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Risk of Thyroid Cancer among Caribbean Hispanic Patients with Familial Adenomatous Polyposis

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Abstract

Background & Aims—Familial adenomatous polyposis (FAP) is an inherited form of colorectal cancer (CRC) characterized by hundreds of adenomatous polyps in the colon and rectum. FAP is also associated with thyroid cancer (TC), but the lifetime risk is still unclear. This study reports the standardized incidence ratio of TC in Hispanic FAP patients.

Methods—TC incidence rates in patients with FAP were compared with the general population through direct database linkage from the Puerto Rico Central Cancer Registry (PRCCR) and the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR) between the periods of January 1, 2006 to December 31, 2013. The study population consisted of 51 Hispanic patients with FAP and 3,239 with TC from the general population. The Standardized incidence ratio (SIR) was calculated using the Indirect Method, defined as observed TC incidence among patients with FAP in PURIFICAR's cohort (2006–2013) divided by the expected TC incidence based on the PR population rates (2006–2010). SIR values were estimated by sex (male, female and overall). This study received IRB approval (protocol # A2210207).

Results—In Hispanic patients with FAP the standardized incidence ratio (SIR) (95% CI) for TC was 251.73 (51.91 – 735.65), with higher risk for females 461.18 (55.85–1665.94) than males 131.91 (3.34–734.95).

Conclusions—Hispanic FAP patients are at a high risk for TC compared to the general population. Our incidence rates (SIR) are higher than previous studies, suggesting that this community may be at a higher risk for TC than previously assumed. Implementation of clinical surveillance guidelines and regular ultrasound neck screening in Hispanic FAP patients is recommended.

Keywords

Adenomatous polyposis coli; thyroid cancer; cribriform-morular variant of papillary thyroid cancer (CMV-PTC); β -catenin; Familial Adenomatous polyposis; Hispanics

INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by hundreds of adenomatous polyps in the colorectum during the second decade of life. This condition is caused by a germline mutation in the *Adenomatous polyposis coli* (*APC*) gene, a

tumor suppressor located at chromosome 5q21 [1]. FAP expresses almost complete penetrance; individuals with this disease have close to 100% lifetime risk of developing colorectal cancer (CRC) [2]. Approximately 1 of 8,300 people will develop FAP [2]. Extracolonic manifestations associated with this syndrome include: osteomas, desmoid tumors, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, brain cancer, pancreatic cancer, and thyroid cancer (TC) [3].

TC is the 8th most common malignancy in the United States (US), accounting for 3.8% of all new cancer cases [4]. TC has a 3:1 female to male predominance (20.0 per 100,000 females, 6.7 per 100,000 males) [4]. In Puerto Rico (PR), TC was the 3rd and 14th most commonly diagnosed cancer in females and males, respectively, and accounted for an average of 5.35% of all cancers during the period of 2006–2010 in both sexes combined [5]. An approximate 4:1 female-to-male TC incidence ratio (80.4% female patients: 19.6% male patients) was reported among Hispanics residing in PR [6]. The incidence of TC has increased rapidly since the 1990s, especially in women [7]. This increase in TC has also been noted in US populations and elsewhere [5]. Reports suggests that such increase in TC incidence may be due in part to a greater availability of tests for early detection of the tumor [5]. Females with TC are regularly diagnosed at a younger age; however, the median age of diagnosis is 50 years when combining both sexes [8,4]. Papillary carcinoma is the most common histological type of TC, followed by follicular, medullary, and anaplastic carcinomas [8,9].

A relationship between TC and FAP was first suggested in 1968 [10]. FAP-associated TC is more frequent in females, with reported female-to-male ratios as high as 17:1, and is usually diagnosed before the age of 30 [11–13]. The most common histological type in FAP patients is papillary TC. However, a rare subtype described as a cribriform-morular variant of papillary thyroid cancer (CMV-PTC) appears to be specific for FAP patients [14]. Although, Giardiello et al. determined that the relative risk of developing TC in FAP patients was 7.6 [15], until recently, clinical surveillance guidelines for this malignancy remain vaguely defined. There is limited information describing both the clinicopathologic characteristics and TC incidence risk in Hispanic FAP patients. Is important to highlight that FAP is responsible for less than 1% of all CRC cases [16], this implies that having FAP and TC is very unusual. The purpose of this study was to describe the clinicopathologic phenotype of Hispanics residing in PR with FAP-TC and to determine the TC incidence risk in this population.

