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ORIGINAL ARTICLE

Prevalence of and risk factors for thyroid carcinoma in patients with familial adenomatous polyposis: results of a multicenter study in Japan and a systematic review

Haruki Sada[1] · Takao Hinoi[1,12] · Hideki Ueno[2] · Tatsuro Yamaguchi[3] · Yasuhiro Inoue[4] · Tsuyoshi Konishi[5] · Hirotoshi Kobayashi[6] · Yukihide Kanemitsu[7] · Fumio Ishida[8] · Hideyuki Ishida[9] · Naohiro Tomita[10] · Nagahide Matsubara[10] · Kenichi Sugihara[11]

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Abstract

Purpose To investigate the recent Japanese prevalence of thyroid cancer and its characteristics in familial adenomatous polyposis (FAP) patients, through the development of surveillance programs.

Methods The subjects of this study were 282 (93.1%) FAP patients for whom information on thyroid cancer was available, from among 303 patients registered in "the Retrospective Cohort Study of Familial Adenomatous Polyposis in Japan" database. We evaluated the prevalence and risk factors for thyroid cancer and integrated and/or compared our findings with those of previous reports, using a systematic review, including a meta-analysis.

Results Thyroid cancer was diagnosed in 16 women (11.4%) and 2 men (1.4%), at 17–41 years and 39–57 years of age, respectively. The prevalence of thyroid cancer was 6.4%, with a female-to-male ratio of 8:1, which is comparable to reports from other countries. A young age of < 33 years at the FAP diagnosis and female gender were identified as independent risk factors for thyroid cancer.

Conclusions FAP-associated thyroid cancer predominantly affects young women, both in Japan and other countries. Since FAP is generally diagnosed when patients are in their 20 s or older, regular screening for thyroid cancer is recommended for all FAP patients, but especially women, from their early 20 s.

Keywords Familial adenomatous polyposis · Meta-analysis · Prevalence · Risk factor · Thyroid cancer

✉ Takao Hinoi
thinoi@hiroshima-u.ac.jp

[1] Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

[2] Department of Surgery, National Defense Medical College, Saitama, Japan

[3] Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

[4] Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Japan

[5] Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[6] Department of Surgery, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan

[7] Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

[8] Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan

[9] Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

[10] Division of Lower GI Surgery, Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan

[11] Tokyo Medical and Dental University, Tokyo, Japan

[12] Present Address: Department of Surgery, Institute for Clinical Research, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, 3-1, Aoyama-cho, Kure-shi, Hiroshima 737-0023, Japan

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary polyposis syndrome, caused by a germline mutation of the *APC* gene on chromosome 5q21 [1–3]. Data from national registries [4–6] suggest that its incidence varies between 2.3 and 3.2 cases per 100,000 individuals. FAP is characterized by numerous colorectal adenomas, which, if left untreated, will inevitably progress to cancer: the leading cause of death of these patients [3, 7]. Early diagnosis, prophylactic proctocolectomy, intensive and continuous surveillance, as well as familial studies, have all contributed to a decrease in mortality from colorectal cancer [3, 8], and the management of extracolonic manifestations of FAP has played a pivotal role [9, 10].

Among the various extracolonic manifestations of FAP, thyroid cancer has been reported in approximately 1.0–2.0% of patients [11–15]. The majority of FAP-associated thyroid cancers are papillary carcinomas, representing a specific histological subtype, referred to as the cribriform-morular variant-papillary thyroid cancer (CMV-PTC) [16–18]. FAP-associated thyroid cancer is more common in women than in men [11–15, 19–25] and is usually diagnosed earlier than sporadic thyroid cancer. However, to what extent other backgrounds, such as geographical or racial differences affect the prevalence and characteristics of extracolonic manifestations, including thyroid cancers, in FAP patients has not been investigated in depth. Furthermore, since few reports on FAP-associated thyroid cancers in Japanese patients were published in the 1990s [13, 26], the recent prevalence has not been updated, despite the development of surveillance programs and diagnostic modalities such as ultrasonography [US] and computed tomography. For the appropriate surveillance to detect thyroid cancer in patients with FAP, we should define the racial and geographical differences and risk factors of thyroid cancer occurrence, including age and sex. The present study first investigated the incidence and risk factors for thyroid cancer among Japanese patients with FAP, using "the Multicenter Retrospective Cohort Study of FAP in Japan" database supported by the Japanese Society for Cancer of the Colon and Rectum. Then, we compared and/or integrated the findings of previous reports with those of our own series, using a systematic review, including a meta-analysis, to demonstrate the validity of the results we obtained and to consider the most appropriate surveillance program and treatment strategy for thyroid cancer in patients with FAP, both in Japan and in other countries.

Patients and methods

Study design

A total 303 patients with a clinical or genetic diagnosis of FAP, who had undergone initial surgery for colorectal lesions between 2000 and 2012, were registered in 23 institutions in the Multicenter Retrospective Cohort Study of patients with FAP in the Japan database [27]. We investigated the incidence and risk factors for thyroid cancer in 282 of these patients with FAP (93.1%), for whom information regarding thyroid cancer was available. We also studied the following details about thyroid cancer from the database; presence or absence of thyroid cancer, date of its diagnosis, number of occurrences, histology, treatment, surgical procedure, and date of surgery. All patient data were collected anonymously from each institution. The Ethical Review Board of the Japanese Society for Cancer of the Colon and Rectum and the institutional ethics committees approved the study protocol. Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Quantitative variables and categorical values are presented as the median with the range, and numbers with percentage, respectively. A univariate analysis was performed using the Fisher's exact test. A multivariate analysis was performed using logistic regression to establish the independent risk factors for thyroid cancer in patients with FAP. Significant variables in the univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using the Statistical Package for the Social Sciences for Windows software program, version 22.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p < 0.05$ was considered significant.

