# **Heritability and Genetic Predisposition in Thyroid Carcinoma: A Comprehensive Analysis of Histological Subtypes and Global Variations**

## **Part 1: Introduction to Thyroid Cancer and Heritability**

### **1.1. Overview of Thyroid Cancer**

Thyroid cancer, the most frequently occurring malignancy of the endocrine system, has demonstrated a notable increase in global incidence in recent decades.1 This trend, particularly for papillary thyroid carcinoma (PTC), may be partially attributed to enhanced diagnostic scrutiny and the detection of smaller, subclinical tumors.9 Understanding the genetic underpinnings of thyroid cancer is crucial, especially in light of its rising prevalence.

The World Health Organization (WHO) classification of thyroid neoplasms, with its latest iteration in 2022, provides a framework for categorizing these tumors based on cellular origin, histopathological features, and molecular characteristics.14 The main categories include:

* **Follicular cell-derived neoplasms**: These constitute the majority of thyroid cancers and are broadly divided into benign tumors, low-risk neoplasms (e.g., Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features - NIFTP), and malignant neoplasms. Malignant follicular cell-derived tumors include:
  + Papillary Thyroid Carcinoma (PTC) and its numerous subtypes.
  + Follicular Thyroid Carcinoma (FTC), categorized by invasiveness (minimally invasive, encapsulated angioinvasive, widely invasive).
  + Oncocytic Carcinoma of the Thyroid (OCA), formerly Hürthle cell carcinoma, also categorized by invasiveness.
  + Follicular-derived Carcinomas, High-Grade, which encompass Poorly Differentiated Thyroid Carcinoma (PDTC) and Differentiated High-Grade Thyroid Carcinoma (DHGTC).
  + Anaplastic Thyroid Carcinoma (ATC), the most undifferentiated and aggressive form.
* **Thyroid C-cell-derived carcinoma**: This category is primarily Medullary Thyroid Carcinoma (MTC).
* **Other rare types**: These include mixed medullary and follicular cell-derived carcinomas, salivary gland-type carcinomas, and tumors of uncertain histogenesis.14

The increasing detection of thyroid cancer, especially small PTCs, presents a challenge for heritability studies. It becomes important to discern whether an observed rise in familial clustering is due to a genuine increase in the expression of genetic susceptibility or a consequence of more intensive surveillance and diagnosis within families, potentially unmasking clinically silent, indolent tumors. This consideration is vital for accurately interpreting genetic epidemiological data.

### **1.2. Defining Heritability in Thyroid Cancer**

Understanding the genetic contribution to thyroid cancer requires a clear distinction between several related, yet distinct, epidemiological and genetic concepts:

* **Heritability (h2)**: This is a population-level statistic that quantifies the proportion of the total variation in the susceptibility to a disease (phenotypic variation) within a specific population that can be attributed to genetic differences among individuals in that population.42 Heritability estimates are typically derived from studies of twins, comparing concordance rates for the disease in monozygotic (identical) twins, who share nearly 100% of their genes, with dizygotic (fraternal) twins, who share approximately 50% of their genes, similar to other siblings. It can also be estimated from large family-based studies. It is important to note that heritability is specific to the population and environment in which it is measured.
* **Familial Risk**: This term describes the observation that individuals with a family history of a particular disease, such as thyroid cancer, have an increased likelihood of developing the disease themselves compared to individuals without such a family history. Familial risk is often expressed as a relative risk (RR) or an odds ratio (OR).14 This increased risk is due to a combination of shared genetic factors, shared environmental exposures within the family, and potentially shared lifestyle factors.
* **Genetic Predisposition**: This refers to an individual's increased susceptibility to a disease due to the presence of specific inherited genetic variants (germline mutations). These can range from high-penetrance mutations in single genes, which confer a substantial risk and are often associated with hereditary cancer syndromes (e.g., *RET* mutations in medullary thyroid cancer), to common, low-penetrance variants that each contribute a small amount to the overall risk (polygenic risk).17

The user's query specifically requests the "heritability rate." This report will prioritize presenting formal heritability estimates (h2) where such data are available from the provided research. In instances where direct heritability estimates for specific subtypes or regions are lacking, the discussion will shift to familial risk and the prevalence of known germline mutations, with explicit clarification of these distinctions. This approach is necessary because while the body of research on genetic links to thyroid cancer is extensive, formal heritability calculations are less common for every nuanced category requested.

### **1.3. Importance of Understanding Thyroid Cancer Heritability**

Elucidating the heritability of thyroid cancer and its various subtypes carries significant implications for clinical practice and public health:

* **Genetic Counseling and Risk Stratification**: Accurate heritability data and knowledge of associated genetic syndromes inform risk assessment for individuals with a family history of thyroid cancer, guiding discussions about genetic testing and potential implications for relatives.14
* **Screening and Prevention**: Identifying individuals at high genetic risk allows for targeted screening protocols, potentially leading to earlier diagnosis and intervention, which can be particularly impactful for aggressive subtypes or in the context of hereditary syndromes.8
* **Etiological Research**: Heritability studies can pinpoint the overall genetic contribution, paving the way for research aimed at identifying specific susceptibility genes and understanding their roles in thyroid carcinogenesis. This includes investigating both high-penetrance genes in rare syndromes and common, low-penetrance variants contributing to polygenic risk.
* **Personalized Medicine**: A deeper understanding of the genetic architecture of thyroid cancer, including subtype-specific heritability, can contribute to the development of personalized prevention strategies and, potentially, more tailored therapeutic approaches in the future.

The observation that thyroid cancer exhibits high heritability, even if specific high-penetrance genes are not identified for every case, suggests a substantial underlying genetic influence on population risk. This encourages continued investigation into polygenic risk scores, gene-environment interactions, and the molecular mechanisms driven by identified susceptibility loci.

## **Part 2: Overall Heritability of Thyroid Cancer**

The heritability of thyroid cancer, representing the proportion of disease risk variance in a population attributable to genetic factors, has been investigated through various epidemiological approaches, most notably twin studies and large-scale family cancer databases.

### **2.1. Evidence from Twin Studies**

Twin studies, which compare disease concordance rates between monozygotic (identical) and dizygotic (fraternal) twins, are a cornerstone for estimating heritability.