METHODS

Study Design

Risk assessment for TC in patients with FAP was performed starting January 1, 2006 until December 31, 2010. Due to the limited number of pediatric TC cases in PR (n=47, 1.43%), we excluded all FAP patients younger than 19 years of age (n=11, 17%). Some authors suggest that thyroid screening in the pediatric FAP population should start as early as 12 years of age [17] however, there are no established guidelines regarding this matter. This study was approved by the UPR Medical Sciences Campus Institutional Review Board (protocol # A2210207). An informed consent was obtained from 51 Hispanic patients with FAP.

Study population

Data was gathered from two already existing population-based registries. Individuals with FAP are participants in the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR; http://purificar.rcm.upr.edu/index_eng.html). This is a population-based registry of Hispanics individuals living in PR with a clinical, medical and/or genetic diagnosis of CRC, FAP, among other hereditary colorectal cancer syndromes. This registry contains information on the proband's medical history, environmental exposures and family cancer history. Participants are referred to the UPR Cancer Genetics Clinic where they are offered a range of services including genetic counseling, genetic testing, and endoscopies (diagnostic and surveillance)^[18]. Individuals with TC were obtained from the state- and CDC-funded Puerto Rico Central Cancer Registry (PRCCR). The PRCCR collects all relevant information regarding the diagnosis and treatment of cancer to reduce morbidity and mortality in the Puerto Rican population. Incident cases of primary thyroid neoplasm are identified using the third edition of the International Classification of Disease for Oncology (ICD-O3) [19]. The cases included in this study were those diagnosed from January 1, 2006 to December 31, 2010. TC was categorized by histology subtype according to ICD-O3: Papillary (8050, 8260, 8340–8341, 8343–8344, 8350), Follicular (8290, 8330–8332, 8335), Medullary (8345–8346, 8510), and Anaplastic (8012, 8020–8021, 8030–8032). The histological presence of the cribriform-morular variant of papillary thyroid cancer (CMV-PTC) has not yet been coded in existing cancer registries or the National Cancer Institute. The cancer status of all FAP patients in PURIFICAR was verified using the PRCCR database. CMV-PTC was determined using immunohistochemistry (IHC) analysis using the following markers: TTF-1, PAX8, 6F11, ER, PR and β -catenin [20]. All patients with FAP following their serial colonoscopies at the UPR genetic clinic were referred to undergo a sonographic examination of the thyroid. Additionally, thyroid sonograms referrals were mailed to all FAP patients who did not visit the genetic clinic or had their referrals expired. A total of 31 (60.8%) of the 51 FAP patients underwent screening thyroid ultrasound. Unfortunately, not all FAP patients could be screened for the different extracolonic manifestations, and only those who were examined were included. This explains the varying denominators frequencies reported on the extracolonic manifestations in the FAP cohort (Table 1). Three patients were found to have sonograms suggestive of a tumor lesion in the thyroid; these were referred to undergo a fine needle aspiration biopsy to confirm diagnostic.

Statistical Analysis

Clinical and pathological characteristics were described using frequency distributions for categorical variables and summary measures for quantitative variables. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc.). PURIFICAR and PRCCR databases were linked using Link Plus v.2.0 software (Release 2.0, CDC, Atlanta). Neoplasms were limited to invasive primaries. The standardized incidence ratio (SIR) was estimated using the indirect method, defined as observed TC incidence among PURIFICAR's FAP cohort divided by the expected TC incidence based on the PR population rates (2006–2010). SIR values were estimated by sex. We excluded all patients with FAP diagnosis prior to the study period. STATA 12.0 (STATA Corp.) was used for the statistical analysis of the SIR. Patient 9072.01 is described in this study, but was excluded from risk analysis due to diagnosis prior to 2006.

RESULTS

Clinical characteristics of patients with FAP

The study population consisted of 51 Hispanic patients diagnosed with FAP (34 males and 17 females). The mean age of FAP diagnosis was 31.2 years and the mean age of recruitment was 42.6 years (Table 1). In 49% of these patients, a mutation in the *APC* gene was detected; FAP was clinically diagnosed in the remaining patients based on the presence of hundreds of colonic adenomatous polyps (phenotype of FAP). From our registry, we identified that 24% of the FAP patients had history of CRC. Of the 44 FAP patients who underwent endoscopy, 20 (45.5%) had small bowel adenomas (Table 1). Thyroid nodules were the most commonly diagnosed extracolonic manifestation (48.4%) followed by epidermal cysts (9.8%), desmoids (7.5%), and osteomas (2.7%).

