22. FAMILIAL PAPILLARY THYROID CARCINOMA

CARL D. MALCHOFF, M.D., PH.D. AND DIANA M. MALCHOFF, PH.D.
University of Connecticut Health Center, 263 Farmington Avenue Farmington, CT 06030

INTRODUCTION

Prior to 2000 papillary thyroid carcinoma (PTC) was considered by most to be a sporadic disorder without familial predisposition. In contrast to this traditional teaching and as understood early on by Dr. Nadir Farid [1], approximately 5 percent of all PTC are familial. The evidence that supports this familial susceptibility is reviewed here and potential clinical implications are discussed. In addition, PTC may be a relatively infrequent component of other familial tumor syndromes. Although recent findings strongly support a familial PTC predisposition, the final proof will require the identification of the susceptibility genes. There is not yet convincing evidence to suggest that other nonmedullary thyroid carcinomas (follicular thyroid carcinoma, anaplastic thyroid carcinoma, and insular thyroid carcinoma) are familial.

EVIDENCE FOR AN INHERITED SUSCEPTIBILITY TO PTC

It is reasonable to suggest that any malignancy may have a familial predisposition. Cancer is caused by multiple gene mutations that are acquired over time by the cancer progenitor cell. Although these are usually somatic mutations, it would not be surprising if the first gene mutation was inherited (germline mutation). Family members possessing this hypothetical gene mutation would be at increased risk for developing PTC. Such a hypothetical susceptibility gene could persist in the population. It takes years to decades for the thyroid cancer progenitor cell to develop into a malignancy, since it must acquire other necessary gene mutations. Even then the malignancy is slow

growing. If such an inherited gene mutation did not disrupt other essential functions, then those individuals carrying this susceptibility gene mutation would not be at any reproductive disadvantage. By chance alone the gene mutation could persist within a population. Therefore, one can make a theoretical argument that a familial predisposition to PTC may occur.

Epidemiological studies, pedigree analysis, and pathology studies all provide evidence for a familial susceptibility to PTC. Although no single type of study is sufficient to prove a familial susceptibility, taken as a whole, the evidence is strong. This evidence led investigators with access to large kindreds to perform linkage studies that further support a familial predisposition to this disorder. Interestingly, the linkage studies suggest that familial PTC (fPTC) is a heterogeneous disorder caused by more than one susceptibility gene.

Epidemiologic studies have consistently found that first-degree relatives of those with PTC have a 4 to 10 fold increased risk of PTC [2–7]. Most other malignancies in these same studies do not show this familial association. Therefore, it seems unlikely that the observed PTC association is due to an ascertainment bias. Other interpretations of this association include a predisposition caused by an environmental exposure. It seems unlikely that this would be an unusual environmental factor such as radioactive iodine released from nuclear tests, since the association has been observed in multiple studies on different continents and is not limited to populations with the greatest exposure to radiation. This does not exclude the possibility that the susceptibility gene may act by increasing the risk of malignancy as a result of exposure to a more common environmental factor.

A number of large kindreds with fPTC have been described [8–15]. These kindreds are further evidence for a familial predisposition to PTC. Against this interpretation, it can be argued that these kindreds represent the rare association of multiple sporadic thyroid carcinomas, and that the number of affected family members has been exaggerated by ascertainment bias. That is, once two family members have been identified an aggressive search for thyroid carcinoma in other family members may identify microscopic (<1 cm) papillary thyroid carcinomas that have no clinical significance, and, as opposed to large PTC (>1 cm), are relatively common at post mortem examination. However, this is probably not the case, since the PTC within kindreds differs from sporadic PTC in two subtle characteristics. First, fPTC generally presents at a younger age than sporadic disease [16]. Second, there is a greater prevalence of multifocal disease in fPTC than in sporadic PTC [16, 17]. Multifocal disease within the thyroid suggests that a predisposing factor (possibly an inherited genetic susceptibility) is present. Finally, analyses of large kindreds with genetic linkage studies have identified statistically significant associations of PTC with specific chromosomal regions, and these are discussed in the next section. For all these reasons it seems likely the familial association of PTC does not represent the rare association of sporadic PTC, but represents a true familial predisposition.

In summary, the epidemiologic observation of an increased incidence of PTC in first degree relatives of PTC subjects, the presence of large kindreds in which affected