* **Lichtenstein et al. (2000, NEJM)**: This seminal study analyzed extensive twin registry data from Sweden, Denmark, and Finland to assess the role of heritable factors in various cancers.43 While the study concluded that inherited genetic factors make a minor contribution to susceptibility for *most* types of neoplasms, it identified a significant heritable component for cancers at a few specific sites, such as prostate, colorectal, and breast cancer.43 Thyroid cancer was included in the scope of cancers analyzed.43 However, the provided research materials do not contain the specific heritability estimate (h2) for thyroid cancer derived from this particular study.174 This contrasts with the general understanding from other sources that thyroid cancer is among the more heritable malignancies.
* **Nordic Twin Study of Cancer (NorTwinCan) - Mucci et al. (2016, JAMA)**: This large-scale prospective study, encompassing twin registries from Denmark, Finland, Norway, and Sweden, provided updated estimates of familial risk and heritability for a range of cancers.42 The study reported an overall cancer heritability of 33% and provided specific estimates for several cancers, including melanoma (58%), prostate cancer (57%), and breast cancer (31%).44 Similar to the Lichtenstein study, the available abstracts and summaries of the Mucci et al. (2016) paper do not explicitly state the heritability estimate for thyroid cancer, although it was likely included in their comprehensive analysis.175
* **Swedish Family Cancer Database (Czene et al., 2002, as cited in other reviews)**: Analysis of the Swedish family cancer database indicated that among 15 cancer sites, thyroid cancer had the highest proportion of susceptibility attributable to genetic factors.4 This finding strongly suggests a significant heritable component for thyroid cancer.
* **General Conclusions from Twin and Family Studies**: Despite the lack of a specific heritability percentage for thyroid cancer from the abstracts of the two most prominent Nordic twin studies in the provided materials, other data from Utah and Sweden consistently suggest that thyroid cancer is one of the most heritable cancer types.4 This apparent high heritability for thyroid cancer, when compared to the "minor contribution" of genetics to "most neoplasms" as suggested by Lichtenstein et al. for a broader cancer spectrum, positions thyroid cancer as a notable malignancy with a potentially stronger genetic underpinning than many others.

### **2.2. General Estimates of Genetic Contribution to Thyroid Cancer Risk**

Beyond formal heritability estimates from twin studies, familial aggregation studies provide strong evidence for a genetic component in thyroid cancer:

* **Familial Relative Risk (FRR)**: First-degree relatives (parents, siblings, offspring) of individuals with thyroid cancer have a substantially increased risk of developing the disease, estimated to be 4 to 12 times higher than that of the general population.14 For instance, a Taiwanese study reported a 5.47-fold increased risk for first-degree relatives.4
* **Proportion of Cases with Germline Mutations**: Approximately 5-15% of non-medullary thyroid cancer (NMTC) cases are attributed to germline mutations, indicating a direct inherited cause in a significant minority of patients.4

The combination of high familial relative risks and the proportion of cases linked to known germline mutations suggests that while identifiable high-penetrance genes account for some familial cases (especially in syndromic contexts), a considerable portion of the observed heritability is likely due to polygenic inheritance (the combined effect of multiple common, low-penetrance genetic variants) or yet-to-be-identified rarer genes of moderate penetrance. This complex genetic architecture underscores the challenges in fully dissecting the hereditary basis of all thyroid cancer occurrences.

**Table 1: Heritability Estimates for Thyroid Cancer from Major Twin Studies**

| **Study** | **Population(s)** | **Cancer Type(s) Analyzed** | **Thyroid Cancer Heritability Estimate (%)** | **Notes** |
| --- | --- | --- | --- | --- |
| Lichtenstein et al. (2000) 43 | Swedish, Danish, Finnish twins | 28 anatomical sites; specific heritability for 11 sites (prostate, colorectal, breast explicitly mentioned with h2 values) | Not explicitly stated in provided snippets | Concluded inherited genetic factors make a minor contribution for *most* neoplasms but a large effect for a few. Thyroid cancer was included in the study's overall scope. |
| Mucci et al. (2016) - NorTwinCan 44 | Nordic countries (Denmark, Finland, Norway, Sweden) twins | Multiple cancer types (melanoma, prostate, nonmelanoma skin, ovary, kidney, breast, corpus uteri heritability explicitly mentioned) | Not explicitly stated in provided snippets | Overall cancer heritability 33%. Significant familial risks for most cancer types. Thyroid cancer likely included, but specific heritability estimate not provided in the available abstract. |
| Swedish Family Cancer Database 4 | Swedish population | 15 cancer sites | Highest among 15 cancer sites (specific % not given) | This study suggests thyroid cancer has a very high proportion of susceptibility accounted for by genetic factors, implying high heritability, though a specific percentage is not provided in the citing snippets. |

## **Part 3: Heritability and Genetic Predisposition by Thyroid Cancer Histological Type (WHO 2022 Classification)**

The genetic contribution to thyroid cancer varies significantly across its diverse histological subtypes. While Medullary Thyroid Carcinoma (MTC) has a well-defined and substantial hereditary component linked to *RET* proto-oncogene mutations, the heritability of Non-Medullary Thyroid Cancers (NMTCs)—comprising Papillary (PTC), Follicular (FTC), Oncocytic (OCA), Poorly Differentiated (PDTC), and Differentiated High-Grade Thyroid Carcinomas (DHGTC)—is more multifaceted. It involves a combination of rare high-penetrance genetic syndromes, familial clustering without an identified syndrome (non-syndromic FNMTC), and likely contributions from polygenic risk factors. The 2022 WHO classification, with its emphasis on molecular profiles and refined subtype definitions (e.g., invasiveness criteria for FTC and OCA; the distinct entity of DHGTC), is pivotal for advancing research into subtype-specific heritability.14

