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Optimizing diagnosis, surveillance, and management of hereditary polyposis syndromes

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Optimizing diagnosis, surveillance, and management of hereditary polyposis syndromes

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Aan Arno

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Chapter 1

Introduction and outline

General introduction

Colorectal cancer (CRC) is a major cause of death in Western countries. A combination of nature (genetic susceptibility, gender) and nurture (environmental factors, life style) determines an individual's risk of developing CRC. Cancer development is the result of a complex sequence of cellular events via molecular pathways. Most CRCs are preceded by adenomatous polyps. These adenomas are histologically benign, but a percentage of these will inevitably undergo malignant transformation, known as the adenoma-carcinoma sequence.

Patients with certain germline genetic defects develop multiple colorectal polyps and have consequently an extremely high risk of developing cancer. Although these patients constitute only a small proportion of all CRC cases, this group with hereditary polyposis syndromes offers opportunities for research. From the scientific point of view, these patients provide insight into cancer development as they will almost certainly develop CRC. From the patient's and doctor's point of view, it is important to develop guidelines for diagnosis, treatment, and surveillance. Moreover, identification of family members at risk will allow timely screening and treatment, and consequently prevention from cancer development.

This thesis describes several clinical aspects of various hereditary polyposis syndromes, including familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), and *PTEN* hamartoma tumor syndrome (PHTS), and provides recommendations for clinical management of these syndromes.

Part I Familial adenomatous polyposis (FAP)

The main clinical characteristic of FAP is the development of a multitude of colorectal polyps, and consequently, a high risk of developing CRC. The prevalence of FAP is about 1 in 10,000 individuals (1).

Genetics

Genetically, FAP is an autosomal dominant condition caused by a germline mutation in the tumor suppressor gene *adenomatous polyposis coli* (*APC*), which is located on chromosome

5q21-22 (2). The main tumor suppressing function of *APC* resides in its capacity to regulate the Wnt signal transduction pathway. In the absence of Wnt signals, a dedicated complex of proteins, including APC, axin, and glycogen synthase kinase-3β (GSK3β) phophorylates β-catenin, resulting in its ubiquitylation and degradation by the proteasome. Signalling by Wnt factors prevents forming of a protein/APC complex. As a result, β-catenin is stabilized and translocates into the nucleus, where it interacts with nuclear T-cell-factor (TCF) transcription factors to drive the transcription of specific target genes like *MYC* and *cyclin D1*. These play a role in cell proliferation, apoptosis, and cell-cycle progression and thus are relevant in tumor formation (3). Since the identification of the *APC* gene in 1991 (2,4,5) as the cause of FAP, several reports described an obvious association between the location of a certain *APC* mutation and the number of colorectal polyps in the individual patient. In Chapter 2 of this thesis, these genotype-phenotype correlations in FAP are reviewed.

Surgical considerations

Clinically, patients with a germline *APC* gene mutation develop hundreds to thousands colorectal adenomatous polyps from adolescence. Without treatment, virtually all patients will develop CRC before the age of 40 years (6). To prevent development of CRC, patients need frequent colonoscopic examinations (7). In the case of endoscopically unmanageable polyposis, patients are referred for a prophylactic colectomy. The two main surgical options are subtotal colectomy with ileorectal anastomosis (IRA) and total proctocolectomy with ileal pouch-anal anastomosis (IPAA). After IRA, the rectum is left situ, whereas after IPAA the rectum is totally removed. The IRA procedure has a lower risk of complications and a more favourable functional outcome than IPAA surgery (8,9). However, a disadvantage of IRA is the remaining risk of developing polyps and cancer in the rectum. After IPAA, there is virtually no risk of developing rectal cancer because the rectal mucosa is removed. For most patients with more than 10-15 rectal adenomas, an IPAA is recommended (7). In patients with few or no rectal polyps the surgical decision needs a careful deliberation of the pros and cons of both procedures. It might be helpful to additionally consider genetic information in the decision. In

Chapter 3 and 4, we assessed whether the risk of rectal excision and rectal cancer after IRA for patients with different severity of polyposis can be predicted by the *APC* mutation site.

Fertility

As prophylactic surgery is usually performed in the second or third decade of life, also future factors have to be taken into account, including family planning. Fertility problems are a common long-term complication after extended abdominal surgery, mainly thought to be caused by adhesions which are provoked by surgical damage (9). A previous study showed significantly more fertility problems in female FAP patients who had an IPAA procedure, compared to those who had undergone an IRA (11). Chapter 5 contains the results of a study among Dutch female FAP patients addressing fertility problems due to colorectal surgery.

Extracolonic manifestations

Beside colorectal polyposis, FAP patients can suffer from a variety of other disease characteristics (12). These extra-colonic manifestations include duodenal adenomas and duodenal cancer; several malignancies including thyroid cancer, hepatoblastoma, and brain tumors; benign tumors including gastric polyps, adrenal adenomas, osteomas, epidermoid cysts, fibromas, lipomas, and desmoid tumors; other abnormalities as congenital hypertrophy of the retinal pigment epithelium (CHRPE) and supernumerary teeth (12). By prophylactic colectomy, the colorectal cancer risk of FAP patients decreases and life expectancy increases. As a consequence, extracolonic manifestations have become relatively more important. The clinically most threatening are duodenal cancer and desmoid tumours, since these cause significant morbidity and mortality in FAP patients (13,14,15).

