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Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis

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Abstract

Familial adenomatous polyposis has been associated with several extraintestinal cancers, but the relative and absolute risks of these malignancies have not been determined. Extraintestinal cancers reportedly associated with adenomatous polyposis (thyroid gland, adrenal gland, pancreas, and biliary tract) were identified in polyposis patients and their at risk relatives in The Johns Hopkins Registry. The incidence rates of identified tumours were then compared with the general population through person year analysis with adjustment for population. For comparison, the incidence rates of the two most common cancers not associated with polyposis (breast cancer in women and lung cancer) were also calculated. There was an increased relative risk of thyroid cancer (relative risk 7·6; 95% confidence limits (CL) 2·5–17·7) and pancreatic adenocarcinoma (relative risk 4·46; 95% CL 1·2–11·4) in polyposis patients and at risk relatives. The absolute risk was 26·8 and 21·4 cases/100 000 person years, respectively. No cases of adrenal or biliary cancer were found in this cohort. There was no increased relative risk of lung cancer (95% CL 0·04–1·4) or breast cancer (95% CL 0·04–1·4) over the general population. The relative risks of thyroid and pancreatic cancer are increased in familial adenomatous polyposis, but the absolute lifetime risk is low. Screening for pancreatic cancer may not be worthwhile with currently available methods, but careful physical examination of the thyroid gland is warranted along with consideration for ultrasonography.

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Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterised by the development of hundreds of colorectal adenomas in young adults.[1] If prophylactic colectomy is not performed, virtually all affected subjects will develop colorectal cancer by the fifth decade of life. Recently, investigators have discovered that this disorder is caused by germline mutation of the adenomatous polyposis coli gene located on chromosome 5q21.[2-5]

FAP can be associated with various extracolonic lesions. Benign extraintestinal manifestations include osteomas, exostoses, epidermoid cysts, dental abnormalities, pigmented ocular fundic lesions, and small bowel adenomas.[6-8] FAP patients are also at increased risk for intestinal cancers especially duodenal and periampullary carcinomas.[9] Extraintestinal cancers have been reported in association with FAP as well. These include malignancy of the thyroid gland,[1 6 7 10-18] adrenal gland,[1 6 7 19-21] biliary tree,[1 6 7 22] and pancreas.[6] A formal risk assessment, however, of these malignancies in FAP has not been reported.

The purposes of this study were to define further the cancers in the FAP phenotype, to determine the magnitude of risk of these extraintestinal cancers, and to evaluate the need for surveillance of FAP patients for these neoplasms. The risks of cancer of the thyroid gland, adrenal gland, pancreas, and biliary tree identified in subjects affected with and at risk for FAP in The Johns Hopkins Polyposis Registry were compared with the general population of the United States through person year analysis. For comparison, the risks of the two most common cancers that have not been associated with FAP (lung and breast cancer) were also calculated.

Methods

Data were collected from The Johns Hopkins Polyposis Registry that contains 197 pedigrees with FAP.[9] Patient information was obtained on all registry subjects through chart review and was subsequently computerised using dBase III Plus software (Ashton-Tate, Torrance, California).

For risk assessment, FAP patients were considered at risk for extraintestinal cancer from birth until death. First degree relatives of FAP patients were considered at risk from birth up to 55 years, by which time the phenotype is expressed in virtually all affected subjects.[1] Both FAP patients and at risk relatives contributed person years accordingly. Study time was until date of last contact (n=285), death (n=360), date of diagnosis of extraintestinal cancer (n=13), or closing date of the study (n=733). The period for analysis started on 1 January 1969, and ended 31 December 1987. These dates were chosen because population rates of cancer for comparison were available from Surveillance, Epidemiology, and End Results (SEER)[23] only for this period. Person years at risk were calculated according to sex, race, and age specific categories up to 84 years of age during five year calendar time periods of study using a computer program for cohort analysis.[24] The ratio of observed tumours to the expected number was computed with a test of significance and 95% confidence limits assuming a Poisson distribution.[24 25] This observed/expected ratio indicated the relative risk and compared the specific extraintestinal cancer risk in the study population with that in the general population. The expected numbers for specific extraintestinal cancers were calculated by multiplying the person years with corresponding age, race, sex, and calendar time specific incidence rates for specific observed

TABLE I *Patients with familial adenomatous polyposis from The Johns Hopkins Registry who developed extraintestinal cancer*

Age at diagnosis of cancer (y)	*Race*	*Sex*	*Location of cancer*
29	W	M	Thyroid
27	W	F	Thyroid
27	W	F	Thyroid
29*	W	F	Thyroid
18	B	F	Thyroid
52	W	F	Pancreas
47	W	M	Pancreas
32	W	M	Pancreas
78	W	M	Pancreas
60	W	F	Lung
45	W	M	Lung
57	W	F	Breast
50	W	F	Breast

*Patient at risk for FAP. All others were affected with FAP.

extraintestinal cancers obtained from SEER data.[23] Thus, the relative risk was adjusted for race, age, sex, and also calendar time (to account for possible secular trends). The absolute risk was defined as the number of observed carcinomas per total person years.