**Table 2: Overview of Hereditary Syndromes and Key Germline Mutations Associated with Thyroid Cancer Subtypes (WHO 2022)**

| **Thyroid Cancer Type/Subtype (WHO 2022)** | **Associated Hereditary Syndrome(s)** | **Key Germline Gene(s) Implicated** | **Estimated Proportion of Subtype Attributable to Syndrome/Gene (if available)** | **Key Snippets** |
| --- | --- | --- | --- | --- |
| **Medullary Thyroid Carcinoma (MTC)** | Multiple Endocrine Neoplasia type 2A (MEN2A), Multiple Endocrine Neoplasia type 2B (MEN2B), Familial MTC (FMTC) | *RET* | ~25% of all MTC cases are hereditary (germline *RET* mutations in >95% of hereditary cases) | 176 |
| **Papillary Thyroid Carcinoma (PTC) - General** | Familial Adenomatous Polyposis (FAP)/Gardner Syndrome | *APC* | PTC risk in FAP: 2-12% | 73 |
|  | Cowden Syndrome (PTEN Hamartoma Tumor Syndrome) | *PTEN* | Thyroid cancer risk in Cowden: >10% (often FTC, but PTC occurs) | 73 |
|  | Carney Complex Type 1 | *PRKAR1A* | Thyroid cancer risk: 4-60% (PTC or FTC) | 73 |
|  | Werner Syndrome | *WRN* | Thyroid cancer risk: ~18% (PTC, FTC, or ATC) | 72 |
|  | DICER1 Syndrome | *DICER1* | Increased risk of DTC (often multinodular goiter background); specific PTC proportion varies | 79 |
| **PTC - Cribriform-Morular Variant** | Familial Adenomatous Polyposis (FAP) | *APC*, *CTNNB1* (somatic) | Strongly associated with FAP | 76 |
| **Follicular Thyroid Carcinoma (FTC)** | Cowden Syndrome | *PTEN* | FTC is the most common thyroid malignancy in Cowden syndrome | 76 |
|  | Carney Complex Type 1 | *PRKAR1A* | FTC can occur | 76 |
|  | Werner Syndrome | *WRN* | FTC can occur | 76 |
|  | DICER1 Syndrome | *DICER1* | FTC reported in pediatric/adolescent cases | 28 |
| **Oncocytic Carcinoma of the Thyroid (OCA)** | Cowden Syndrome | *PTEN* | Can occur | 21 |
|  | Birt-Hogg-Dubé Syndrome | *FLCN* | Oncocytic neoplasms reported | 21 |
|  | Familial clustering (TCO locus) | *GRIM-19* (candidate) | Increased incidence in familial context | 21 |
| **Anaplastic Thyroid Carcinoma (ATC)** | Werner Syndrome | *WRN* | ATC can occur | 76 |
|  | MUTYH-Associated Polyposis (MAP) | *MUTYH* (germline biallelic) | MUTYH mutations identified in some ATC cases, germline status needs clarification for familial ATC risk | 122 |
| **Poorly Differentiated Thyroid Carcinoma (PDTC)** | DICER1 Syndrome | *DICER1* | PDTC reported in pediatric/adolescent cases, some with germline *DICER1* | 28 |

*Note: This table summarizes key associations. The penetrance of thyroid cancer in these syndromes varies, and not all individuals with these germline mutations will develop thyroid cancer. The distinction between syndromic and non-syndromic familial thyroid cancer is important.*

### **3.1. Papillary Thyroid Carcinoma (PTC)**

PTC is the most common type of thyroid cancer and constitutes the majority of cases within Familial Non-Medullary Thyroid Cancer (FNMTC) clusters.14

3.1.1. Heritability and Familial Non-Medullary Thyroid Cancer (FNMTC)

FNMTC, defined by the occurrence of NMTC in two or more first-degree relatives without other predisposing environmental factors or known hereditary syndromes, accounts for approximately 3-9% (with some estimates up to 5-15%) of all NMTC cases.14 The likelihood of a true hereditary basis increases with the number of affected relatives: if two first-degree relatives are affected, the probability of the cancer being hereditary is estimated at 31-38%, rising to over 94% if three or more are affected.39 This distinction is important, as families with only two affected members might represent sporadic co-occurrences, especially given the rising incidence of PTC, whereas families with three or more affected members are more strongly indicative of a significant underlying genetic predisposition.

3.1.2. Syndromic Associations Predisposing to PTC

Approximately 5% of FNMTC cases occur as part of well-defined hereditary cancer syndromes.14 These include:

* **Familial Adenomatous Polyposis (FAP) and Gardner Syndrome**: Caused by germline mutations in the *APC* gene. Patients have a 2-12% lifetime risk of developing PTC, often the cribriform-morular variant.72
* **Cowden Syndrome (PTEN Hamartoma Tumor Syndrome)**: Caused by germline mutations in the *PTEN* gene. The lifetime risk for thyroid cancer (PTC or FTC) is estimated to be between 3% and 38% (often cited as >10%).148
* **Carney Complex Type 1**: Associated with germline mutations in the *PRKAR1A* gene. The risk of thyroid tumors (PTC or FTC) ranges from 4% to as high as 60% in some reports.72
* **Werner Syndrome**: Caused by germline mutations in the *WRN* gene. Patients have an approximately 18% risk of developing thyroid cancer, which can be PTC, FTC, or ATC.72
* **DICER1 Syndrome**: Caused by germline mutations in the *DICER1* gene. This syndrome predisposes to various tumors, including multinodular goiter and an increased risk of differentiated thyroid cancer (often PTC) in childhood and adolescence.14

3.1.3. Non-Syndromic Familial PTC

The majority (approximately 95%) of FNMTC cases are non-syndromic, meaning they occur without the other characteristic features of the syndromes listed above.14 The genetic basis for most non-syndromic FNMTC is complex and not fully elucidated, likely involving polygenic inheritance (multiple low-penetrance genes) and possibly some yet-to-be-identified moderate-penetrance genes. Candidate genes and loci implicated in non-syndromic FNMTC include:

* *FOXE1* (Forkhead Box E1) on chromosome 9q22.14
* *SRGAP1* (SLIT-ROBO Rho GTPase Activating Protein 1) on 12q14.14
* *HABP2* (Hyaluronan Binding Protein 2), particularly the G534E variant, though its role is debated and appears common in general populations.14
* *CHEK2* (Checkpoint Kinase 2).14
* Other loci and genes such as *WDR77*, *BROX*, *TITF-1/NKX2.1*, *PTCSC2*, *PTCSC3* have also been implicated in specific populations or families.14 The genetic heterogeneity and population-specific findings in non-syndromic FNMTC underscore the difficulty in identifying universal high-penetrance susceptibility genes for this form of PTC. This suggests that a combination of multiple genetic variants, each with a small to moderate effect, likely contributes to the familial risk in many cases.

3.1.4. Heritability/Familial Risk for Specific PTC Subtypes (WHO 2022 Context)

Data on specific heritability rates for each WHO 2022 PTC subtype are generally sparse. Much of the existing literature on FNMTC predates this detailed subclassification or groups variants.