Duodenal adenomas and duodenal cancer

Almost all FAP patients develop duodenal adenomas: The cumulative incidence was calculated to be 90% at age 70 (16). FAP patients have a nearly 5% risk of duodenal cancer (16). As duodenal cancer is difficult to treat, it is important to prevent development of duodenal cancer and to detect and remove precancerous lesions. In 1989 a classifcation was proposed

to determine the severity of duodenal polyposis based on polyp number, size, histology, and severity of dysplasia (17). This Spigelman classification is currently used to estimate the probability of duodenal cancer and to determine surveillance intervals (7). In the case of advanced duodenal adenomatosis and a high cancer risk, performing a prophylactic duodenectomy should be considered. However, this procedure has a substantial risk of complications. To gain more insight into the clinical course of FAP patients with advanced duodenal polyposis and/or duodenal cancer, a retrospective study was performed addressing this topic (Chapter 6).

Type II diabetes and FAP

Recent genome wide analysis studies (GWAS) showed certain polymorphisms to be associated with type II diabetes (18). Remarkably, these polymorphisms are known to be involved in the Wnt pathway. Chapter 7 describes a concise research project which aimed to assess whether type II diabetes is more common in FAP patients than in the general population.

Part II Desmoid tumors

Desmoid tumors belong to the broad group of histologically benign fibrous tumors known as fibromatoses, and more specifically to the deep (musculo-aponeurotic) fibromatoses (19). Although benign in name, these tumors have an unpredictable and sometimes aggressive growth pattern, leading to serious morbidity or even mortality by local infiltration and pressure on surrounding vital structures. In Chapter 8 characteristics of patients with desmoid tumors in the Dutch FAP population are described.

Sporadic versus FAP-related desmoid tumors

Desmoid tumors are extremely rare in the general population, but do occur in about 10% of FAP kindreds (20). As FAP is a rare syndrome, most desmoids diagnosed by pathologists and other physicians are sporadic ones. However, because of the severity of FAP for both a patient and his/her family members, it is crucial to detect patients with FAP. In Chapter 9 clinical

characteristics of sporadic and FAP-related desmoid tumors were compared, to assess whether an underlying FAP syndrome can be identified by clinical variables.

Risk factors

The etiology of desmoids tumors is yet unelucidated. Several previous studies suggested risk factors for desmoid development, including female hormones, pregnancy, abdominal surgery, a positive family history of desmoids, and distal *APC* gene mutations (20). In Chapter 10 risk factors for desmoid development were assessed in a large international cohort of FAP patients.

Management

The treatment of desmoid tumors is a topic of controversy (21). Due to the complex mesenterial location of most FAP-related desmoid tumors, and because surgical trauma can provoke desmoid growth, surgery is not an attractive option. Generally, the initial pharmacological treatment consists of non-steroidal anti-inflammatory drugs (NSAIDs) and/or hormonal therapy, most often tamoxifen. More aggressive therapeutic options include cytotoxic chemotherapy and radiation therapy. However, despite intensive therapy desmoid tumors can still cause severe morbidity and mortality, especially if located at intra-abdominal sites. Because desmoid tumors are rare, initiating a randomized controlled trial is difficult. Moreover, the unpredictable growth pattern of desmoid tumors makes interpretation of the effects of therapies difficult. To gain insight into therapeutic strategies, in Chapter 11 the management of desmoid tumors in Dutch FAP patients was evaluated.

Part III Other polyposis syndromes

Beside FAP, there is a spectrum of other hereditary syndromes with polyposis as a clinical feature. Because these syndromes are rare, establishing evidence-based guidelines for surveillance and management is challenging.

MUTYH-associated polyposis

The most recently discovered polyposis syndrome is *MUTYH*-associated polyposis (MAP). In 2002, mutations in the base-excision repair gene *MUTYH* were identified as a cause for polyposis (22). Contrary to FAP, MAP has a recessive mode of inheritance and patients with bi-allelic mutations in the *MUTYH* gene are affected. Clinically, most MAP patients who present symptomatically were on average 45 years at diagnosis and most of them had between ten and a few hundred colorectal adenomas (23). Nearly 60% had colorectal cancer at a mean age of 48 years (23). Clinically, the MAP phenotype resembles that of an attenuated form of *APC*-associated polyposis (AFAP), and patients with MAP are recommended to undergo the AFAP screening protocol (24). However, information on the natural history of MAP is still scarce. In Chapter 12, the results of diagnosis and treatment of MAP patients for almost a decade were evaluated, with the aim to elucidate the natural history of tumor development in MAP.

PTEN hamartoma tumor syndrome

Germline mutations in the tumor suppressor gene Phosphatase and tensin homolog (*PTEN*) cause a variety of rare syndromes with hamartomatous polyps in several organs as a common characteristic. Moreover, patients with *PTEN* hamartoma tumor syndrome (PHTS) have an increased risk of several malignant tumors, particularly of the breast, thyroid, and endometrium (25). The mode of inheritance of PHTS is dominant. Within families, the phenotypic expression is variable. Guidelines for management include regular surveillance for breast cancer, thyroid cancer, and endometrial cancers, which are clearly associated with PHTS (NCCN guidelines for detection, prevention, and risk reduction; Genetic/familial high-risk assessment: Breast and ovarian – Cowden syndrome. www.nccn.org [accessed 21-12-2010]).

However, there are also other clinical features with unclear cancer risks, for which no guidelines were established. Recent reports showed that the majority of patients with a *PTEN* mutation have colorectal polyposis, and that also colorectal carcinoma is common in these patients (26,27,28). In Chapter 13, the frequency and nature of colorectal polyps were assessed, and the risk of developing CRC was calculated.

Research questions

The central research question of this thesis is:

How can the diagnosis, surveillance, and management of patients with hereditary polyposis syndromes be optimized?

