

Inheritance	Type I (Warner) ³⁰ Autosomal dominant with high degree of penetrance.	Type II (Sipple) ³¹ Autosomal dominant with high degree of penetrance.
Clinical and pathological features Thyroid	Thyroid disorder in 20% usually adenoma, but may include differentiated carcinoma (not medullary), colloid goiter, thyroiditis or thyrotoxicosis.	Medullary carcinoma, frequently multifocal. Elevated serum calcitonin with exaggerated response to calcium or glucagon infusion may facilitate diagnosis of carcinoma or C-cell hyperplasia. Increased serum and tissue histaminase activity can serve as biochemical marker for primary and metastatic carcinoma. (Histaminase is found normally in human intestine, kidney and placenta.) Ectopic production of serotonin and prostaglandins may give rise to carcinoid and diarrheal syndromes, respectively.
Adrenal medulla		Pheochromocytoma may be bilateral. Diffuse or local hyperplasia may precede tumor formation.
Adrenal cortex	Adenoma, diffuse hyperplasia or carcinoma. Cushing's syndrome may be secondary to ectopic secretion of ACTH. Aldosteronoma.	Diffuse hyperplasia secondary to ACTH secretion by medullary thyroid carcinoma.
Parathyroid	Hyperparathyroidism due to adenoma or hyperplasia in most patients.	Less common and characteristically hyperplasia rather than adenoma. More likely a secondary response to the hypocalcemic action of calcitonin, than an expression of genetic pleiotropism.
Pancreas	Adenoma, hyperplasia (microadenomatosis) or carcinoma of non-beta islet cells. Accompanied frequently by elevated fasting serum gastrin and intractable peptic ulcer diathesis (Zollinger-Ellison syndrome). Glucagon and insulin-secreting adenomas have also been described.	
Pituitary	Adenomas in about 65% of patients. Frequently non-functional, but may give rise to acromegaly or Forbes-Albright syndrome (amenorrhea and galactorrhea).	
Other phenotypic features	Bronchial and intestinal carcinoid tumors, multiple lipomas, schwannomas and thymomas.	Multiple mucosal neuromas of lips, tongue, eyelids, segmental ganglioneuromatosis of large intestine resulting in megacolon, neurofibromas, café au lait spots and marfanoid body habitus. These phenotypic features in conjunction with medullary carcinoma and pheochromocytoma are now designated MEA III.

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patients, or four times that expected. The observed risk of thyroid cancer in women with breast cancer was statistically significant at the one percent level. The incidence of breast cancer in 827 patients with thyroid cancer, although not statistically significant, was 0.9 per year per 1,000 patients or 1.5 times expectation. The magnitude of increase in the incidence of thyroid cancer in our breast cancer patients did not exceed that observed throughout our population of hospital cancer registry patients. We observed a 5.7-fold excess of second primary carcinomas of the thyroid in 41,341 cancer patients and after 123,531 person-years of follow-up. Because the incidence of breast cancer was not seen to increase significantly in thyroid cancer patients, and because of the generally observed increase of second primary thyroid cancers, we were unable to determine if a common etiology for both breast and thyroid cancer might have existed.

Experimentally, ionizing radiation and hypothyroidism augment tumorigenesis in the thyroid and breast. Previous case control studies of women with breast cancer that used conventional tests of thyroid function failed to provide unequivocal evidence that hypothyroidism predisposes to breast cancer.³³ Although a positive correlation has been suggested for countries at increased risk of endemic goiter and breast cancer mortality, a similar correlation is not evident between thyroid cancer and breast cancer incidence. For example, the Chinese women living in Hawaii do not exhibit an increased risk of breast cancer. Although a study in Japan suggested that the risk of breast cancer was significantly increased in women with Hashimoto's thyroiditis, this was not confirmed, at least in the population studied at the Mayo Clinic.^{34, 35}

Thyrotropin-releasing hormone (TRH) from the hypothalamus is not only required for the normal synthesis and secretion of thyroid stimulating hormone (TSH), but also stimulates the secretion of prolactin. The concentration of plasma-free thyroxine regulates the responsiveness of TSH to TRH and may also influ-

ence TRH secretion. Mitra³⁶⁻³⁸ described a prolactin-thyroxine antagonism in the rat whereby, in the absence of thyroid hormones, the mammatrophic effect of endogenous prolactin was enhanced.

Prolactin is a sustaining factor in the growth of mammary carcinoma in some laboratory animals. For example, in the absence of the ovaries and adrenals, prolactin alone can maintain the growth of an existing mammary carcinoma in the rat. The role of prolactin in human breast cancer is less certain. Significant prolactin stimulation occurs during pregnancy and lactation, yet pregnancy before age 30 is relatively protective against breast cancer when compared with the risk noted in nulliparous women or in women whose first pregnancy is after age 30, and neither the duration nor the frequency of lactation is significantly correlated with the risk of breast cancer.³⁹ Blood prolactin concentrations are not consistently aberrant in women with breast cancer, although elevated prolactin, estradiol and estrone levels have been detected in the daughters of breast cancer patients.⁴⁰

Mitra and Hayward⁴⁶ studied the role of the thyroid in breast cancer by assessing the adaptive alterations in the hypothalamic-pituitary-thyroid axis. By measuring levels of TSH before and after TRH stimulation, they observed evidence of hypothyroidism in 10 percent of women with early breast cancer, 14 percent with advanced breast cancer, and in none of their age-matched hospital controls. The plasma concentration of TSH was significantly higher in patients with breast cancer. These recent studies are of interest if we recall that Sommers in 1955 reported in a controlled necropsy study that pituitary amphophil hyperplasia ("thyrotropic basophils") and thyroid atrophy were present with significantly greater frequency in breast cancer patients. Thyroid atrophy was interpreted as the most significant anatomical alteration in explaining an "endocrine imbalance that predisposed to breast cancer."⁴¹

The role of the thyroid in breast cancer is a question that has been pursued since at least the time of Beatson in 1896.⁴²