* **Classical PTC (cPTC)**: Constituting about 50-68% of PTCs, cPTC is the most common form in FNMTC clusters.180 General PTC familial risk data largely reflects cPTC. Regional metastasis is common, reported in 39-90% at presentation in various series, with distant metastasis rates around 1-10%.180 A US-based study (SEER data) reported a 1% distant metastasis rate for cPTC.182
* **Follicular Variant PTC (FVPTC)**:
  + The WHO 2022 classification distinguishes **Invasive Encapsulated Follicular Variant PTC (IEFVPTC)** as a malignant RAS-like tumor, separate from the low-risk Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP).14 This reclassification is critical, as previous studies grouping all FVPTCs might have obscured subtype-specific genetic predispositions. NIFTPs, being indolent and RAS-like, likely have a different heritable component, if any, compared to more aggressive BRAF-driven PTCs or IEFVPTC.
  + Overall FVPTC (pre-2022 classification) showed a 16% regional and 2% distant metastasis rate in US SEER data.182
  + A Korean study on encapsulated PTCs found that E-FVPTC had a 3% lymph node metastasis rate and four cases presented with distant metastasis.184
  + Data from a single European institution indicated that diffuse FVPTC had 100% central nodal metastasis, while encapsulated FVPTC (EFVPTC) and non-encapsulated FVPTC (NFVPTC) in that small series showed 0% central nodal metastasis.185 This suggests significant heterogeneity within FVPTC that the new classification aims to address.
* **Aggressive PTC Variants (Tall Cell, Hobnail, Diffuse Sclerosing, Columnar Cell, Solid)**: These variants are known for more aggressive clinical behavior.72
  + **Tall Cell Variant (TCV)**: Regional metastasis rates range from 39.6% to 56.3%, and distant metastasis rates from 6.2% to 8.3% in US studies.186 Germline *DICER1* variants have been associated with some aggressive PTCs, including TCV.136 Somatic *BRAF* mutations are frequent.19
  + **Hobnail Variant (HVPTC)**: Systematic reviews report lymph node metastasis rates of 60-75% and distant metastasis rates of 23-40%.148 Germline *DICER1* variants are also implicated here.136 Somatic *BRAF* and *TP53* mutations are common.188
  + **Diffuse Sclerosing Variant (DSVPTC)**: Shows higher rates of lymph node (OR 5.85) and distant metastases (OR 3.83; up to 28%) compared to cPTC.190 Somatic *RET/PTC* rearrangements are common.108
  + **Columnar Cell Variant (CCV)**: US data suggests nodal metastasis in 49.4% and distant metastasis in 3.01%.193
  + **Solid Variant (SVPTC)**: Regional metastasis rates reported at 62% in one study and 7.1% at diagnosis in another.194
  + While somatic mutations driving aggressiveness in these PTC variants are increasingly understood, the specific germline predispositions for familial clustering of these particular aggressive histological forms, beyond general FNMTC susceptibility, remain an area of active investigation. The heritability of "aggressiveness" itself within PTC families is not well quantified.
* **Oncocytic Variant of PTC (OVPTC)**: Recognized in WHO 2022.14
  + A study reported 5/10-year distant metastasis incidence of 3.4%/4.5%.196
  + Familial clustering of oncocytic neoplasms is linked to the TCO locus and *GRIM-19* as a candidate gene.21 Germline *DICER1* variants are also associated.136

### **3.2. Follicular Thyroid Carcinoma (FTC)**

FTC is the second most common type of differentiated thyroid cancer.197 It is also part of the FNMTC spectrum, although PTC is more commonly found in familial clusters.14

3.2.1. Syndromic Associations Predisposing to FTC

FTC is a known component of several hereditary syndromes:

* **Cowden Syndrome (*PTEN* mutations)**: FTC is the most common thyroid malignancy in this syndrome.14
* **Carney Complex Type 1 (*PRKAR1A* mutations)**.14
* **Werner Syndrome (*WRN* mutations)**.14
* **DICER1 Syndrome (*DICER1* mutations)**: Particularly in pediatric and adolescent FTC.14

3.2.2. FTC Subtypes by Invasiveness (WHO 2022) and Heritability

The WHO 2022 classification categorizes FTC into minimally invasive (capsular invasion only), encapsulated angioinvasive (vascular invasion with or without capsular invasion), and widely invasive subtypes.14

* **Minimally Invasive FTC (MIFTC)**: Characterized by limited capsular invasion only. Generally associated with a good prognosis.197 Distant metastasis rates at initial treatment are reported to be low (1-9%).18
* **Encapsulated Angioinvasive FTC (EAFTC)**: Defined by vascular invasion within an encapsulated tumor. This is a new distinct entity in WHO 2022.14 Studies reclassifying older cohorts based on WHO 2022 show that EAFTC has an intermediate prognosis for disease-specific survival (DSS).16 In a Serbian study, 8.3% of patients who developed distant metastases during follow-up had EAFTC, and 33.2% of those with distant metastases prior to surgery had EAFTC.199
* **Widely Invasive FTC (WIFTC)**: Shows extensive infiltration into adjacent thyroid tissues and/or blood vessels and has a poorer prognosis.197 Distant metastasis rates at initial treatment are higher, ranging from 8% to 45%.18 In the Serbian cohort, 58.3% of patients developing distant metastases during follow-up had WIFTC.199
* **Heritability Data by Invasive Subtype**: Specific heritability estimates or detailed familial aggregation studies for each of these WHO 2022 invasive subtypes of FTC are not extensively available in the provided snippets. Most familial studies group FTCs more broadly or predate this specific classification.14 The reclassification aims to improve risk stratification, which may, in turn, help in future genetic studies to identify if certain germline predispositions are linked to specific invasive patterns.
  + **Insight**: The WHO 2022 subclassification of FTC by invasiveness (MIFTC, EAFTC, WIFTC) is crucial for prognosis. While direct heritability data for these specific new subtypes is sparse, it's plausible that underlying genetic predispositions could influence the invasive potential of FTC. Future familial and genetic studies should adopt this classification to explore such links.
    - **Chain of Thought**: The WHO 2022 classification for FTC (and OCA) introduces categories like EAFTC and EAOTC, which have intermediate prognoses.16 This refined classification based on invasion patterns is significant because the degree of invasiveness is a key prognostic factor and is biologically driven. If certain germline variants predispose to more (or less) aggressive tumor biology, they might manifest as a tendency towards specific invasive subtypes (e.g., WIFTC vs. MIFTC). Therefore, future genetic studies on familial FTC/OCA should stratify by these WHO 2022 subtypes to uncover potential genotype-phenotype correlations related to invasiveness.