This question is addressed from several perspectives, leading to the subquestions:

Can genetic information be applied for management decisions in FAP?

Can risk factors be identified for postoperative fertility problems?

What is the outcome of patients with advanced duodenal adenomatosis or duodenal cancer?

What are the implications of recent findings on the Wnt pathway and type II diabetes?

What are the characteristics of FAP patients with desmoid tumors?

Can differences between FAP-related and sporadic desmoids be used to predict a FAP syndrome?

What are risk factors for desmoid tumor development?

What is the outcome of different treatment strategies for desmoid tumors?

What is the natural course of *MUTYH*-associated polyposis?

What is the risk of gastrointestinal lesions in patients with a *PTEN* mutation?

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Chapter 2

Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): A review of the literature

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Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): A review of the literature

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Abstract

Mutations in the adenomatous polyposis coli (APC) gene cause familial adenomatous polyposis (FAP). Disease severity and the presence of extracolonic manifestations seem to be correlated with the location of the mutation on the APC gene. In this review, large studies describing genotype–phenotype correlations in FAP were evaluated and categorized. Attenuated FAP (AFAP, <100 colorectal adenomas) is correlated with mutations before codon 157, after codon 1595 and in the alternatively spliced region of exon 9. Severe polyposis (>1000 adenomas) is found in patients with mutations between codons 1250 and 1464. Mutations in the remainder of the APC gene cause an intermediate phenotype (hundred to thousands of adenomas). Congenital hypertrophy of the retinal pigment epithelium (CHRPE) and desmoid tumours are associated with mutations between codons 311 and 1444 and after codon 1444, respectively. No consistent correlations were found for upper gastrointestinal tumours. Genotype–phenotype correlations in FAP will be useful in decisions concerning screening and surgical management of FAP.
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Keywords: Familial adenomatous polyposis; Genotype–phenotype correlations; Extracolonic manifestations; Adenomatous polyposis coli gene

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1. Introduction

Familial adenomatous polyposis (FAP) is a colon cancer predisposition syndrome which is inherited in an autosomal dominant manner. It is caused by germline mutations in the adenomatous polyposis coli (APC) gene. Since the first description of FAP in 1847 [1], the syndrome has been extensively investigated and described in the literature.

In 1975, the clinical characteristics and natural history of FAP were described by Bussey. Patients develop hundreds to thousands of adenomatous polyps in their colorectum during their second and third decade of life. Because of the large number of polyps, they almost inevitably develop colorectal carcinoma by the age of 40–50 years. A clinical diagnosis of FAP can be made when more than 100 adenomatous polyps are identified in the colorectum [1]. About 10% of FAP patients have a milder course of disease with less than 100 colorectal adenomas and a later onset of disease. This variant is termed attenuated FAP (AFAP) [2].

In FAP patients not only colorectal adenomas but also various extracolonic manifestations are observed, including desmoid tumours, osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium (CHRPE), lipomas, epidermoid cysts and upper gastrointestinal polyps. Moreover, cancers of the thyroid, brain and hepatobiliary tract are found to be associated with FAP.

The prevalence of FAP is estimated at 1 in 5000–10,000 [3]. Periodical screening of the colorectum by sigmoidoscopy is recommended, starting between 10 and 12 years. In most patients, a preventive colectomy is performed by the age of 20 years [4].

In 1991, the APC gene (chromosome 5q21-22) was identified and found to be mutated in FAP patients [5–7]. The coding region of the gene consists of 15 exons, encoding a protein consisting of 2843 amino acids. The APC gene is a tumour suppressor gene. It contains a variety of functional domains and is involved in several cellular processes, including transcription, cell cycle control, migration, differentiation and apoptosis [8,9]. Mutations follow the classical two-hit model of tumour suppressor inactivation. FAP patients inherit one germline mutation and develop tumours from those cells in which a second hit, or loss of the other allele of APC, is somatically acquired [8,10]. The vast majority of germline mutations in the APC gene result in a truncated nonfunctional protein [11,12].

Since the identification of the APC gene, more than 825 germline mutations have been reported to the APC mutation database (http://www.perso.curie.fr/Thierry.Soussi/APC.html) [11]. In Fig. 1, the frequency of mutations throughout the APC gene is shown. Mutational hotspots are located at codons 1309 and 1061, accounting for approximately 17% and 11% of all germline APC mutations, respectively [11]. Because of the accumulation of mutations from codon 1250 to 1464, this region is termed the "mutation cluster region" (MCR) [13,14].

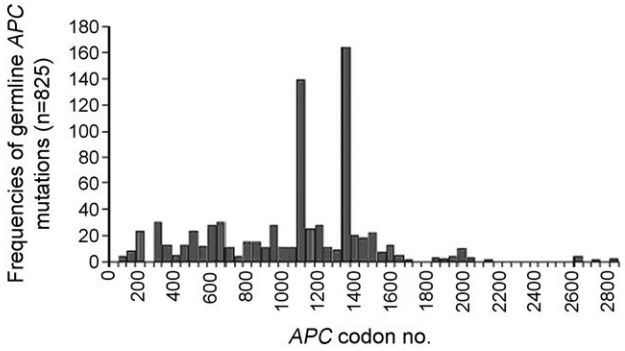

Fig. 1. Distribution of germline mutations in the APC gene. Data were retrieved from the online APC mutation database at http://www.perso.curie.fr/Thierry.Soussi/APC.html.

APC's role in colorectal tumourigenesis is not limited to FAP; the majority of sporadic colon tumours harbour mutations in the APC gene [12]. The study of the APC gene in FAP has therefore also implications for colorectal cancer research in general.