Meta-analysis

We searched the National Library of Medicine database, MEDLINE (provider PubMed), without date restrictions. Limits were applied to text availability, in relation to "abstract available". The terms "FAP," "familial adenomatous polyposis," "thyroid cancer," and "thyroid" were used in combination with the Boolean operators "AND" and "OR." The date of the last search was June 30, 2015. The titles and abstracts of all identified manuscripts were examined to identify potential hits. First- and second-level screening was carried out in an unbiased manner by two independent authors (TH and HS) with conflicts of opinion resolved through discussion.

Pooled odds ratios (ORs) and 95% confidence intervals were calculated and the outcomes of individual studies were compared using the fixed-effect model. Forest plots were constructed for visual display of ORs of individual studies. Heterogeneity between individual studies was assessed using the I^2 statistic as a measure of the proportion of total variation in estimates that could be attributed to heterogeneity, where I^2 values of 25, 50 and 75% corresponded to cut-off points for low, moderate, and high degrees of heterogeneity, respectively. To assess publication bias in the comparison of sexual differences in the incidence of thyroid cancer in FAP patients, we measured the funnel plot asymmetry using Egger's regression test. A quantitative meta-analysis was performed using the R 3.0.2 statistical software program (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient clinical characteristics

We screened 282 (93.1%) of the 303 patients included from the Multicenter Retrospective Cohort Study of FAP in Japan database, for thyroid cancer (140 women, 49.6% and 142 men, 50.4%). The median age at diagnosis of FAP was 31 (range 10–75) years old and the median age at initial surgery for colorectal lesions was 33 (range 12–75) years old. Thyroid cancer was diagnosed in 18 patients (6.4%): 16 women (11.4% of all female patients) and 2 men (1.4% of all male patients) (Table 1). Germline *APC* mutations were identified in 31 of the 282 patients (11.0%). Three of the 18 patients with thyroid cancer were analyzed for germline mutations of *APC*, which were confirmed in all of them.

Table 1 Backgrounds of patients

Variable	
Sex	
Male	142 (50.4%)
Female	140 (49.6%)
Median age at diagnosis of FAP (range)	31 (10–75)
Median age at the first operation for colonic lesion (range)	33 (12–75)
Colonic phenotype	
Sparse	148 (52.5%)
Profuse	68 (24.1%)
Attenuated	32 (11.3%)
Unknown	34 (12.1%)
Thyroid cancer	
Yes	18 (6.4%)
No	264 (93.6%)

FAP familial adenomatous polyposis

The median age at the diagnosis of FAP among the 18 patients with thyroid cancer was 30 (range 16–55) years old and the median age at the diagnosis of their thyroid cancer was 27.5 (range 17–57) years old. After the exclusion of one patient (5.6%) with multiple systemic metastases from colon cancer, 17 patients (94.4%) underwent surgical intervention, including total thyroidectomy ($n=11$; 64.7%), subtotal thyroidectomy ($n=1$; 5.9%), and lobectomy ($n=4$; 23.5%), within several years of the diagnosis of thyroid cancer. The median age at initial surgery for thyroid cancer was 27.5 (range 17–41) years old. Thyroid cancer was diagnosed in the two men at 39 and 57 years of age, respectively. In the women, thyroid cancer was diagnosed at a relatively young age. Pathological findings revealed papillary thyroid cancer in all 15 patients, and CMV-PTC was noted in 8 (53.3%) (Table 2).

Three women (patients no 7, 15 and 18 in Table 2) underwent surgery for thyroid cancer prior to the diagnosis of FAP. The diagnosis of FAP was made 2 years after thyroid surgery in one patient with CMV-PTC, but 4 and 15 years, respectively, had passed from the initial thyroid surgery to the FAP diagnosis in the patients with unreported CMV-PTC. Thyroid cancer was diagnosed within 2 years after the diagnosis of FAP in six women and two men, and more than 2 years after the diagnosis of FAP in four women (Table 2).

Risk factors for the development of thyroid cancer in patients with familial adenomatous polyposis

Univariate and multivariate analyses identified female gender and a young age of <33 years at the diagnosis of FAP as independent risk factors for thyroid cancer in Japan (Table 3). Consistent with this result, the diagnosis of FAP in female patients increased approximately linearly, while the incidence of thyroid cancer occurring in female patients with FAP plateaued around the 40 s (Fig. 1).

Meta-analysis search results

In total, 203 records were identified from primary searches of the electronic database. First-level screening identified 29 potentially eligible articles. A full-text review excluded 16 articles. Thirteen articles met the selection criteria and were included in our analysis of the incidence of thyroid cancer in patients with FAP. Ten articles were selected to evaluate the sex differences in FAP patients with thyroid cancer (Table 4). The search history is summarized in Fig. 2.