### **3.3. Oncocytic Carcinoma of the Thyroid (OCA)**

Formerly known as Hürthle cell carcinoma, OCA is now a distinct entity in the WHO 2022 classification, characterized by >75% oncocytic cells and lacking PTC nuclear features.14 It accounts for 3-5% of thyroid cancers.17

**3.3.1. Heritability and Familial Clustering**

* Oncocytic thyroid tumors show an increased incidence in the familial context (FNMTC).21 Both benign and malignant oncocytic tumors can occur within the same family.
* The "Tumor with Cell Oxyphilia" (TCO) locus at 19p13.2 has been associated with susceptibility to oncocytic thyroid tumors.21 *GRIM-19* is a candidate gene in this locus.
* Germline mutations in genes like *FLCN* (Birt-Hogg-Dubé syndrome) can predispose to oncocytic neoplasms.21
* A study using SEER data (2004-2018) on 3,264 HCTC (OCA) patients found that 11.7% had regional disease and 4.0% had distant metastases at diagnosis.204 Another study cited a 10-year cancer-specific survival of 92.6% for a cohort where 4.24% had metastatic disease at diagnosis.203 It's estimated 1 in 4 people with HCC (OCA) will develop metastatic disease at some point.203

3.3.2. OCA Subtypes by Invasiveness (WHO 2022) and Heritability

Similar to FTC, the WHO 2022 classification categorizes OCA into minimally invasive, encapsulated angioinvasive, and widely invasive subtypes.14

* A study reclassifying 52 OCA cases according to WHO 2022 found that 15 (28.8%) were reclassified as encapsulated angioinvasive OCA (EAOTC). Ten-year DSS rates were 100% for MIOTC, 92.9% for EAOTC, and 56.5% for WIOTC, indicating improved risk stratification with the new classification.16
* Specific heritability data for these invasive subtypes of OCA are still emerging. The distinct genetic landscape of OCA (e.g., frequent mitochondrial DNA mutations, alterations in nuclear genes like *EIF1AX*, *TP53*, *NF1*, *KDM5C*, *PTEN*) compared to FTC suggests that familial predispositions might also differ.27
  + **Insight**: The recognition of OCA as a distinct entity from FTC, with its own unique genetic drivers (often mitochondrial) and clinical behavior, implies that its heritable components are also likely distinct. Familial clustering of oncocytic tumors (TCO locus) supports this. Future research should focus on identifying germline variants specifically predisposing to OCA and its invasive subtypes.
    - **Chain of Thought**: OCA was previously often grouped with or considered a variant of FTC. However, WHO 2017 and 2022 establish it as a separate entity due to distinct molecular features (e.g., mitochondrial DNA mutations, different nuclear gene mutation profiles like less RAS, more EIF1AX, TP53) and often more aggressive behavior/poorer RAI avidity.17 This biological distinctiveness strongly suggests that its heritable basis will also differ from that of conventional FTC. The identification of the TCO locus specifically for oncocytic tumors 21 further supports this. Therefore, lumping OCA with FTC in familial studies would obscure OCA-specific genetic risk factors.

### **3.4. Medullary Thyroid Carcinoma (MTC)**

MTC arises from parafollicular C-cells and accounts for <5% of thyroid cancers, but a disproportionate 13% of thyroid cancer-related deaths.205

**3.4.1. High Heritability and *RET* Proto-Oncogene**

* Approximately 25-30% of MTC cases are hereditary, caused by autosomal dominant germline pathogenic variants in the *RET* proto-oncogene.205 In children and young adults, hereditary MTC (hMTC) can comprise 85% or more of cases.177
* The remaining 70-75% are sporadic, though somatic *RET* mutations are found in about 50-60% of these.205
* Genetic testing for germline *RET* mutations is recommended for all MTC patients due to the implications for family members and risk stratification.205
* Even in apparently sporadic MTC, germline *RET* mutations can be found in 1-10% of cases, depending on the population and screening intensity.208 A large Italian study reported 6.2% 229, while a Turkish study found 5.2%.228

**3.4.2. Hereditary MTC Syndromes**

* **Multiple Endocrine Neoplasia type 2A (MEN2A)**: Accounts for ~60-95% of hereditary MTC cases. Characterized by MTC, pheochromocytoma (in ~50%), and primary hyperparathyroidism (in ~20-30%).73 Most MEN2A cases (95%) are inherited, with ~5-9% arising from de novo *RET* mutations.209
* **Multiple Endocrine Neoplasia type 2B (MEN2B)**: Accounts for ~5% of MEN2 cases. Characterized by early-onset, aggressive MTC (in all patients), pheochromocytoma (~50%), mucosal neuromas, marfanoid habitus, and gastrointestinal issues; parathyroid disease is rare.73 About 50% of MEN2B cases are due to de novo *RET* mutations, often paternal in origin.212
* **Familial Medullary Thyroid Carcinoma (FMTC)**: MTC is the only clinical manifestation. Accounts for 10-20% of MEN2 cases (or hereditary MTC).73 Now often viewed as a variant of MEN2A with lower penetrance for other endocrine tumors.223
* **Insight**: The high proportion of MTC attributable to identifiable germline *RET* mutations makes it a paradigm for inherited cancer. The genotype-phenotype correlations within *RET* mutations (e.g., specific codons like 634, 918) predict disease aggressiveness and guide prophylactic thyroidectomy timing, especially in MEN2B where MTC can be very aggressive from infancy.205
  + **Chain of Thought**: The *RET* gene is central to MTC. Different mutations within *RET* lead to MEN2A, MEN2B, or FMTC, each with varying aggressiveness and age of onset for MTC.205 This strong genotype-phenotype correlation is a hallmark of MTC genetics and has direct clinical applications, such as determining the optimal age for prophylactic thyroidectomy in asymptomatic *RET* carriers to prevent MTC development. This is a clear example of how understanding heritability and specific genetic drivers translates into preventative medical action.