In 30–50% of patients with the FAP or AFAP phenotype, no germline APC mutation is detected [14,15]. In 10–15% of mutation-negative patients with the classical phenotype large genomic deletions were detected. These deletions were not found in AFAP patients [16,17]. Recently, another polyposis-causing gene was detected on chromosome 1p33-34, the MUTYH gene. Mutations in this gene have been found to be associated with a recessively inherited form of colonic polyposis. MUTYH mutations appear to cause an attenuated phenotype and have been reported in 10–30% of FAP and AFAP patients without an APC mutation [18–21].

In several studies, an association between the location of APC mutation and the phenotype in FAP patients was described. Number of polyps, age of onset and occurrence of extracolonic manifestations seem to correlate with specific mutation sites. This opens new perspectives to translational medicine: genetic knowledge could direct mutation analysis and probably be helpful in making therapeutic decisions.

The aim of this review is to describe current knowledge of genotype–phenotype correlations in FAP. Firstly the severity of the colonic disease in relation with the site of the mutation will be reviewed, secondly the relation between site of mutation and extracolonic manifestations will be described.

2. Methods

A literature search was performed using Pubmed for the years 1991–2005. The following search terms (both as MeSH terms and as keywords) were used to identify potentially relevant studies: familial adenomatous polyposis, genotype–phenotype correlations, adenomatous polyposis coli gene, extracolonic manifestations, upper gastrointestinal tumours, congenital hypertrophy of the retinal pigment epithelium and desmoid tumours. Studies reporting

genotype–phenotype correlations in series of at least 10 patients were included, patients being either unrelated persons or within large families. Case reports were excluded. References from the retrieved articles were scanned in order to identify further papers.

3. Colorectal polyposis

3.1. Classification

Several clinical variants of the FAP phenotype have been described, with variable age of onset of polyposis, number of polyps and age of onset of colorectal cancer. In the literature various terms are used, including profuse, classic, sparse and attenuated polyposis.

Profuse polyposis is defined as severe polyposis (over 5000 polyps) at young age (first and second decades). The average age of onset of colorectal cancer is approximately 34 years [22].

In the classical and sparse phenotype, patients develop hundred to thousands of colorectal adenomas in their second and third decades of life [8,22]. Mean age of colon cancer in untreated individuals is about 40 years. Extracolonic manifestations are common [1,22]. In the attenuated phenotype patients have fewer than 100 polyps and cancer onset is delayed [23]. Some investigators reported limited expression of extracolonic manifestations in AFAP [2,24].

Although dividing the continuous spectrum of the FAP phenotype may seem arbitrary, it might be helpful for directing genetic testing, estimating the colorectal cancer risk and thereby guide therapeutic decisions [25].

Grouping the phenotypes is difficult for several studies use their own definition to describe the severity of FAP. Furthermore, it is impossible to count thousands of polyps exactly so the exact polyp number often is unknown. Therefore, we chose to make a classification without exact polyp numbers (Table 1). According to this classification, the profuse and intermediate phenotype are the "severe" and "mild" variants of classical FAP.

3.2. Genotype–phenotype correlations

Since 1991, many genotype–phenotype correlations in FAP have been described.

Table 2 shows an overview of these data, based on the literature.

3.2.1. Profuse polyposis

In 1992, the first genotype–phenotype correlation was described [22]. A relation between a truncating mutation between codons 1250 and 1464 and a profuse type of polyposis (>5000 colorectal polyps) was observed. Patients with mutations in other regions of the APC gene had the intermediate phenotype, which was characterized by hundreds to thousands of colorectal polyps. The average age of onset for developing colorectal cancer in the profuse phenotype was 34 years, compared to 42 years in the intermediate phenotype [22].

These observations were supported by other studies, in which APC germline mutations between codons 1250 and 1311 correlate with the development of over 5000 colorectal polyps [26–27]. However, the association is not absolute: in one study, four new mutations were found between codons 1250 and 1464, but no profuse polyposis was recognized [28].

Codon 1309 mutations are associated with severe polyposis and early onset of symptoms [13,27,29,30]. If untreated, mortality of colorectal cancer in patients with a 1309 mutation is on the average 10 years earlier compared to FAP patients with other mutations [29].

3.2.2. Intermediate polyposis

Nagase et al. [22] supposed that codon 1249 might define the 5′ border of the profuse phenotype. This observation was confirmed by studies of large numbers of patients [26,27]. The majority of germline mutations of the APC gene which cause the intermediate phenotype are located between codon 157 (exon 4) and codon 1595 (exon 15), excluding the mutation cluster region (MCR), where the profuse phenotype is found [13,22,27,28,30,31].

3.2.3. Attenuated polyposis

Spirio et al. [23] have shown that mutations located close to the 5′ end of the APC gene or in the alternatively spliced region of exon 9 result in a generally mild and variable phenotype of FAP. Soravia et al. [32] reported that mutations in patients with an attenuated phenotype were located in three distinct regions of the APC gene: at the 5′ end spanning exons 4 and 5, within exon 9 and at the 3′ distal end of the gene. Rectal-polyp sparing was observed and usually <100, mainly right-sided colonic adenomas were seen at colonoscopy. Extracolonic manifestations were reported occasionally. Particularly 5′ mutations exhibited great variability; the phenotype of some affected patients was quite similar to that of classical FAP [32,33]. Other investigators

Table 1
Classification of FAP severity

	Phenotype	No. of colorectal adenomas	Age of onset
Classical	Profuse	Thousands	1st and 2nd decade
	Intermediate	Hundred to thousands	2nd and 3rd decade
Attenuated	Attenuated	<100	4th and 5th decade