Incidence of thyroid cancer in FAP patients

We selected 13 articles published between 1987 and 2014 to investigate the incidence of thyroid cancer in patients with FAP. A meta-analysis, including present research revealed that

Table 2 Clinicopathological features of thyroid cancer associated with familial adenomatous polyposis in Japan

Case No.	Sex	Age atFAP diagnosis	Age at TC diagnosis	Age at colorectal operation	Age at thyroid operation	Number of TC	Histo-logical diagnosis	CMV-PTC	Survival
1	F	32	32	32	32	1	PTC	+	37 y.o., alive
2	F	34	35	34	36	3	PTC	+	39 y.o., alive
3	F	23	24	25	25	1	PTC	+	27 y.o., alive
4	F	20	25	20	25	2	PTC	+	33 y.o., alive
5	F	31	41	31	41	1	PTC	+	41 y.o., alive
6	M	55	57	54	No operation	1	PTC	N.R	58 y.o., dead(CRC)
7	F	24	22	24	22	1	PTC	+	24 y.o., alive
8	F	30	34	30	34	1	PTC	+	38 y.o., dead(CRC)
9	M	39	39	39	39	1	PTC	-	46 y.o., alive
10	F	NR.	29	29	29	N.R	PTC	N.R.	29 y.o., alive
11	F	16	25	27	25	N.R.	N.R.	N.R.	28 y.o., alive
12	F	23	24	24	24	N.R.	PTC	N.R.	29 y.o., alive
13	F	N.R.	N.R.	29	N.R.	N.R.	N.R.	N.R.	33 y.o., alive
14	F	31	31	31	33	1	PTC	–	31 y.o., alive
15	F	21	17	26	17	N.R.	N.R.	N.R.	29 y.o., alive
16	F	26	26	23	26	Multiple	PTC	+	36 y.o., alive
17	F	30	N.R	30	30	N.R.	PTC	N.R.	34 y.o., dead(CRC)
18	F	32	17	39	17	1	PTC	N.R.	43 y.o., alive

N.R. not reported, *FAP* familial adenomatous polyposis, *TC* thyroid cancer, *PTC* papillary thyroid cancer, *CMV-PTC* cribriform-morular variant-PTC, *y.o.* years old, *CRC* colorectal cancer

Table 3 Risk factors for thyroid cancer in Japan

Variable	Thyroid cancer + (*N* = 18)		Thyroid cancer − (*N* = 264)		*p* value (Univariate analysis)	*p* value (Multivariate analysis)
Sex						
Male	2	(11.1%)	140	(53.0%)	< 0.001	0.006
Female	16	(88.9%)	124	(47.0%)		
Age at diagnosis						
< 33	13	(81.3%)	129	(54.0%)	0.039	0.048
≥ 33	3	(18.8%)	110	(46.0%)		
Colonic phonotype						
Sparse	13	(81.3%)	141	(59.0%)	0.116	
Profuse	1	(6.3%)	68	(28.5%)		
Attenuated	2	(12.5%)	30	(12.6%)		

the incidence of thyroid cancer in patients with FAP in this study was 1.6% (Fig. 3). When compared chronologically, it was apparent that the prevalence of thyroid cancer in FAP patients in studies published from 2002 was higher than that in studies published in 1998 or earlier.

Sex differences in the incidence of thyroid cancer in familial adenomatous polyposis patients

Ten articles were selected to examine the sex differences in the incidence of thyroid cancer among patients with FAP.