Clinical characteristics of patients with TC

Incident cases of patients diagnosed with TC in FAP patients 20 years during 2006–2010 (81.8% female; 6.8% male) were identified using the database from the PRCCR (Table 2). TC was diagnosed more frequently in females between the ages of 40–59. Whereas in males, TC was more common between the ages of 50–60. The most common histological type of cancer was papillary 89.9% followed by follicular 6.1%. Medullary and anaplastic carcinoma combined represented less than 2% (Table 2).

In our FAP cohort, 4 of 51 patients (7.8%) were diagnosed with TC; 3 females and 1 male (Table 3). The age of diagnosis for TC ranged from 27–52 years, with a mean age of 39.8 years. Total thyroidectomy was performed in 2 patients, whereas the other 2 had a subtotal thyroidectomy. The maximal size of the thyroid tumors measured from 0.5 to 1.1cm (Table 3). Immunostaining for β -catenin was performed in 2 patients with histological findings consistent with the CMV-PTC (Figure 1). Immunostaining for β -catenin was not performed in the remaining two cases of FAP-associated TC (FAP-TC) since tumor block was not available. In normal cells, β -catenin should be present in very low levels at the cytoplasm and only localized on the cell membrane [14]. Loss of functionality of the APC protein results in abnormal localization of β -catenin in the nucleus [21]. Both patients displayed abnormal localization of β -catenin in the nucleus confirming the diagnosis of CMV-PTC and demonstrating the effect between the mutated *APC* gene and TC. These two cases had multiple lesions in the right and left lobes of the thyroid gland (Table 3). In the third and fourth cases, the patients expressed unilateral papillary lesions and were not stained for β -catenin.

Standardized Incidence Ratio (SIR) of TC in patients with FAP

The SIR (95% CI) for TC in the 3 patients with FAP used during analysis was 251.73 (51.91–735.65). The risk in females was higher 461.18 (55.85–1665.94) than in males 131.91 (3.34–734.95) (Table 4).

DISCUSSION

FAP is associated with multiple extra-intestinal manifestations including TC [3]. Few studies have evaluated the prevalence and incidence of thyroid malignancy in Hispanics FAP individuals. In our registry (PURIFICAR), the overall prevalence of FAP-TC was 7.8% (including 3 incident cases diagnosed during study period 2006–2010, plus 1 additional preceding prevalent case diagnosed prior to 2006 [patient 9072.01]). Females had a higher prevalence of TC (5.9%) than males (2.0%) even though the female FAP population (33.3%) is smaller than the male FAP population (66.7%). Our report supports previously published studies, where FAP-TC occurs at a much higher frequency in females than males [11–13]. However, the overall prevalence of TC is higher than the reported prevalence in other racial/ethnic groups. In a study from a Singapore Polyposis Registry, the prevalence of TC was 4.9% [22]. Other collective studies on FAP-TC have described prevalence rates ranging from 1.2% to 12% [23–26]. Cumulative analysis suggests that as patients undergo systematic screening and ultrasound examinations, the rate of FAP-TC may be higher than previously expected [24,25].

Recent data have shown that FAP patients are usually diagnosed with TC at a younger age than the general population [27], in which the median age of diagnosis is 50 years (range 45–54) [4]. Similarly, in PR, the median age of diagnosis for TC in the general population in males and females is 54 and 50 years, respectively [5]. Previous investigations have reported a median age of FAP-TC between the ages 23–44 [24,25,27,28]. In this study, the mean age of diagnosis for TC was 39.8. All 3 female patients with FAP and TC were diagnosed at or before the age of 45. Interestingly, the male was diagnosed later at age 52. This fits the general trend where males are diagnosed with TC at a later age.

This study reports a high risk for TC in individuals with FAP (SIR = 251.73; 95% CI: 51.91–735.65) compared with the general Hispanic population in PR. Females (SIR = 461.18; 95% CI: 55.85–1665.94) had almost 3.5 times the elevated risk for TC than males (SIR = 131.91; 95% CI: 3.34–734.95). These risk estimates are likely conservative since 1 patient with FAP and TC was excluded from the analysis because the malignancy occurred prior to the study period. Due to the nature of the statistical analysis, which uses data from the population-based cancer registry, the assessment could not be adjusted by family history of TC, lifestyle, weight, diet, etc. (variables not collected by the PRCCR).