Table 2
Severity of FAP and reported sites of mutation

Phenotype	Codon no.	Authors, year	References
Profuse	1250–1464	Nagase, 1992; Bertario, 2003	[22,27]
	1250–1311	Enomoto, 2000	[26]
	1309–1324	Ficari, 2000	[27]
	1309	Caspari, 1994; Gebert, 1999; Friedl, 2001; Bertario, 2003	[29,30,13,27]
Intermediate	157–1416	Walon, 1997	[28]
	170–1578 (except 1309)	Friedl, 2001	[13]
	179–625	Giardiello, 1997	[34]
	181–1110	Enomoto, 2000	[26]
	208–232	Ficari, 2000	[27]
	213–1249	Nagase, 1992; Bertario, 2003	[22,27]
	414–423	Gebert, 1999	[30]
	437–1114	Ficari, 2000	[27]
	491–1028	Michils, 2002	[31]
	1347–1474	Michils, 2002	[31]
	1465–1597	Nagase, 1992; Bertario, 2003	[22,27]
	1465	Enomoto, 2000	[26]
	1556	Ficari, 2000	[27]
Attenuated	Exons 3 and 4, 141–177	Spirio, 1993	[22]
	5′ 158	Giardiello, 1997	[34]
	5′ 168	Soravia, 1998	[32]
	157–175	Enomoto, 2000	[26]
	139–156	Friedl, 2001	[13]
	Exon 4	Moisio, 2002	[15]
	438–469	Spirio, 1993	[23]
	Exon 9	vd Luijt, 1995; Soravia, 1998	[36,32]
	398	Young, 1998	[37]
	386	Gebert, 1999	[30]
	363	Rozen, 1999	[38]
	367	Ficari, 2000	[27]
	332	Friedl, 2001	[13]
	1556–1627	Walon, 1997	[28]
	1860–1862	vd Luijt, 1996	[35]
	1979	Brensinger, 1998	[24]
	2644	Brensinger, 1998	[24]
	2047	Soravia, 1998	[32]
	1596–2557	Friedl, 2001	[13]

confirmed a correlation between 5′ mutations and an AFAP phenotype [13,15,26,34].

The same variable, but in general attenuated phenotype is associated with 3′ mutations. Mutations beyond APC codon 1600 are relatively rare [12,13,24,28,32,35]. This may be caused by limitations of the current methods for mutation detection.

The third region which is associated with AFAP is the alternatively spliced site of exon 9 (codon 312–412) [13,23, 27,30,32,36–38]. Despite the consistent relation between this exon 9 mutation and mild disease, intrafamilial phenotypic variability has been reported [36,38]. Furthermore, the attenuated phenotype seems not to be restricted to the alternatively spliced region of exon 9, as it was observed in two kindreds with different mutations within exon 9, but located outside the alternatively spliced region [32].

Although AFAP patients have milder disease, starting later in life, it should be realized that colorectal cancer was frequently found in these families, even among patients with few polyps [33,35,37].

4. Extracolonic manifestations

The majority of FAP patients (over 70%) develop extracolonic manifestations [27]. Most extracolonic manifestations have little clinical significance, but some lesions can cause serious complications and even lead to death.

Estimated prevalences of a number of extracolonic manifestations are listed in Table 3. The occurrence of extracolonic manifestations often will not be noted by the gastroenterologist treating the FAP patient, particularly in case of benign lesions, so exact prevalences are not known.

The most common extracolonic manifestation is congenital hypertrophy of the retinal pigment epithelium (CHRPE). The presence of these benign and asymptomatic retinal lesions can be used in identifying asymptomatic carriers in FAP families without a known APC mutation [30,39].

Other benign lesions include osteomas, dental abnormalities, epidermoid cysts and lipomas. These lesions are often present many years before colorectal polyps develop, but may also occur in individuals without FAP [39].

Table 3
Prevalence of extracolonic manifestations in FAP patients (Vasen [4], Bertario [27])

Extracolonic manifestations	Prevalence (%)
CHRPE[a]	70–75
Osteoma and dental abnormalities	70–90
Upper GI tumours	
Duodenal adenoma	50–90
Fundic gland polyposis	40–50
Gastric antrum adenoma	5–20
Epidermoid cysts and lipoma	25–50
Desmoids	10–15
Other malignancies	
Thyroidcarcinoma, hepatoblastoma, brain tumours	3

[a] Congenital hypertrophy of the retinal pigment epithelium.

Although desmoid tumours are histologically benign, they contribute significantly to morbidity and mortality rates in FAP. These locally invasive tumours cause obstruction and perforation of surrounding structures. Recurrence rate after excision is high [40]. The development of desmoids has been linked to surgical trauma and to a strong family history of desmoids [41].

A large number of FAP patients develop upper gastrointestinal polyps. They include benign fundic gland polyps, potentially malignant duodenal polyps and gastric adenomas, which are very rare. Dysplastic duodenal polyps occur 10–20 years after colorectal polyp development and tend to be concentrated in the second part of the duodenum in the peri-ampullary region. The risk of developing duodenal carcinoma in FAP is between 1% and 5% [39].

As is typical with hereditary cancer syndromes, there is an increased risk for other malignancies, including thyroid cancer, hepatoblastoma and brain tumours [4].

4.1. Genotype–phenotype correlations

Genotype–phenotype correlations of extracolonic manifestations in FAP reported in the literature are shown in Table 4. Desmoids and upper gastrointestinal tumours are clinically most important, because these lesions are common and cause serious morbidity and even mortality in FAP patients. Clinical relevance of the other extracolonic manifestations, except CHRPE, is limited and genotype–phenotype correlations have not been well established.