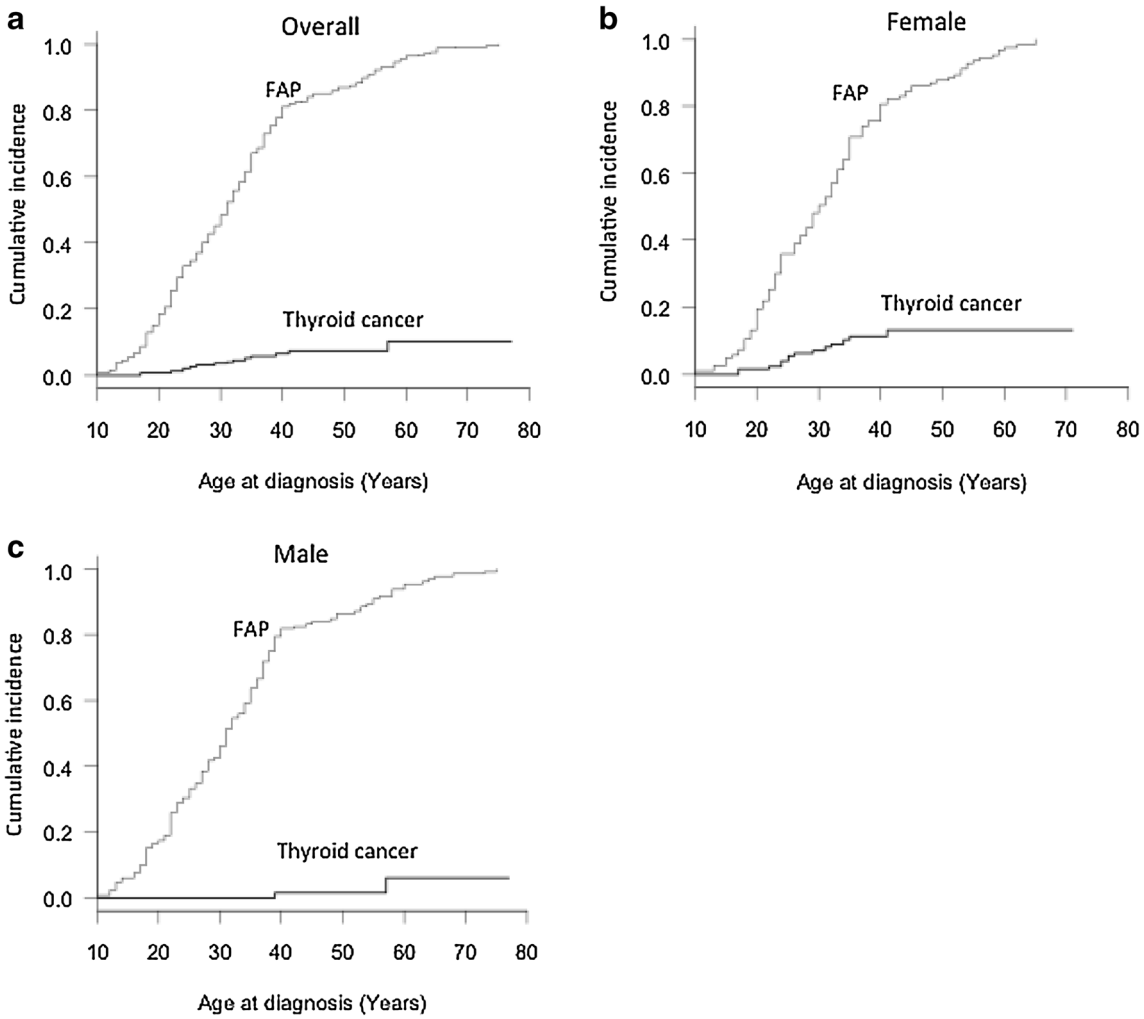

Fig. 1 The cumulative prevalence of familial adenomatous polyposis (FAP) and FAP-associated thyroid cancer. The cumulative prevalence of thyroid cancer in women with FAP peaks and plateaus at around 40 years of age. Overall (**a**), female patients (**b**), male patients (**c**)

A meta-analysis revealed a female-to-male OR of 6.9:1 (Fig. 4). In a sub-group analysis of study characteristics, including the year of publication and the location of the study, the female-to-male OR was 6.8:1 in articles published between 1987 and 1999 vs. 6.9:1 in articles published since 2000. The female-to-male OR was 7.7:1 in Asian populations and 6.3:1 in Western populations. There was no obvious heterogeneity in sexual differences in the incidence ($I^2 = 0\%$) and Egger's regression asymmetry test revealed no significant publication bias (bias = 0.9; $p = 0.07$).

Discussion

The prevalence of thyroid cancer in patients with FAP has been reported to range from 0.4 to 11.8% [11–15, 19–25, 28]. The prevalence in our meta-analysis was 1.6%, but it was apparently higher in reports published from 2002 onward than those published in 1998 or earlier. In the three latest articles, published since 2010 [23–25], the prevalence of thyroid cancer ranged from 4.0 to 6.1%, which is comparable to the incidence of 6.4% in the current cohort study of patients with FAP between 2000 and 2012. Furthermore, the prevalence of thyroid cancer in patients with FAP has increased over time in Japan, from 1.1% in 1993 [13] to 6.4% in the present study.

There are several potential explanations for this increase. First, it is likely that advances in imaging modalities for the diagnosis of thyroid cancer, including the widespread use of US, has improved the ability to detect subclinical thyroid cancer in patients with FAP, which could affect the prevalence. The use of US for thyroid cancer screening was described in the three latest reports included in our meta-analysis [22, 23, 25], and this might have affected the thyroid cancer detection rate. However, we cannot confirm that the increased prevalence was caused by the shift in screening

Table 4 Characteristics of the studies included in the analysis

	Study	Year	Location	Years included	Patients with FAP (n)	Rate of thyroid cancer (%)	Number of Patients with thyroid cancer(F:M)
1	Plail et al. [11]	1987	UK	1925–1987	998	0.7	7:0
2	Bülow et al. [19]	1988	Denmark	1943–1985	245	0.8	2:0
3	Giardiello et al. [12]	1993	US	1969–1987	1391	0.4	4:1
4	Iwama et al. [13]	1993	Japan	–1990	1050	1.1	9:2
5	Bülow et al. [14]	1997	UK	1959–1995	3727	1.2	44:1
6	Perrier et al. [20]	1998	US	1949–1995	2754	0.5	11:1
7	van der Linde et al. [21]	1998	Netherlands	1985–1995	601	0.7	4:0
8	Ho et al. [28]	2002	Hong Kong	1995–2001	70	5.7	4:0
9	Truta et al. [15]	2003	North America	1980–2003	1194	1.3	16:0
10	Herraiz et al. [22]	2007	US	1994–2007	51	11.8	6:0
11	Jarrar et al.[a] [23]	2011	US	2008–2009	192	2.6	8:2
12	Steinhagen et al.[a] [24]	2012	US	2001–2010	66	6.1	4:0
13	Steinhagen et al.[a] [25]	2014	US	2010–2012	50	4.0	2:0
14	Present research	2014	Japan	2010–2012	303	6.4	16:2