Few studies have estimated the incidence risk of FAP and TC using SIR analysis. In a study with 1,391 affected or at-risk FAP individuals, 5 had TC. Compared to the general population, the group reported a relative (O/E) and absolute risk of 7.6 and 26.8, respectively [15]. In an earlier study of 998 patients with FAP, 7 females developed TC while 0 males developed such malignancy [29]. This group described that females with FAP below the age of 35 have 160 times the risk for TC that of a normal individual [29]. Meanwhile, in a more recent study of 205 FAP participants, 15 developed TC. The investigators calculated a relative risk of 153 [26]. Taken together, the high incidence of TC among the general Hispanic community and Hispanics with FAP may suggest that Hispanics may be at a higher risk for TC than previously thought.

Currently, there is very limited information describing the prevalence of thyroid nodules among the FAP population. Previous authors have described that the incidence of thyroid nodules in FAP patients may be higher than in the general population [25,26]. In a study of 28 FAP patients who underwent thyroid ultrasound, 22 (79%) had thyroid nodules [25]. Furthermore, in a recent study of 205 patients diagnosed with FAP who were also screened with thyroid ultrasound, 106 (51.7%) were found to have thyroid nodules [26]. In our study, thyroid nodules were the most commonly diagnosed extracolonic manifestation among our FAP cohort. 31 patients were screened with thyroid ultrasound, and approximately half (48.4%) were found to have nodules. Unfortunately, there are no studies describing the incidence of thyroid nodules in the general population of PR Hispanics.

The risk of development of a specific phenotypic manifestation is often dictated by the mutation position in the *APC* gene [1]. Several studies have attempted to find the genotype-phenotype correlation in *APC* gene mutations and TC. Septer et. al described an increased risk for TC among individuals with *APC* gene mutations at the 5' of exon 15, mostly proximal to codon 528 and those close to codons 1061 and 1309 [30]. Patients in our Hispanic cohort had mutations located at amino acid (aa.) positions 640, 955, and 1055. Two of the mutations (aa. 955 and 1055) were located on exon 15, which supports the previous reported correlation. For patient 9250.01, the mutation was next to codon 1061 and in patient 9316 it was located proximal to codon 528. Interestingly, these mutations were out of the mutation cluster region (codons 1286–1513), where many of the extracolonic manifestations usually do occur [31]. If true, this could suggest that patients with mutations in similar regions might benefit from regular thyroid screening and ultrasound analysis.

CMV-PTC is a rare and unusual neoplasm that develops in patients with FAP [14]. The permanent activation of the *Wnt* pathway and the abnormal nuclear and cytoplasmic accumulation of β -catenin define the morphological and pathological characteristics seen in these tumors. These features include cribriform, trabecular, solid, follicular, papillary and morular patterns of growth [14]. As in classic papillary carcinoma, CMV-PTC may be associated with multifocal lesions [14]. In the present study, two of the females FAP patients with TC had total thyroidectomy and presented with bilateral lesions and multiple tumors. The remaining patients had a subtotal thyroidectomy and a solitary tumor (Table 3). We performed immunostaining for cytoplasmic and nuclear β -catenin expression to reveal the association caused by the germline mutation and CMV-PTC [20]. In wild type form, the *APC* protein forms a complex with glycogen synthase kinase 3 β (GSK-3 β), β -catenin, and Axin. This complex is in the Wnt transduction-signaling pathway, where it targets β -catenin for phosphorylation and degradation. When a mutation occurs, GSK-3 β is unable to phosphorylate β -catenin. This causes an accumulation of β -catenin in the cytoplasm and nucleus rather than in the cell membrane, transcriptionally activating other oncogenes and causing tumorigenesis [3]. In this study, 2 patients (Table 3) were stained for β -catenin and in both cases the protein was aberrantly expressed (Figure 1). This analysis suggests not only that a diagnosis of FAP should imply a risk for TC, but also that recognition of CMV-PTC could be considered a surrogate marker for the diagnosis of FAP.

