrocarbons (PAH) or heme iron which promote carcinogenesis. Research in Kuwait found a positive relationship between consumption of fish and beef with thyroid malignancy. Meanwhile, in Sweden and Norway there was no definite relationship between thyroid malignancy and the consumption of all types of red meat.<sup>20</sup>

#### e. Macronutrient

Based on research by Franceschi et al, various types of starchy foods, containing lipid, and protein have a direct relationship with thyroid malignancy. Overconsumption of nutriment rich in iodine, such as green vegetables and fruits, fish, has a protective outcome. Marcello et al. in Brazil 2012 reported that excessive intake of protein and carbohydrates was related with an increased risk of thyroid malignancy, while on the other hand absorption of fiber and fat, as well as physical activity could reduce the risk of thyroid malignancy. The mechanism of thyroid malignancy due to

excessive protein consumption is not known, but it is believed to be related to elevated levels of nitrosamines in some meat products which enhanced the risk of thyroid malignancy. Another mechanism is believed to be due to regulation of insulin-like growth factor I (IGF-1) activity, such as insulin, which is an increase in the risk of malignancy. IGF-1 accumulation is found in the consumption of animal meat protein.<sup>1</sup>

f. Micronutrient

Based on research in Italy, micronutrients other than iodine, such as high consumption of retinol showed a definite association with the risk of thyroid malignancy, while beta-carotene decreased the risk of thyroid malignancy.<sup>20</sup>

### Environmental Factor

Several types of pollutants such as pesticides and industrial chemicals can damage endocrine functions, which are grouped into environmental endocrine disrupting chemicals (EDCs).

a. Pesticides

Dichlorodiphenyltrichloroethane (DDT) and hexachlorobenzene (HCB) leads to disruption in thyroid hormone production. Dichlorodiphenyltrichloroethane lowers the activity of thyroid hormones, while HCB contains very toxic compounds, with thyroid hormones as the main target. In several studies, other types of pesticides such as atrazine, alachlor, imazethapyr, chlorpyrifos, glyphosate and metolachlor were not linked with the risk of thyroid malignancy.<sup>19</sup>

b. Nitrates

Nitrates are widely circulated pollutant contaminants that can be found in meat, some types of vegetables, and also contaminated drinking water. Contamination by nitrates is especially common in agricultural areas where drinking water is contaminated due to the use of nitrogen-rich fertilizers.<sup>20</sup> Consumption of nitrates can interfere iodide uptake by the thyroid, thereby impairing thyroid function. Nitrates result in reduced thyroid hormone production so that it is compensated by increasing TSH.<sup>17</sup> High TSH release associated to increased risk of thyroid hypertrophy and lead to thyroid abnormality along with malignancy.<sup>19</sup> Inoue-Choi et al. stated that a group of female who consumed drinking water contaminated with nitrate with levels >5 mg/L for 5 years or more had a 2.6 times higher risk of thyroid malignancy in comparison with a group of female whose drinking water contained nitrate contamination < 5mg/l.<sup>1,19</sup>

c. Metals

Metals found in food, water, and air can affect human wellness. Several metals have been categorized as definite and probable carcinogens by the International Agency for Research on Cancer (IARC). Carcinogenic metals are arsenic, beryllium, cadmium, chromium and nickel. The metals that EDCs disrupt the hormone system include arsenic, cadmium, lead, mercury, manganese, and zinc.<sup>19</sup>

### Physical Activity

There is a association between physical activity and the risk of thyroid malignancy. Physical activity with more frequent intensity and longer duration becomes a preventive intervention to reduce risk factors for thyroid malignancy.<sup>21</sup> From the hypothesis, it is found that physical activity can reduce the risk of malignancy through several pathways, including DNA repair and hormonal pathways, chronic inflammatory effects, and reducing inflammatory markers. In addition, exercise has been linked to the formation of an anti-inflammatory circumstances through elevated anti-inflammatory cytokines such as IL-1ra and IL10 in healthy individuals.<sup>21</sup>

### History of Thyroid Disease

Risk factors associated with thyroid malignancy is a history of benign thyroid tumors and goiter disease. Based on a case-control research by Mack et al. in the United States, there was a significant association between benign thyroid disease and thyroid malignancy. Study by Meinhold et al in the United States also showed that although the incidence of thyroid malignancy is low in men, those with a history of benign thyroid disease have a very high risk of thyroid malignancy.<sup>1</sup>

### Conclusion

Thyroid malignancy accounts for around 1-2% of entire malignancies diagnosed annually in the US and has the highest annual mortality rate of any endocrine malignancy. Thyroid malignancy mortality is estimated at 0.3% of all malignancy deaths in 2016. Various risk factors are associated with thyroid malignancy. Risk factors that need to be known are individual risk factors and their relationship to family history such as thyroid malignancy, and also exposure to radiation. The majority of thyroid malignancies are idiopathic

Although the exact cause of thyroid malignancy is still unclear, risk factors such as family history of thyroid disease, radiation exposure, excessive or insufficient consumption of iodine for a long time, diabetes, high estrogen levels in women, smoking, alcohol consumption, body weight. excess, processing of red meat at high temperatures, excessive consumption of protein and carbohydrates, pollutants such as pesticides and industrial chemicals such as nitrates and metals that can be found in the air, water and food, lack of physical activity, history of benign thyroid tumors and goiter disease can increase the risk of malignancy thyroid.

While several factors such as adequate iodine consumption, daily coffee consumption, consuming lots of fruits and vegetables, consuming seafood, consuming micronutrients such as beta-carotene, increasing physical activity, can reduce the risk of thyroid malignancy.

Screening of existing factors is required in individuals with an increased risk of thyroid malignancy. Early detection is also needed so that management and goals of therapy for patients can be planned to reduce the worsening of the prognosis and the occurrence of complications in patients.

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