FAP familial adenomatous polyposis, *F* female, *M* male

[a]Prospective study

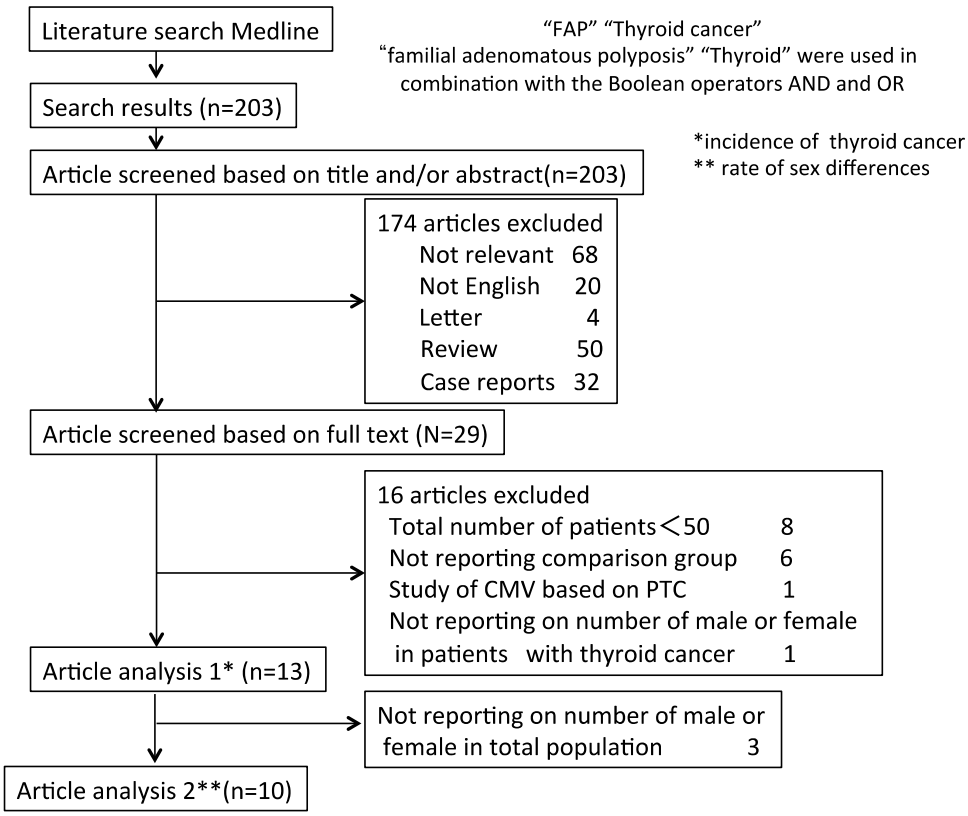

Fig. 2 Study selection flowchart. A total of 203 records were identified by a primary search of the electronic database. Thirteen articles met the selection criteria and were included in the analysis of the incidence of thyroid cancer in FAP patients, and 10 articles were selected for the investigation of sex differences related to thyroid cancer in FAP patients

modality from physical examination alone to US because the details of screening methods were not specified in the other 10 publications or in this database. Thus, the detection rate according to imaging modality should be investigated in future studies. Second, routine surveillance of thyroid cancer in FAP patients was previously considered unnecessary because of the favorable prognosis of thyroid cancer compared with that of gastrointestinal malignancies [13, 19].

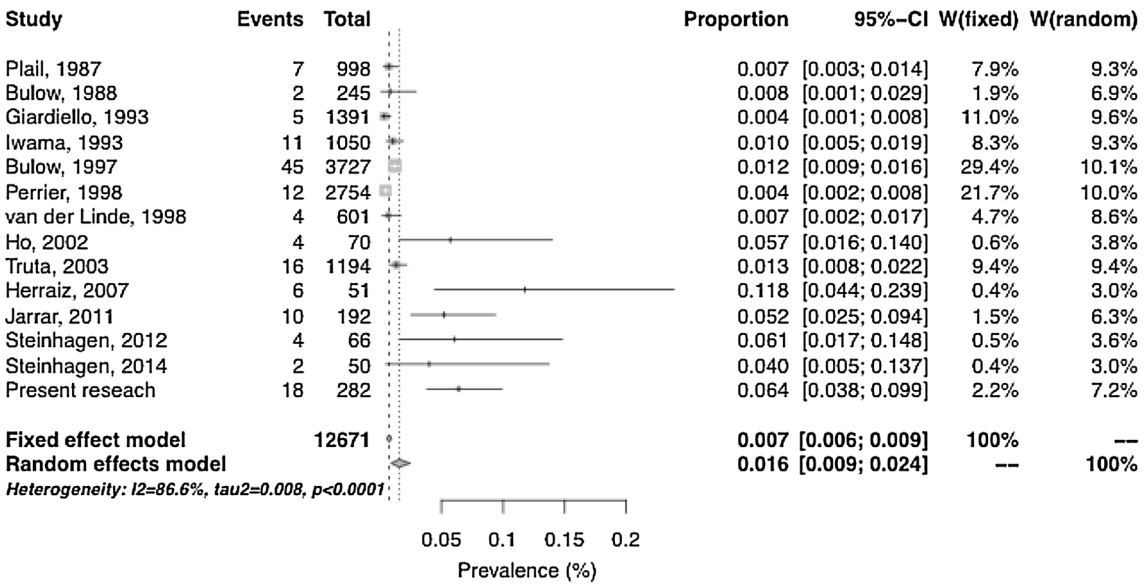

Fig. 3 Meta-analysis of the incidence of thyroid cancer in familial adenomatous polyposis patients. A meta-analysis of the 13 studies published from 1987 to 2014 revealed an incidence of thyroid cancer of 1.6% in familial adenomatous polyposis patients in Japan