**3.4.3. Metastasis in Hereditary vs. Sporadic MTC**

* Hereditary MTC often presents as bilateral and multifocal disease, potentially at an earlier stage if identified through family screening.135
* Sporadic MTC typically arises as a solitary unilateral nodule.135
* Overall, MTC has a high propensity for early regional lymph node metastasis (70% of palpable nodules) and distant metastasis (10% at presentation for sporadic cases).205 Some studies suggest *RET*-mutant MTC (which includes all hereditary forms and many sporadic ones) exhibits more aggressive clinical behavior, including higher rates of lymph node and distant metastasis.205
* A European study (EU5 countries) found that *RET* mutation-positive advanced MTC (aMTC) had a numerically higher rate of metastatic disease (87%) compared to the overall aMTC population (79%).176 Since hereditary MTC is almost entirely *RET* mutation-positive, this suggests a higher metastatic propensity in hereditary forms, although specific rates for hereditary vs. sporadic were not directly provided in that study for the metastatic outcome.
* The International MTC Grading System (IMTCGS), based on mitotic count, necrosis, and Ki-67, helps stratify MTC into low- and high-risk for recurrence and metastasis, applicable to both sporadic and hereditary forms.205

### **3.5. Anaplastic Thyroid Carcinoma (ATC)**

ATC is the rarest (<2% of thyroid cancers) but most aggressive form, responsible for a disproportionately high mortality rate.236

**3.5.1. Familial Risk and Germline Predisposition**

* ATC is generally considered sporadic, with familial cases being exceedingly rare.117
* However, ATC often arises from pre-existing differentiated thyroid cancer (DTC), such as PTC or FTC (up to 70% of ATC cases have a coexisting DTC component).42 Therefore, individuals with a germline predisposition to DTC (e.g., FNMTC syndromes) might theoretically have an increased risk of ATC as a result of dedifferentiation, although this progression is not common.
  + **Insight**: The link between ATC and prior DTC implies that any germline factors predisposing to DTC could indirectly increase ATC risk if those DTCs dedifferentiate. However, the specific genetic events driving dedifferentiation to ATC are primarily somatic.
    - **Chain of Thought**: ATC often develops from a pre-existing DTC through the accumulation of additional somatic mutations (e.g., *TP53*, *TERT* promoter, *PIK3CA*, *CDKN2A*).34 If an individual has a germline predisposition to DTC (familial or syndromic), they have an increased chance of developing DTC. While most DTCs do not progress to ATC, the initial presence of DTC is a prerequisite for this pathway of ATC development. Thus, a germline predisposition to DTC could be seen as an indirect, albeit remote, risk factor for ATC arising via dedifferentiation. Direct germline predisposition specifically to ATC itself (de novo ATC without prior DTC) is not well established as a common mechanism.
* **Syndromic Associations**: Werner syndrome (*WRN* gene mutations) is associated with an increased risk of ATC, alongside PTC and FTC.148
* **MUTYH Mutations**: Recent research identified germline *MUTYH* variants (Y165C, G382D), associated with MUTYH-Associated Polyposis (MAP), in a small percentage (2.34% of 727 cases, with these specific variants predicted to be germline) of ATC cases. Some of these occurred without concurrent *BRAF* mutations, suggesting *MUTYH* variants might independently contribute to ATC pathogenesis in a subset of patients.122 The heritability implications for families require further study.

**3.5.2. Metastasis Rates**

* ATC is characterized by rapid local invasion and early distant metastasis.236
* Up to 50-58% of patients have distant metastases at presentation.236 Metastases occur in up to 75% of patients during the disease course.236
* Regional lymph node involvement is seen in up to 40% of cases.236
* Common metastatic sites: Lungs (most common, ~80% of metastatic cases), bone (6-15%), brain (5-13%).236 Cardiac metastasis is rare (<2%).241
* Data from a study in South Africa indicated that 33% of ATC patients presented with metastatic disease.21

### **3.6. Poorly Differentiated Thyroid Carcinoma (PDTC) and Differentiated High-Grade Thyroid Carcinoma (DHGTC)**

PDTC and the newer WHO 2022 entity DHGTC represent tumors with features intermediate in aggressiveness between well-differentiated thyroid carcinomas (DTC) and ATC.14 DHGTC includes PTC, FTC, or OCA with high-grade features (increased mitotic activity ≥5/2mm2 and/or tumor necrosis).17

**3.6.1. Familial Risk and Germline Predisposition**

* PDTC and DHGTC can arise from pre-existing DTCs through the accumulation of additional genetic alterations.34 Therefore, familial predispositions to DTC might indirectly increase the risk of developing these more aggressive forms, although the rate of such dedifferentiation in FNMTC versus sporadic NMTC is not well quantified in the provided snippets.149
* **DICER1 Syndrome**: Germline *DICER1* mutations have been linked to PDTC in pediatric and adolescent patients.28 Some FNMTC cases with a background of multinodular goiter in childhood/adolescence may also be associated with germline *DICER1* mutations.31
* **Other Germline Factors**: While specific high-penetrance genes for familial PDTC/DHGTC in adults are not well-defined beyond general FNMTC susceptibility genes, the genetic landscape of these tumors often involves somatic mutations in genes like *BRAF*, *RAS*, *TP53*, and *TERT* promoter, which are also seen in ATC progression.245
* **Insight**: The development of PDTC/DHGTC often represents a progression from a well-differentiated carcinoma. Therefore, any heritable factors increasing the risk of the initial DTC could indirectly contribute to the risk of these higher-grade tumors. However, the specific germline variants that might accelerate or predispose to this dedifferentiation step in familial settings are not yet clearly understood.
  + **Chain of Thought**: PDTC and DHGTC are often seen as stages in a tumor progression model, where a well-differentiated thyroid cancer (PTC or FTC) acquires additional mutations (e.g., in *TP53*, *TERT* promoter) leading to dedifferentiation and more aggressive behavior.31 If FNMTC cases are inherently more prone to genomic instability or accumulate these "second hit" mutations more readily than sporadic DTCs, this could lead to a higher rate of progression to PDTC/DHGTC. However, the snippets do not provide direct evidence comparing dedifferentiation rates in FNMTC vs. sporadic NMTC.149 This remains an important area for research.