Risk assessment was performed for selected cancers reported to be associated with FAP including thyroid carcinoma (ICD 193·0, 9th revision) and pancreatic cancer (ICD 157·0–0·9, 9th revision). No adrenal or biliary cancers occurred in the study population. The relative risks of FAP associated malignancies were compared with the two most commonly occurring cancers in the United States, lung cancer (ICD 162·0–0·9, 9th revision) and breast cancer (ICD 174·0–0·9, 9th revision), which are not thought to be associated with FAP. Only women were included in the breast cancer analysis.

Results

The person year analysis included 1391 affected or at risk subjects from FAP families and they contributed 18 682·6 person years of follow up. For breast cancer risk analysis, 711 women contributed 9698·13 person years. These subjects included 604 white men, 646 white women, 76 black men, and 65 black women.

Table I lists the FAP patients with extraintestinal cancers analysed in this study. These cancers all occurred within different pedigrees. All patients except one (asterisk in Table I) were affected by FAP. Of the five patients with thyroid cancer, three had papillary carcinoma and two patients had mixed papillary/follicular carcinoma. No patient in this cohort developed adrenal or biliary cancer.

Table II shows the results of person year analysis of thyroid, pancreas, lung, and breast cancer. Statistically significantly raised relative risks of thyroid and pancreatic cancer were seen. The absolute risk was 26·8 and 21·4 cases/100 000 person years respectively. Based on an 80 year life span, the lifetime, absolute risk for thyroid cancer was 2·1/100 persons and for pancreatic cancer was 1·7/100 persons. The relative risks for lung and breast cancer were not statistically significantly different from the general population of the United States.

TABLE II *Risk analysis of extrainterestinal cancers in patients with familial adenomatous polyposis (The Johns Hopkins Polyposis Registry) as compared with the general population of the United States (SEER data)*

Site, ICD 9th revision	*Patient number (person years)*	*Number of carcinomas*	*Relative risk (O/E)*	*95% confidence limits*	*Rate per 100 000 (person years)*
Thyroid 193·0	1391 (18 682·6)	5	7·6	2·5 to 17·7	26·8
Pancreas 157·0–0·9	1391 (18 682·6)	4	4·5	1·2 to 11·4	21·4
Lung 162·0–0·9	1391 (18 682·6)	2	0·4	0·4 to 1·4	10·7
Breast 174·0–0·9	711 (9698·1)	2	0·4	0·04 to 1·3	20·6

O/E = Observed/expected.

Discussion

In this study, statistically significantly increased relative risks of thyroid and pancreatic cancer were found in FAP families. Of note, all but one of the thyroid and pancreatic cancers occurred in known affected patients. These relative risks are presumably conservative for two reasons. Firstly, the analysis included first degree relatives of FAP patients from birth to withdrawal at the relatively late age of 55 years. Fifty five years old was chosen because the FAP phenotype can first be expressed in middle age and therefore affected and unaffected persons could not be distinguished with certainty until this age. Consequently, some persons included in the study group do not have germline mutation of the APC gene, and patients with the mutated gene are probably at even higher relative risk. When genotyping for the APC gene mutation becomes readily available, analysis of only affected persons can be done. Secondly, we used overall risks without distinction to specific morphology, further diluting the risk estimates because the SEER data contain all histological types of malignancy for a particular organ site. This approach was used because underreporting of the morphology of specific types of cancer in the SEER data would lead to overestimation of risk. Importantly, no biliary or adrenal cancers were identified in this cohort indicating no significantly increased risk.

A concern raised by the comparison of a registry based population to the general United States population is detection bias – that is, surveillance of the population in the registry may lead to a higher diagnostic yield of certain diseases compared with the SEER data. For this reason, the relative risk in this cohort of the two most common cancers (lung and breast) in the United States population were also analysed. These malignancies have not been reported in association with FAP, and the risk of both these cancers was not significantly different from the general population. This result strengthens the specificity of our findings and makes it less likely that confounding variables account for the association of thyroid and pancreatic cancer with FAP. Confounding factors could be a problem if certain lifestyle characteristics, for example, smoking, diet etc, were more common in our study group than in the reference population. In the event, however, an overall increase in the risk of malignancy would be expected instead of only the specific sites previously associated with FAP.

In our series of FAP patients, thyroid cancer occurred in the third decade of life. This is consistent with previous reports.[1 6 7 10-18] Of 39 other reported patients with FAP and thyroid malignancy, 34 patients had thyroid malignancy diagnosed between 15 and 35 years of age. Although the relative risk of both thyroid and pancreatic cancer was much higher than the general population, the absolute lifetime risk of each of these malignancies in FAP patients was about 2%. With present diagnostic techniques, screening for pancreatic cancer in this population seems unwarranted, but may become worthwhile with advances in molecular biological markers, endoscopic ultrasonography or other techniques. By contrast with the pancreas, the thyroid gland is easily accessible to physical examination, and careful palpation in FAP patients is certainly warranted at each examination. In addition, ultrasound examination in the third decade of life may be justified, but a formal cost benefit study of this strategy is needed.

Finally, the present study calls renewed attention to the importance of genetic changes of the APC gene on chromosome 5q21. When mutated in the germline, this gene may be instrumental in the formation of extraintestinal cancers as well as the intestinal adenomas and carcinomas that are hallmarks of FAP. What part somatic mutation of this tumour suppressor gene plays in thyroid and pancreatic cancer unassociated with FAP has yet to be determined.

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