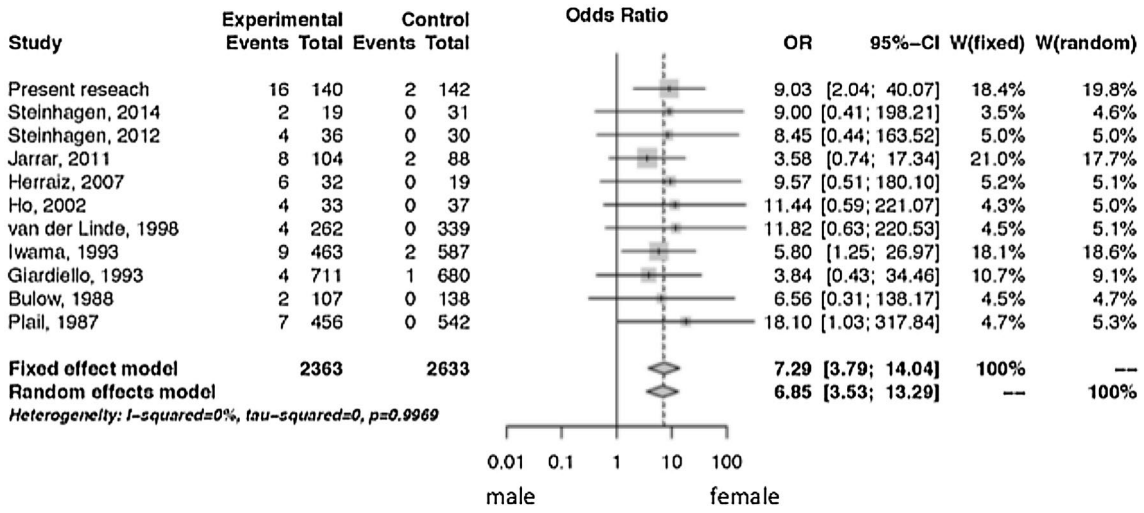

Fig. 4 Meta-analysis of the sex differences related to thyroid cancer in familial adenomatous polyposis patients. A meta-analysis of the sex differences in the rate of thyroid cancer among familial adenomatous polyposis patients revealed that the female-to-male odds ratio was 6.85:1

However, prophylactic gastrointestinal surgery and intensive surveillance programs have contributed to better survival, which may increase the detection of thyroid cancer in later studies. Third, the prevalence of thyroid cancer is reported [29] to be increasing in the general population, which may also influence the incidence of FAP-associated thyroid cancer. Although the increasing prevalence can be attributed to the early detection of subclinical diseases by US, the possibility that other environmental factors could be influencing the true incidence of both sporadic and FAP-associated thyroid cancers cannot be excluded [22].

It is also important to consider who should be offered intensive surveillance for FAP-associated thyroid cancer. The incidence of thyroid cancer is higher in women [30, 31], and the tendency is more remarkable in patients with FAP than in the general population. The incidence of thyroid cancer in the general population in Japan was reported to be 2.8 and 0.7% in women and men, respectively [31], whereas that among the FAP patients in our series was 11.4 and 1.4%, respectively, the female-to-male ratio being 8:1. A meta-analysis of sex differences in the risk factors for thyroid cancer in the present study also revealed a female-to-male ratio

of 6.9:1, with little difference between Asian and Western countries or between years of publication. With respect to age, FAP-associated thyroid cancer is generally reported to develop at a relative young age [23, 32], suggesting that US screening should be started in the teen years. Consistent with these reports from the United States, the incidence of thyroid cancer in the general population of Japan was reported to peak in the 60 s [30], whereas it developed in FAP patients at a much younger age in our Japanese cohort study. The diagnosis was made in most female patients when they were in their 20 s or older, with two being diagnosed at 17 years of age. The current Japanese cohort study also revealed that female sex and a young age of < 33 years at FAP diagnosis were independent risk factors for thyroid cancer in a multivariate analysis. Given the relatively favorable prognosis and age at diagnosis, thyroid cancer screening with US is recommended for women with FAP, from their early 20s. According to a recent report from Japan, ERα expression might be associated with the development of thyroid cancer in FAP patients [33]. These authors also suggested the possibility of spontaneous regression of thyroid cancer. This raises a very important issue as to when surveillance for thyroid cancer in FAP patients should start and stop. In our study, thyroid cancer was found in FAP patients as young as 17 years of age and plateaued in the fourth decade of life. This seems compatible with when menstruation starts and stops. Since the natural history of thyroid cancer in FAP patients is still unclear, it might be reasonable to perform surveillance for thyroid cancer in female FAP patients from the start of menstruation until menopause. Although the mechanism remains unclear, the prevalence of thyroid cancer plateaued in female FAP patients in their 40s. In contrast, FAP-associated thyroid cancer in women ≥ 40 years of age and in men was less frequent. Therefore, it may not be as important to perform surveillance with US for thyroid cancer in these populations.

The diagnostic context was also an important finding of the current study. A recent report on the incidence, prevalence and sexual difference of CMV-PTC, a histological feature characteristic of FAP, among all thyroid carcinomas developing in FAP patients, revealed a higher incidence than reported previously. The incidence in younger female patients was also higher than that in another Japanese single institution study by Uchino et al. [33]. Consistent with that study, in which CMV-PTC was observed in 8 of 11 FAP patients with thyroid cancer, we identified eight cases of CMV-PTC among ten cases for which histology records were available in the database. However, there were also eight cases for which the histology was not reported. Despite the impact of these excluded cases, the frequency of CMV-PTC was 80% (eight cases of CMV-PTC among ten cases of PTC) when these cases were excluded from the analysis, and this was comparable to the frequency of CMV-PTC in the previous report from Japan. Thyroid cancer was diagnosed and treated surgically in three women prior to their FAP diagnosis and the interval between the diagnoses of thyroid cancer and of FAP seemed dependent on the pathological findings of CMV-PTC, which may be a clue for detecting FAP. However, in two of these patients, it was unknown whether CMV-PTC had been diagnosed and it was also difficult to investigate further because our multicenter database was anonymized in a way that prevented data from being linked to any patient. Thus, we are unable to clarify whether a histological diagnosis of CMV-PTC before the diagnosis of FAP could help diagnose FAP before the occurrence of the colonic features of FAP in general practice. Conversely, thyroid cancer was diagnosed within 2 years after the FAP diagnosis in eight patients, and 4, 5, 9, and 10 years after the FAP diagnosis in another four. Because of the nature of the study, data were also unavailable about whether thyroid cancer screening was performed at the first diagnosis of FAP or whether colonoscopy was performed at the first diagnosis of thyroid cancer, especially thyroid cancer presenting with a CMV-PTC phenotype. However, the results of our series suggest that physicians should consider starting thyroid screening with US from the time of the FAP diagnosis, especially for young women.