Although the current study uses a well-characterized cohort of FAP individuals enrolled in PURIFICAR and validated tumor data from the PRCCR, there are several limitations to

consider. First, the nature of the analysis using cases with TC from the PRCCR to calculate the SIR prevented adjustment for potential confounders (family history of TC, lifestyle, weight, diet, etc) since this registry does not collect those variables. Second, the small sample size of Hispanic FAP patients in our cohort could represent an underestimation of the potential risk of TC in Hispanic patients with this syndrome. However, to reflect the incidence of TC more accurately in our registry, all FAP cases were directly merged and cancer diagnosis was confirmed with the PRCCR. Moreover, risk analyses were adjusted by age.

CONCLUSION AND SIGNIFICANCE

In summary, the risk and incidence rate (SIR) of TC in Hispanic patients with FAP seems to be higher than in other reported groups [15,23–25]. This investigation supports the new ACG Guidelines for FAP, which recommend annual thyroid ultrasounds [32]. In PR, mutation analysis of the *APC* gene is costly and not covered by most health insurance companies unless the patients have been diagnosed with CRC [18]. Diagnosis of familial polyposis syndromes is mainly based on clinical phenotype [18]. However, when a germline *APC* mutation is identified in an individual, other family members can be tested using single site mutation analysis, which proposes a more affordable alternative [18]. Such analysis identifies at-risk family members that may benefit from adequate surveillance strategies. Thus, detection of *APC* mutation may help reduce the risk for CRC and other extra-intestinal cancers such as TC, a highly prevalent malignancy in the Hispanic population.

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Abbreviations

FAP	Familial adenomatous polyposis
CRC	Colorectal cancer
TC	Thyroid cancer
PRCCR	Puerto Rico Central Cancer Registry
PURIFICAR	Puerto Rico Familial Colorectal Cancer Registry
SIR	Standardized incidence ratio
PRH	Puerto Rican Hispanic
CMV-PTC	cribriform-morular variant of papillary thyroid cancer
PR	Puerto Rico

UPR	University of Puerto Rico
ICD-O3	International Classification of Disease for Oncology
IHC	immunohistochemistry
APC	<i>Adenomatous polyposis coli</i>
US	United States
CDC	Centers for Disease Control and Prevention

REFERENCES

1. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. *Hum Mol Genet*. 2001; 10(7):721–733. [PubMed: 11257105]
2. Reed TE, Neel JV. A genetic study of multiple polyposis of the colon with an appendix deriving a method of estimating relative fitness. *American journal of human genetics*. 1955; 7(3):236–263. [PubMed: 13258558]
3. Groen EJ, Roos A, Muntinghe FL, Enting RH, de Vries J, Kleibeuker JH, Witjes MJ, Links TP, van Beek AP. Extra-intestinal manifestations of familial adenomatous polyposis. *Annals of surgical oncology*. 2008; 15(9):2439–2450. [PubMed: 18612695]
4. SEER Stat Fact Sheets: Thyroid Cancer. Rockville: National Cancer Institute; 2015. <http://seer.cancer.gov/statfacts/html/thyro.html> [Accessed December 4, 2015]
5. Tortolero-Luna, G.; Zavala-Zegarra, D.; Perez-Rios, N.; Torres-Cintrón, CR.; Ortiz-Ortiz, KJ.; Traverso-Ortiz, M.; Veguilla-Rosario, I.; Vazquez-Cubano, N.; Merced-Velez, MF.; Ojeda-Reyes, G.; Hayes-Velez, FJ.; Ramos-Cordero, M.; Lopez-Rodriguez, A.; Perez-Rosa, N. Cancer in Puerto Rico: 2006–2010. San Juan, PR: Puerto Rico Central Cancer Registry; 2013.
6. Ramirez-Vick M, Nieves-Rodriguez M, Lugaro-Gomez A, Perez-Irizarry J. Increasing incidence of thyroid cancer in Puerto Rico, 1985–2004. *Puerto Rico health sciences journal*. 2011; 30(3):109–115. [PubMed: 21932710]
7. Holt EH. Care of the pregnant thyroid cancer patient. *Current opinion in oncology*. 2010; 22(1):1–5. [PubMed: 19812492]
8. Moo-Young TA, Panergo J, Wang CE, Patel S, Duh HY, Winchester DJ, Prinz RA, Fogelfeld L. Variations in clinicopathologic characteristics of thyroid cancer among racial ethnic groups: analysis of a large public city hospital and the SEER database. *American journal of surgery*. 2013; 206(5):632–640. [PubMed: 24157347]
9. Surveillance E, and End Results Program. Table 26.22 Percent Distribution and Counts by Histology among Histologically Confirmed Cases, 2006–2010. Both Sexes by Race. 2014
10. Camiel MR, Mule JE, Alexander LL, Benninghoff DL. Association of thyroid carcinoma with Gardner's syndrome in siblings. *The New England journal of medicine*. 1968; 278(19):1056–1058. [PubMed: 5644968]
11. Perrier ND, van Heerden JA, Goellner JR, Williams ED, Gharib H, Marchesa P, Church JM, Fazio VW, Larson DR. Thyroid cancer in patients with familial adenomatous polyposis. *World journal of surgery*. 1998; 22(7):738–742. discussion 743. [PubMed: 9606291]
12. Cetta F, Pelizzo MR, Curia MC, Barbarisi A. Genetics and clinicopathological findings in thyroid carcinomas associated with familial adenomatous polyposis. *The American journal of pathology*. 1999; 155(1):7–9. [PubMed: 10393829]
13. Harach HR, Williams GT, Williams ED. Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm. *Histopathology*. 1994; 25(6):549–561. [PubMed: 7698732]
14. Tomoda C, Miyauchi A, Uruno T, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Kuma S, Kuma K, Kakudo K. Cribriform-morular variant of papillary thyroid carcinoma: clue to early