**3.6.2. Metastasis Rates**

* **PDTC**: Regional lymph node metastasis occurs in 50-85% of cases, and distant metastasis in up to 85% of cases.242 In a Polish study, 14.3% had distant metastases at diagnosis, and an additional 28.6% developed them during follow-up.243 A Canadian study of 21 PDTC patients reported distant metastasis in 38.1%.244 In a Southeast Asian (Philippines) cohort, 27.8% had nodal and 27.8% had distant metastasis.246
* **DHGTC**: Data specific to DHGTC metastasis rates are still emerging due to its recent classification. However, given its definition includes high-grade features, it is expected to have a significant metastatic potential, often similar to or worse than PDTC. One study reported distant metastasis in 45.5% of DHGTC cases compared to 17.9% in non-HGDTC cases in an advanced disease cohort.126 Another institutional review found distant metastases or locoregional recurrence in 7 out of 32 DHGTC cases.30 Metastasis is reported in approximately 20-50% of patients with DHGTC/PDTC.45

### **3.7. Other Rare Thyroid Carcinomas**

* **3.7.1. Salivary Gland-Type Carcinomas of the Thyroid**
  + These include Mucoepidermoid Carcinoma (TMEC), Sclerosing Mucoepidermoid Carcinoma with Eosinophilia (SMECE), and Secretory Carcinoma (SC) of the thyroid.14
  + **TMEC**: Regional lymph node metastases in 48%; distant metastases in 20% (lung 14%, bone 6%).247
  + **SMECE**: Regional lymph node metastases in 35%; distant metastases in 14% (lung 9%, liver 4%).247
  + **SC**: Regional lymph node metastases in 64%; distant metastases in 27% (liver 27%, lung 18%).247
  + **Heritability**: No specific heritability data or strong familial links are reported in the provided snippets for these rare subtypes. Their rarity makes such studies challenging.
* **3.7.2. Mixed Medullary-Follicular Carcinoma (MMFC)**
  + A rare entity with components of both MTC and follicular cell-derived carcinoma.14
  + One study using the US National Cancer Database (NCDB) reported that nearly 70% of MMFC patients present with distant metastasis.248
  + **Heritability**: Given the MTC component, *RET* gene analysis would be relevant. However, specific heritability patterns for MMFC itself are not well-defined in the snippets. The follicular component's genetic drivers might interact with the C-cell component's genetics.
    - **Insight**: The dual nature of MMFC suggests a complex genetic etiology. The MTC component implies a potential role for *RET* mutations (germline or somatic), while the follicular component could involve pathways typical of FTC or PTC. Whether specific germline variants predispose to this mixed phenotype or if it arises from collision or transdifferentiation events influenced by separate genetic predispositions is unknown.
      * **Chain of Thought**: MMFC presents a unique challenge for understanding heritability because it combines two distinct cell lineages. The MTC part immediately brings *RET* into consideration.43 If a germline *RET* mutation is present, that explains the MTC component's heritability. The follicular component could arise sporadically or be influenced by FNMTC susceptibility genes if the patient also carries those. Alternatively, one tumor type might induce changes leading to the other. The high rate of distant metastasis (70% 248) suggests an aggressive biology, which could have genetic underpinnings that are distinct from "pure" MTC or FTC.

## **Part 4: Geographical and Ethnic Variations in Thyroid Cancer Heritability**

Data on direct heritability rates (h2) for thyroid cancer and its subtypes across different geographical regions and ethnic groups are limited in the provided research. However, variations in the prevalence of familial thyroid cancer (specifically FNMTC) and the frequency of certain germline mutations suggest that genetic susceptibility may differ across populations.

* **FNMTC Prevalence Variations**:
  + **Europe**:
    - A Spanish study reported an FNMTC prevalence of 6.6% in their DTC cohort.8
    - An Italian study involving 33 FNMTC kindreds was noted, but overall prevalence in a larger Italian cohort was not specified in that snippet.168
    - A Polish study indicated FNMTC accounts for 3-9% of all thyroid cancers.4
  + **Asia**:
    - A Korean study reported a high FNMTC prevalence of 9.6%.50
    - A Taiwanese study found the prevalence of NMTC in first-degree relatives of NMTC patients to be 0.64% (compared to 0.16% in the general population), indicating significant familial risk.4
  + **North America**:
    - Studies in the US suggest FNMTC accounts for 3-9% or 5-15% of NMTC cases.4
  + **Australia**:
    - FNMTC is suspected in 3-8% of thyroid cancers.156 A study on Australian FNMTC kindreds investigated *HABP2* G534E but found it did not account for familial clustering in that cohort and was common in the general Australian population.157
  + **Africa, South America, Middle East**: Specific FNMTC prevalence rates from large cohort studies or systematic reviews for these entire regions are not clearly detailed in the provided snippets.7 One study mentioned that the FNMTC-associated *HABP2* G534E variant was present in 1.3% of Hispanic controls from Colombia and 0.54% in an African ancestry group from the ExAC database, compared to higher frequencies in European ancestry populations.167
* **Ethnic and Geographical Differences in Germline Susceptibility Loci**:
  + Genome-Wide Association Studies (GWAS) have identified several low-penetrance susceptibility loci for NMTC (e.g., near *FOXE1*, *NKX2-1*, *DIRC3*, *NRG1*, *SRRM2*). The frequencies of risk alleles at some of these loci can vary between ethnic groups.14
  + A multiethnic GWAS found that risk allele frequencies at 2q35, 5p15.33, and 16q23.2 were significantly higher in Oceanians than in Europeans, potentially contributing to higher DTC incidence in Pacific Islanders.130
  + A study of the Polish population found significant differences in the frequencies of pathogenic variants in genes like *RET*, *CHEK2*, *BRCA1*, *SLC26A4*, and *TERT* compared to other non-Finnish European populations from gnomAD, suggesting population-specific genetic risk profiles.4
  + The *WDR77* germline loss-of-function variants predisposing to familial PTC were reported in two unrelated Chinese families.20
  + The *BROX* gene mutations were identified in Italian FNMTC families.46
  + The prevalence of pathogenic variants in cancer susceptibility genes generally can differ across racial groups, with one large US study (All of Us dataset) finding White participants having the highest prevalence and Asians the lowest for a panel of 84 cancer susceptibility genes.52 This may have implications for thyroid cancer if these genes are involved.
* **Medullary Thyroid Cancer (*RET* mutations)**:
  + While germline *RET* mutations are the primary cause of hereditary MTC worldwide, the prevalence of specific *RET* codons involved can vary geographically. For example, codon 634 mutations are most frequent in many European countries, codon 533 mutations are dominant in Greece, and codon 618 mutations are particularly frequent in Cyprus. A large Italian study showed a high prevalence of codon 804 mutations, while codon 790 mutations were noted in Germany.229 A Vietnamese study found p.M918T to be the most frequent somatic *RET* mutation in their MTC cohort, followed by p.C634R and p.C618R, though these were not confirmed as germline in that specific study group.213 A study in Northwest India found 22 *RET* mutation-positive patients among 78 MTC cases, but specific codon prevalence was not detailed in the abstract.206
* **Insight**: The existing data, though fragmented for precise heritability rates by region and subtype, strongly suggest that both the overall prevalence of familial thyroid cancer and the frequencies of specific susceptibility alleles vary across different ethnic and geographical populations. This underscores the need for population-specific genetic studies to accurately assess heritability and identify relevant risk variants.
  + **Chain of Thought**: The observation of differing FNMTC prevalence rates (e.g., higher in a Korean cohort 50 compared to some European estimates 8) and distinct patterns of *RET* mutations in MTC across countries 206 points towards genuine population-level genetic differences. Furthermore, GWAS studies identifying different risk allele frequencies for NMTC susceptibility loci between, for example, Europeans and Oceanians 130, reinforce this. This genetic diversity means that heritability estimates and the impact of specific genes might not be universally applicable. Therefore, a "one-size-fits-all" approach to genetic risk assessment for thyroid cancer globally is likely insufficient, and region-specific research is paramount.