Table 4
Extracolonic manifestations in FAP and reported sites of mutation

Extracolonic manifestations	Codon no.	Authors, year	References
CHRPE	311–1444	Davies 1995	[43]
	413–1387	Caspari 1995	[42]
	542–1309	Giardiello 1997, Bertario 2003	[34,27]
	473–1307	Walon 1997	[28]
	446–1338	Gebert 1999	[30]
	564–1465	Enomoto 2000	[26]
Desmoid tumours	1924, 1962	Eccles 1996, Scott 1996	[44,46]
	1445–1578	Caspari 1995	[42]
	1444–1560	Davies 1995, Gebert 1999	[43,30]
	1403–1987	Dobbie 1996, Heinimann 1998, Moisio 2002	[45,47] [15]
	1395–1493	Wallis 1999	[48]
	1310–2011	Bertario 2003	[27]
Upper gastrointestinal polyps	1445–1578	Caspari 1995	[42]
Fundic gland polyposis	No correlation	Enomoto 2000	[26]
	1924	Eccles 1996	[44]
Gastric adenomas	1403–1987	Dobbie 1996	[45]
	Exon 4, exon 15	Soravia 1998	[32]
	1395–1493	Wallis 1999	[48]
	564–1465	Enomoto 2000	[26]
Duodenum adenomas	1403–1987	Dobbie 1996	[45]
	Exon 4, exon 15	Soravia 1998	[32]
	1395–1493	Wallis 1999	[48]
	564–1465	Enomoto 2000	[26]
	976–1067	Bertario 2003	[27]
Multiple extracolonic manifestations	3′ 1445	Casparie 1995	[42]
	3′ 1403	Dobbie 1996, Heinimann 1998	[45,47]
	1465, 1546, 2621	Giardiello 1997	[34]
	1556	Walon 1997	[28]
	1979	Brensinger 1998	[24]
	976–1067, 1310–2011	Bertario 2003	[27]

4.1.1. CHRPE

The occurrence of CHRPE is related to a clearly distinct region of the APC gene. In 1995, it was observed that CHRPE appeared to be restricted to families with mutations between codon 311 and codon 1444 [42,43]. This observation was confirmed by several investigators, who associated mutations between codon 311 and codon 1465 with a variable but generally high risk of CHRPE [26–28,30,34].

Giardiello et al. [34] supposed that the presence of CHRPE can guide genetic analysis to reduce costs and this was confirmed by Gebert et al. [30]. He used the CHRPE status to direct mutation analysis to a specific region of the APC gene. He concluded that this combined molecular and clinical screening was an efficient strategy for identifying APC germline mutations.

4.1.2. Desmoids

In 1996, a family in which multiple desmoid tumours were inherited in the absence of the colonic features of FAP was described [44]. An APC mutation at codon 1924 was responsible for this condition. The occurrence of desmoids in FAP has been linked to mutations at the 3′ end of the APC gene, in general downstream codon 1400 [15,27,30,42,43,45–49]. This correlation does not always appear to be consistent [24,25,34]. Mutations beyond codon 1400 are often associated with multiplicity of extracolonic manifestations [24,27,28,34,42,43,45,47].

4.1.3. Upper gastrointestinal tumours

Upper gastrointestinal tumours are common in classical FAP as well as in attenuated FAP. Several locations at the APC gene have been related to upper gastrointestinal polyps. Some studies suggested mutations at the 3′ end, beyond codon 1395 [27,42,45,48], but also exon 4 [32] and codons 564–1465 [26] seem to be associated with gastric and duodenal polyps. Two studies found a high risk for duodenal adenomas beyond codon 934 [26,27].

However, no large study has been performed and the existence of an association between germline APC genotype and the severity of upper gastrointestinal polyposis is controversial [13,50].

5. Discussion

Over the past decades, several genotype–phenotype correlations in FAP were reported. Based on these studies, we have categorized the phenotypes according to severity of the polyposis and the associated site of mutation on the APC gene (Fig. 2). The attenuated phenotype (<100 colorectal polyps) is restricted to mutations before codon 157, after codon 1595 and in the alternatively spliced region of exon 9 [28,34]. A profuse phenotype (thousands of polyps) is associated with mutations from codons 1250 to 1464 [22,24]. An intermediate phenotype (100–1000 polyps) is linked to the remainder of the gene. With regard to extracolonic manifestations, the occurrence of CHRPE seems to be restricted to codons 311–1444 [42] and desmoids generally are related to mutations beyond codon 1444 [42,43]. Upper gastrointestinal tumours often occur in relation to mutations beyond codon 1395 [27,32,42,45,48], but are also described in other regions of the APC gene [26,32].