It is also important to investigate the mortality rate associated with thyroid cancer in FAP patients because thyroid cancers are generally thought to be less life-threating than colorectal cancer or other neoplasms related to FAP, such as duodenal or desmoid tumors. In this study, there were three deaths from colorectal cancer among the FAP patients with thyroid cancer, whereas none of the patients died of thyroid cancer itself. Among 4830 patients whose prognosis was clearly stated, only 2 (0.04%) died of thyroid cancer [14, 20]. As the clinical impact of thyroid cancer screening is still unclear, we do not know whether surgery is required or if observation of the disease course is sufficient. To address this issue, it is important to understand the natural history of thyroid cancer associated with FAP by performing intensive surveillance of these patients from their early 20 s, as proposed in this study.

This study had several limitations. First, because our multicenter database was anonymized to prevent data being linked to the patients and protect the privacy of individual human genetic information, we could neither access blank data or carry out further investigations. This limitation made it especially difficult to determine the actual frequency of PTC-CMV and the impact of specific imaging modalities on the prevalence of thyroid cancer. Second, the screening and diagnostic methods for thyroid cancer may not have been consistent between the participating institutions of the present registry. In particular, the screening methods and indications for fine-needle aspiration of thyroid nodules for the cytological diagnosis of thyroid cancer may have varied between institutions. Third, both

the presence and position of a mutation in the *APC* gene were examined in only 11.0% of the current Japanese FAP cohort, as this examination is not always essential for a diagnosis of FAP. However, *APC* gene testing may be helpful for deciding on surveillance and therapeutic strategies, as some studies [34–36] have reported genotype–phenotype correlations in FAP patients. A genetic abnormality at the 5′ end of exon 15 (outside the *APC* mutation cluster region spanning codons 1286–1513) has been reported to be responsible for thyroid cancer in patients with FAP [15, 34]. Future studies directly analyzing the genotype–phenotype correlations in patients with FAP-associated thyroid cancer using next-generation sequencing technologies should be conducted. Fourth, the present registry excluded patients who had not undergone colorectal surgery. To avoid duplicate registration, FAP patients were registered on the condition that they had undergone initial surgery for colorectal lesions between 2000 and 2012; however, some patients with FAP may have been awaiting prophylactic colectomy. If there was a delay in surgery or surgery was not performed, then these patients would not have been included in the analysis. Fifth, because the follow-up period was relatively short, patients with FAP in whom thyroid cancer developed a long time after the initial surgery may have been excluded. Our meta-analysis of prior studies shows a consistent sex difference related to the risk of thyroid cancer, as does our study. We believe this lends credibility to our data.

In conclusion, the recent prevalence of thyroid cancer in Japanese patients with FAP was 6.4%, which is comparable to that in reports from Western countries since 2000. The female-to-male ratio was 8:1, which is comparable to that in other reports, regardless of the study periods or geographical locations. Furthermore, a young age of <33 years at the diagnosis of FAP was considered a risk factor for thyroid cancer in Japan. In contrast, no apparent benefit of intensive thyroid cancer screening could be demonstrated for women ≥ 40 years of age, or for men. Given that FAP-associated thyroid cancer occurs predominantly in young women and that it is diagnosed in the majority of Japanese patients with FAP in their 20s or older, as in the present study, routine surveillance including US, is recommended for Japanese patients with FAP, especially women, from their early 20s and/or from the time of their FAP diagnosis.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

References

1. Nishisho I, Nakamura Y, Miyoshi Y, Miki Y, Ando H, Horii A, et al. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science. 1991;253:665–9.
2. Kinzler KW, Nilbert MC, Su LK, Vogelstein B, Bryan TM, Levy DB, et al. Identification of FAP locus genes from chromosome 5q21. Science. 1991;253:661–5.
3. Bulow S. Results of national registration of familial adenomatous polyposis. Gut. 2003;52:742–6.
4. Burn J, Chapman P, Delhanty J, Wood C, Lalloo F, Cachon-Gonzalez MB, et al. The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. J Med Genet. 1991;28:289–96.
5. Jarvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. Gut. 1992;33:357–60.
6. Bulow S, Faurschou Nielsen T, Bülow C, Bisgaard ML, Karlsen L, Moesgaard F. The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register. Int J Colorectal Dis. 1996;11:88–91.
7. HJR B. Familial polyposis coli. Baltimore: Johns Hopkins University Press; 1975.
8. Iwama T, Tamura K, Morita T, Hirai T, Hasegawa H, Koizumi K, et al. A clinical overview of familial adenomatous polyposis derived from the database of the Polyposis Registry of Japan. Int J Clin Oncol. 2004;9:308–16. https://doi.org/10.1007/s10147-004-0414-4.
9. Nieuwenhuis MH, De VTotN Cappel, Botma W, Nagengast A, Kleibeuker FM, Mathus-Vliegen JH. EM, et al. Desmoid tumors in a dutch cohort of patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2008;6:215–9. https://doi.org/10.1016/j.cgh.2007.11.011.
10. Maehata Y, Esaki M, Hirahashi M, Kitazono T, Matsumoto T. Duodenal adenomatosis in Japanese patients with familial adenomatous polyposis. Dig Endosc. 2014;26(Suppl 2):30–4. https://doi.org/10.1111/den.12255.
11. Plail RO, Bussey HJ, Glazer G, Thomson JP. Adenomatous polyposis: an association with carcinoma of the thyroid. Br J Surg. 1987;74:377–80.
12. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut. 1993;34:1394–6.
13. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg. 1993;217:101–8.
14. Bulow C, Bulow S. Is screening for thyroid carcinoma indicated in familial adenomatous polyposis? The Leeds Castle Polyposis Group. Int J Colorectal Dis. 1997;12:240–2.
15. Truta B, Allen BA, Conrad PG, Kim YS, Berk T, Gallinger S, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. Fam Cancer. 2003;2:95–9.
16. Harach HR, Williams GT, Williams ED. Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm. Histopathology. 1994;25:549–61.
17. Cameselle-Teijeiro J, Chan JK. Cribriform-morular variant of papillary carcinoma: a distinctive variant representing the sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma? Mod Pathol. 1999;12:400–11.
18. Soravia C, Sugg SL, Berk T, Mitri A, Cheng H, Gallinger S, et al. Familial adenomatous polyposis-associated thyroid cancer: a clinical, pathological, and molecular genetics study.