## **Part 5: Challenges and Future Directions in Thyroid Cancer Heritability Research**

Despite significant advances, research into the heritability of thyroid cancer faces several challenges, and future efforts should focus on addressing these to refine our understanding.

* **Complexity of Polygenic Inheritance**: For non-syndromic FNMTC, which constitutes the majority of familial cases, the genetic basis is likely polygenic, involving multiple common, low-penetrance variants interacting with each other and environmental factors.14 Identifying these variants and their combined effects requires very large-scale GWAS and sophisticated analytical methods.
* **Impact of Overdiagnosis**: The increasing incidence of thyroid cancer, particularly small PTCs due to enhanced detection, can confound studies of familial risk and heritability.9 It is challenging to distinguish true increases in genetic susceptibility from increased ascertainment of indolent, familially clustered cases that might not have become clinically apparent in the past. Future studies need to carefully account for diagnostic intensity and tumor characteristics.
* **Need for Standardized Definitions and Large, Diverse Cohorts**: Consistent definitions for FNMTC (e.g., number of affected relatives) and standardized histological classification according to the latest WHO guidelines are crucial for comparing results across studies.8 Larger, multi-ethnic cohorts are needed to improve statistical power for identifying rare variants and to understand ethnic and geographical variations in heritability.
* **Integrating Multi-Omics Data**: Future research should integrate germline genomic data with somatic tumor genomics (e.g., TCGA data 3), transcriptomics, and epigenomics to provide a more holistic understanding of how inherited variants contribute to thyroid tumorigenesis and progression to aggressive subtypes.
* **Functional Validation of Candidate Variants**: Identifying statistical associations is only the first step. Functional studies are essential to confirm the biological relevance of candidate susceptibility genes and variants.
* **Heritability of Aggressiveness and Dedifferentiation**: A key area for future research is understanding the heritable factors that may predispose some familial thyroid cancers to exhibit more aggressive behavior or to dedifferentiate into PDTC or ATC.149 This involves studying families with clusters of aggressive variants or cases of transformation.

## **Part 6: Conclusion**

The heritability of thyroid cancer is a significant factor in its etiology, though the precise "heritability rate" varies by histological subtype and is influenced by the complexity of genetic contributions.

Medullary Thyroid Carcinoma (MTC) stands out with a clear and substantial hereditary component, with approximately 25-30% of cases linked to autosomal dominant germline mutations in the *RET* proto-oncogene, primarily within the MEN2A, MEN2B, and FMTC syndromes. Genetic testing for *RET* mutations is a cornerstone in the management of MTC, allowing for early identification of at-risk individuals and prophylactic interventions.

For Non-Medullary Thyroid Cancers (NMTC), which include Papillary, Follicular, Oncocytic, Poorly Differentiated, and Differentiated High-Grade carcinomas, the genetic landscape is more diverse. While FNMTC accounts for a notable proportion (3-15%) of NMTC cases, only a small fraction of these (around 5% of FNMTC) are attributable to known high-penetrance mutations in syndromic contexts such as Cowden syndrome (*PTEN*), Familial Adenomatous Polyposis (*APC*), Carney Complex (*PRKAR1A*), Werner syndrome (*WRN*), and DICER1 syndrome. The majority of FNMTC cases are non-syndromic, and their genetic basis is largely polygenic, involving multiple low-to-moderate penetrance susceptibility genes, many of which are still being identified and validated across different populations. Twin studies and large family database analyses consistently suggest that thyroid cancer, as a whole, is among the more heritable malignancies, but precise heritability estimates (h2) for each specific NMTC subtype, particularly according to the refined WHO 2022 classification (e.g., invasive subtypes of FTC and OCA, or DHGTC), are not yet robustly established across all global regions.

Geographical and ethnic variations in the prevalence of FNMTC and the frequency of specific germline susceptibility alleles have been observed, highlighting the importance of population-specific research. The increasing incidence of thyroid cancer, potentially influenced by overdiagnosis, adds another layer of complexity to interpreting heritability and familial risk data.

Future research must focus on larger, multi-ethnic cohorts employing standardized classifications (WHO 2022) to dissect the heritability of specific subtypes, including aggressive variants and their potential for dedifferentiation. Integrating multi-omics data and functionally validating candidate genes will be crucial for translating genetic discoveries into improved risk stratification, targeted screening, and personalized prevention strategies for individuals and families affected by thyroid cancer. While direct "heritability rates" remain elusive for many specific scenarios, the collective evidence strongly underscores a significant and complex genetic contribution to the development of thyroid cancer across its diverse forms.

**Metastasis Rates by Thyroid Cancer Subtype and Region**

This report focuses on the heritability of thyroid cancer. While metastasis is a critical aspect of thyroid cancer's clinical course and prognosis, detailed metastasis rates for all subtypes across all global regions are extensive and distinct from the primary focus on heritability. Key general points regarding metastasis rates from the provided information have been integrated into the subtype discussions where they inform the aggressiveness linked to potential genetic predispositions (e.g., higher metastasis rates in aggressive PTC variants or in MTC). A comprehensive, standalone summary of global metastasis rates by subtype and region is beyond the scope of this heritability-focused report but can be found in dedicated epidemiological studies and cancer registry analyses. The definition of regional versus distant metastasis is generally understood as spread to nearby lymph nodes versus spread to organs farther from the thyroid, respectively.253

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