The understanding of the APC gene and its function is limited to date. APC has been defined as a tumour suppressor gene. In Fig. 2, the known functional domains of the APC gene and the corresponding FAP phenotypes are shown. The heptad repeats play a role in controlling cell adhesion and motility. The β-catenin and DNA binding regions function as a negative regulator of β-catenin levels, thereby controlling genes involved in cell-cycle entry and progression. The

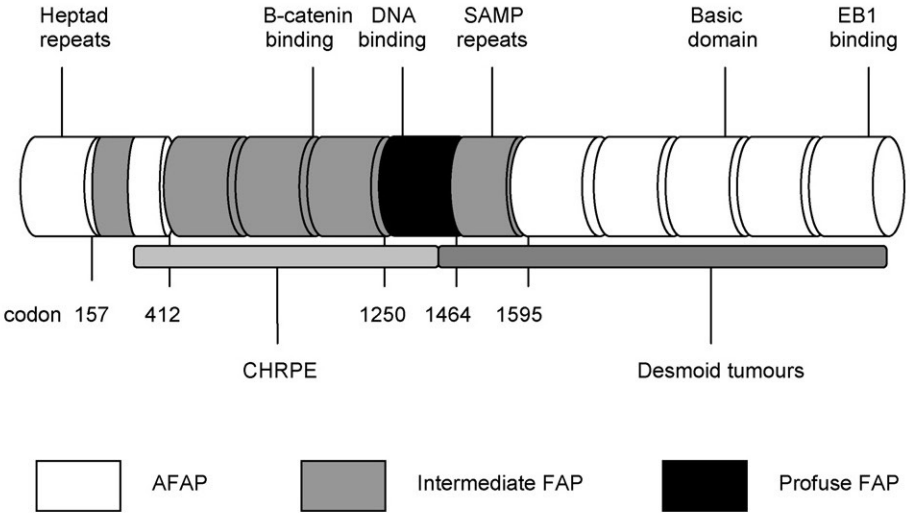

Fig. 2. The APC gene, APC protein domains and FAP phenotype association with germline mutation position. All extracolonic manifestations can be associated with mutations anywhere in the APC gene, except for CHRPE and desmoid tumours, which are more likely to be associated with certain regions of the gene, but may also occur with mutations throughout the gene.

SAMP repeats mediate axin binding and the basic domain interacts with microtubules and is associated with cell migration and cell division [9]. The EB1 binding at the 5′ end is thought to maintain chromosomal stability at mitosis [8]. Although several models of APC function and corresponding phenotype have been developed, no single model explains all current data [9].

The following model is frequently used to explain the variability of FAP phenotypes: FAP patients inherit one germline mutation and in accordance to Knudson's two-hit hypothesis [10], a second hit is required before adenomas can develop. The type of germline mutation appears to determine the nature of the second hit to APC. Patients with germline mutations close to codon 1300 tend to acquire a 'second hit' by allelic loss, whereas patients with germline mutations distant from codon 1300 have truncating mutations. In case of allelic loss, no APC function is left and patients develop severe polyposis. Truncating mutations in the 5′ and 3′ area of the APC gene might cause only a slightly altered functionality by leaving a large part of the APC gene intact, thus resulting in more attenuated phenotypes [54]. The alternative splicing of exon 9 mutations may moderate the effect of the mutation by splicing out that part of the genetic message which contains the mutation [37]. No clear explanation can presently be offered for the genotype–phenotype correlations in extracolonic manifestations. It may be speculated that APC function or stability of truncated proteins vary in different tissues [42]. Another hypothesis is a two-hit mechanism at the APC locus, in which mutations in a specific region have a greater tendency to cause CHRPE or desmoids than do other inactivating APC gene mutations [43].

One should keep in mind that the site of mutation not exactly will predict a certain gene product and a subsequent phenotype. Although very general correlations can be established, inconsistencies and contradictions were reported [28,33,36,38] and they well emphasize the limitations of genotype–phenotype relationships. For example, a codon 1309 mutation does not necessarily result in a phenotype with an early disease onset and severe polyposis [30]. It is likely that additional genetic and environmental factors may play important roles in determining the colonic as well as the extracolonic manifestations [33]. Despite the fact that our intention was to be as complete as possible, the problem of selection was inevitable. We excluded case-reports as well as studies describing few patients.

The known relationships between the site of mutation and expression of disease may have important implications in directing genetic testing [30,34]. Moreover, genotype–phenotype correlations may be used in decisions concerning management of FAP [51,52]. For example, a patient presenting with profuse polyposis in childhood should have mutation screening directed primarily toward codon 1309 [30]. Surveillance in at risk family members of this patient should start in childhood because of an exceptionally early onset of symptoms among patients with a codon 1309 mutation [30]. If genotype–phenotype correlations are used for clinical practice, they should always be used in combination with clinical data. Vasen et al. [51] proposed that in the decision making on prophylactic colectomy in FAP the genotype should be included: patients with a mutation after codon 1250 were shown to be at high risk of rectal excision and rectal cancer after ileorectal anastomosis (IRA) and were advised to have an ileal pouch-anal anastomosis (IPAA) procedure. This strategy has been criticised by Evans et al. [53] because of the inclusion of patients with a 3′ end mutation in the high-risk group of secondary proctectomy. In this review, we have refined the boundaries within the APC gene. Wu et al.[52] also recommended patients with a codon 1309 or 1328 mutation to undergo IPAA, because of their severe phenotype and the poor prognosis for retaining the rectum. Soravia et al. recommended genetic testing to be added to the surgical armamentarium, assisting in surgical decision making for FAP [55]. In contrast to these reports, Bertario et al. [56] observed no difference in survival probability among four groups of patients, divided according to the mutation site. However, in these series, families exhibiting the AFAP phenotype were not considered. Especially, in patients with AFAP the phenotype may be variable. Because rectal cancer after IRA is rarely observed in AFAP patients, such type of operation is the procedure of first choice in those patients with a mutation associated with AFAP. Friedl et al. [13] observed consistent correlations between the APC mutation site and FAP phenotype in a large series of 680 FAP patients, but also described a wide variation in patients with the same mutation. They recommended that clinical decisions regarding the individual patient should not be based on the genotype, but on the colonic phenotype. However, for the subset of patients with mutations after codon 1445 postponement of prophylactic colectomy was advised [13], in view of the high risk of desmoid tumours after surgery. Genetic testing as well as the family history of desmoid tumours will be helpful in identifying patients at high risk of desmoids. CHRPE are associated with a specific APC region, containing codons 311–1444. Although CHRPE are benign and asymptomatic and do not have clinical significance, they may be helpful in detecting high risk family members if genetic testing is not conclusive. Upper gastrointestinal tumours cannot be attributed to a specific APC region.