detection of familial adenomatous polyposis-associated colon cancer. *World journal of surgery*. 2004; 28(9):886–889. [PubMed: 15593462]

15. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, Kelley NC, Hamilton SR. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. *Gut*. 1993; 34(10):1394–1396. [PubMed: 8244108]
16. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet journal of rare diseases*. 2009; 4:22. [PubMed: 19822006]
17. Kennedy RD, Potter DD, Moir CR, El-Youssef M. The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. *Journal of pediatric surgery*. 2014; 49(1):82–86. [PubMed: 24439586]
18. Cruz-Correa M, Diaz-Algorri Y, Mendez V, Vazquez PJ, Lozada ME, Freyre K, Lathroum L, Gonzalez-Pons M, Hernandez-Marrero J, Giardiello F, Rodriguez-Quilichini S. Clinical characterization and mutation spectrum in Hispanic families with adenomatous polyposis syndromes. *Familial cancer*. 2013; 12(3):555–562. [PubMed: 23460355]
19. Fritz, AG.; Percy, C.; Jack, A.; Sobin, LH.; Parking, MD., editors. *International Classification of Disease for Oncology*. 3rd. Geneva: World Health Organization; 2000.
20. Reviewing Pathologist Darcy Broughel-Baer DO, M.P.H. β -catenin testing. New York, NY: Esoterix Genetic Laboratories; 2014.
21. Kurihara K, Shimizu S, Chong J, Hishima T, Funata N, Kashiwagi H, Nagai H, Miyaki M, Fukayama M. Nuclear localization of immunoreactive beta-catenin is specific to familial adenomatous polyposis in papillary thyroid carcinoma. *Japanese journal of cancer research : Gann*. 2000; 91(11):1100–1102. [PubMed: 11092973]
22. Chew MH, Quah HM, Teh KL, Loi TT, Eu KW, Tang CL. Twenty years of familial adenomatous polyposis syndromes in the Singapore Polyposis Registry: an analysis of outcomes. *Singapore medical journal*. 2011; 52(4):246–251. [PubMed: 21552784]
23. Bulow C, Bulow S. Is screening for thyroid carcinoma indicated in familial adenomatous polyposis? The Leeds Castle Polyposis Group. *International journal of colorectal disease*. 1997; 12(4):240–242. [PubMed: 9272455]
24. Steinhagen E, Guillem JG, Chang G, Salo-Mullen EE, Shia J, Fish S, Stadler ZK, Markowitz AJ. The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. *Clin Colorectal Cancer*. 2012; 11(4):304–308. [PubMed: 22425061]
25. Herraiz M, Barbesino G, Faquin W, Chan-Smutko G, Patel D, Shannon KM, Daniels GH, Chung DC. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2007; 5(3):367–373. [PubMed: 17258512]
26. Feng X, Milas M, O'Malley M, LaGuardia L, Berber E, Jin J, Metzger R, Mitchell J, Shin J, Burke CA, Kalady M, Church J, Siperstein A. Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. *Thyroid : official journal of the American Thyroid Association*. 2015; 25(3):325–332. [PubMed: 25585202]
27. Levy RA, Hui VW, Sood R, Fish S, Markowitz AJ, Wong RJ, Guillem JG. Cribriform-morular variant of papillary thyroid carcinoma: an indication to screen for occult FAP. *Familial cancer*. 2014
28. Jarrar AM, Milas M, Mitchell J, Laguardia L, O'Malley M, Berber E, Siperstein A, Burke C, Church JM. Screening for thyroid cancer in patients with familial adenomatous polyposis. *Annals of surgery*. 2011; 253(3):515–521. [PubMed: 21173694]
29. Plail RO, Bussey HJ, Glazer G, Thomson JP. Adenomatous polyposis: an association with carcinoma of the thyroid. *The British journal of surgery*. 1987; 74(5):377–380. [PubMed: 3036290]
30. Septer S, Slowik V, Morgan R, Dai H, Attard T. Thyroid cancer complicating familial adenomatous polyposis: mutation spectrum of at-risk individuals. *Hereditary cancer in clinical practice*. 2013; 11(1):13. [PubMed: 24093640]