Am J Pathol. 1999;154:127–35. https://doi.org/10.1016/s0002-9440(10)65259-5.
19. Bulow S, Holm NV, Mellemgaard A. Papillary thyroid carcinoma in Danish patients with familial adenomatous polyposis. Int J Colorectal Dis. 1988;3:29–31.
20. Perrier ND, van Heerden JA, Goellner JR, Williams ED, Gharib H, Marchesa P, et al. Thyroid cancer in patients with familial adenomatous polyposis. World J Surg. 1998; 22:738–42 (**discussion 743**).
21. van der Linde K, Vasen HF, van Vliet AC. Occurrence of thyroid carcinoma in Dutch patients with familial adenomatous polyposis. An epidemiological study and report of new cases. Eur J Gastroenterol Hepatol. 1998;10:777–81.
22. Herraiz M, Barbesino G, Faquin W, Chan-Smutko G, Patel D, Shannon KM, et al. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol. 2007;5:367–73. https://doi.org/10.1016/j.cgh.2006.10.019.
23. Jarrar AM, Milas M, Mitchell J, Laguardia L, O'Malley M, Berber E, et al. Screening for thyroid cancer in patients with familial adenomatous polyposis. Ann Surg. 2011;253:515–21. https://doi.org/10.1097/SLA.0b013e3181fcba8a.
24. Steinhagen E, Guillem JG, Chang G, Salo-Mullen EE, Shia J, Fish S, et al. 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;11:304–8. https://doi.org/10.1016/j.clcc.2012.01.006.
25. Steinhagen E, Hui VW, Levy RA, Markowitz AJ, Fish S, Wong RJ, et al. Results of a prospective thyroid ultrasound screening program in adenomatous polyposis patients. Am J Surg. 2014;208:764–9. https://doi.org/10.1016/j.amjsurg.2014.03.012.
26. Hizawa K, Iida M, Aoyagi K, Yao T, Fujishima M. Thyroid neoplasia and familial adenomatous polyposis/Gardner's syndrome. J Gastroenterol. 1997;32:196–9.
27. Ueno H, Kobayashi H, Konishi T, Ishida F, Yamaguchi T, Hinoi T, et al. Prevalence of laparoscopic surgical treatment and its clinical outcomes in patients with familial adenomatous polyposis in Japan. Int J Clin Oncol. 2016;21:713–22. https://doi.org/10.1007/s10147-016-0953-5.
28. Ho JW, Chu KM, Tse CW, Yuen ST. Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry. Hong Kong Med J. 2002;8:342–7.
29. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295:2164–7. https://doi.org/10.1001/jama.295.18.2164.
30. Saika K, Matsuda T, Sobue T. Incidence rate of thyroid cancer by histological type in Japan. Jpn J Clin Oncol. 2014;44:1131–2. https://doi.org/10.1093/jjco/hyu179.
31. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, et al. Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2014;44:388–96. https://doi.org/10.1093/jjco/hyu003.
32. 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. J Pediatr Surg. 2014;49:82–6. https://doi.org/10.1016/j.jpedsurg.2013.09.033.
33. Uchino S, Ishikawa H, Miyauchi A, Hirokawa M, Noguchi S, Ushiama M, et al. Age- and gender-specific risk of thyroid cancer in patients with familial adenomatous polyposis. J Clin Endocrinol Metab. 2016;101:4611–7.
34. Septer S, Slowik V, Morgan R, Dai H, Attard T. Thyroid cancer complicating familial adenomatous polyposis: mutation spectrum of at-risk individuals. Hered Cancer Clin Pract. 2013;11:13. https://doi.org/10.1186/1897-4287-11-13.
35. Nieuwenhuis MH, Bülow S, Bjork J, Jarvinen HJ, Bülow C, Bisgaard ML, et al. Genotype predicting phenotype in familial adenomatous polyposis: a practical application to the choice of surgery. Dis Colon Rectum. 2009;52:1259–63. https://doi.org/10.1007/DCR.0b013e3181a0d33b.
36. Groen EJ, Roos A, Muntinghe FL, Enting RH, de Vries J, Kleibeuker JH, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol. 2008;15:2439–50. https://doi.org/10.1245/s10434-008-9981-3.