31. Miyoshi Y, Nagase H, Ando H, Horii A, Ichii S, Nakatsuru S, Aoki T, Miki Y, Mori T, Nakamura Y. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum Mol Genet.* 1992; 1(4):229–233. [PubMed: 1338904]
32. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. American College of G. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *The American journal of gastroenterology.* 2015; 110(2):223–262. quiz 263. [PubMed: 25645574]

Figure 1.
 β -catenin IHC analysis of patients 9250.01 (A) and 9316 (B). Both images show aberrant β -catenin cytoplasmic and nuclear positivity.

Clinical characteristics	n (%)
FAP diagnosis	
APC mutations	25 (49)
Clinical diagnosis	26 (51)
Mean age of diagnosis (yrs)	31.2 ±14.1
Mean age of recruitment (yrs)	42.6 ±14.4
Sex	
Male	34 (66.7)
Female	17 (33.3)
Colorectal Cancer	
Yes	12 (24)
No	38 (76)
Total	50 (100)
Extracolonic Manifestations	
Small bowel adenomas	
Yes	20 (45.5)
No	24 (54.5)
Total	44 (100)
Osteomas	
Yes	1(2.7)
No	36 (97.3)
Total	37 (100)
Desmoids	
Yes	3 (7.5)
No	37 (90.2)
Total	40 (100)
Epidermal cysts	
Yes	4 (9.8)
No	37 (90.2)
Total	41 (100)
Thyroid nodules	
Yes	15 (48.4)
No	16 (51.6)
Total	31 (100)

Table 2

Clinical characteristics of patients 20 years diagnosed with TC in the Puerto Rican population (n=3,239).

Characteristics	n (%)
Mean age of diagnosis (yrs)	
Male	53.8 ±14.1
Female	51.0 ±14.8
Sex	
Male	551 (17.0)
Female	2,688 (82.0)
Histology	
Papillary Ca.	2,912 (89.9)
Follicular Ca.	197 (6.1)
Medullary Ca.	50 (1.5)
Anaplastic Ca.	10 (0.3)
Poorly differentiated	60 (1.9)
Other or unknown	70 (2.2)
All Cancers	3,239 (100)

Table 3

Clinical characteristics of patients with FAP and thyroid cancer

Study ID	9316	9250.01	9358.01	9072.01
APC Mutation (aa position; exon)	c.1917_1918insA (640; 14)	3149delC (1055; 15)	2846insAT (955; 15)	Clinical diagnosis
Sex	F	F	M	F
Age at dx. of FAP	26	30	42	39
Age at dx. of TC	27	40	52	40
TC Histology type	CMV-PTC	CMV-PTC	Papillary	Papillary
No. of thyroid lesions	4	3	1	1
Bilateral thyroid lesions	Yes	Yes	No	No
Maximum tumor size (cm)	0.9	0.5	1.1	1.1
Aberrant β -catenin IHC analysis	+	+	N/A	N/A

Table 4

Risk of TC in patients with FAP compared to the general population of Puerto Rico

Group	Number of thyroid cancers	SIR (95% CI)	Adjusted rate (95% CI)
Males	1	131.91 (3.34 – 734.95)	0.03 (0.0 – 0.18)
Females	2	461.18 (55.85 – 1665.94)	0.11 (0.01 – 0.41)
Combined	3	251.73 (51.91 – 735.65)	0.06 (0.01 – 0.18)