In summary, our study proposes a division of the APC gene, according to the severity of FAP and extracolonic manifestations. Based on current knowledge, the attenuated FAP phenotype generally is restricted to mutations at the beginning and end of the APC gene and the alternatively spliced region of exon 9. The classical phenotype is related to mutations in the middle part of the APC gene, with profuse polyposis between codons 1250 and 1464. It should be noted that all extracolonic manifestations can be associated with mutations anywhere in the APC gene, except for CHRPE lesions, which are mutation-location specific, and desmoid tumours, which are more likely to be associated with certain regions of the gene, but may also occur with mutations throughout the APC gene.

Genotype–phenotype correlations will be useful in genetic testing, surveillance and treatment of FAP patients. If they are used for clinical practice, they should always be used in combination with clinical data. Further investigations are warranted and particularly duodenum adenomas have to be studied, for they are common in FAP patients and responsible for part of the mortality in FAP.

Reviewers

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Chapter 3

Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis

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Genotype-Phenotype Correlations as a Guide in the Management of Familial Adenomatous Polyposis

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Background & Aims: **The options for prevention of colorectal cancer in familial adenomatous polyposis are either a colectomy with ileorectal anastomosis (IRA) or a total proctocolectomy with ileal pouch–anal anastomosis (IPAA). Rectal cancer risk is eliminated by IPAA, but complication rate is higher than in IRA. Mutation analysis might predict severity of polyposis and be helpful in the surgical decision.** ***Methods:*** **Patients from the Dutch Polyposis Registry with an IRA were subdivided according to the site of adenomatous polyposis coli gene mutation into the attenuated (1), intermediate (2), and severe (3) genotype groups. Cumulative risks of secondary rectal excision and rectal cancer were calculated for each group.** ***Results:*** **A total of 174 patients underwent an IRA: 26 patients from group 1, 121 from group 2, and 27 from group 3. Cumulative risks of rectal cancer 15 years after surgery were 6%, 3%, and 8% in groups 1, 2, and 3, respectively. Cumulative risks of rectal excision 20 years after IRA were 10%, 43%, and 74%, respectively. The risk of rectal excision was significantly higher in group 3 than in the other groups ($P < .05$).** ***Conclusions:*** **The risk of secondary rectal excision after IRA can be predicted on the basis of the adenomatous polyposis coli mutation site. An IRA appears to be the appropriate treatment in patients with the attenuated genotype. Patients with a severe genotype are good candidates for an IPAA.**

Familial adenomatous polyposis (FAP) is a cancer predisposition syndrome in which patients develop hundreds to thousands of adenomas in the colorectum. Without surgical resection of the colon, patients inevitably develop colorectal cancer before the age of 45 years.[1] Although FAP classically manifests this way, it is now well-recognized that disease expression varies from mild disease with few colorectal adenomas (attenuated FAP [AFAP]) to profuse polyposis with thousands of colorectal adenomas. A substantial proportion of patients develop extracolonic manifestations like desmoids and upper gastrointestinal tumors.

FAP is caused by germline mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21-q22[2,3] and is transmitted in an autosomal dominant fashion. Since the identification of the gene, several correlations between the site of mutation in the APC gene and the FAP phenotype have been described.[4,5] Three phenotypes can be distinguished: a severe form of FAP, which is associated with mutations located in a region between codons 1250–1464; an AFAP phenotype, associated with mutations at the extreme ends of the APC gene and in the alternatively spliced site of exon 9; and an intermediate expression of disease, which is found in patients with mutations in the remaining part of the gene.[4] With the current techniques, a germline APC mutation is found in 50%–70% of FAP patients,[6,7] suggesting that the polyposis syndrome might be genetically heterogeneous. Management of FAP consists of periodic screening by sigmoidoscopy, starting at an age between 10–12 years. To prevent the development of colorectal cancer, a prophylactic colectomy is usually performed during the second or third decade of life. A colectomy with ileorectal anastomosis (IRA) is an attractive surgical option because of its good functional outcome and low complication rate.[8] Disadvantages are the need for continuous endoscopic follow-up and the possible need for secondary proctectomy because of unmanageable polyps or rectal cancer. The alternative surgical option is total proctocolectomy with ileal pouch–anal anastomosis (IPAA), by which rectal cancer development can be almost avoided. An IPAA is the treatment of choice if patients have a large number of rectal adenomas,[9–11] or if the patient will not comply with follow-up examinations after IRA. However, in a subset of patients the clinical data will not help to make a decision. For example, a 30-year-old patient from a family with attenuated polyposis presents with multiple colonic and rectal adenomas. Should an IPAA be performed in such a case, with a substantial risk of complications,[12] or should an IRA be advised, with the probability of rectal excision later in life? What type of surgery should be performed in a 20-year-old patient with hundreds of colonic adenomas and only a few rectal polyps, from a family with a severe polyposis phenotype? In these cases, mutation analysis might offer a more rational basis for the surgical decision.[13,14]

The aims of this study were to investigate the cumulative rectal cancer risk and the cumulative risk of rectal excision after

Abbreviations used in this paper: AFAP, attenuated familial adenomatous polyposis; APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis.

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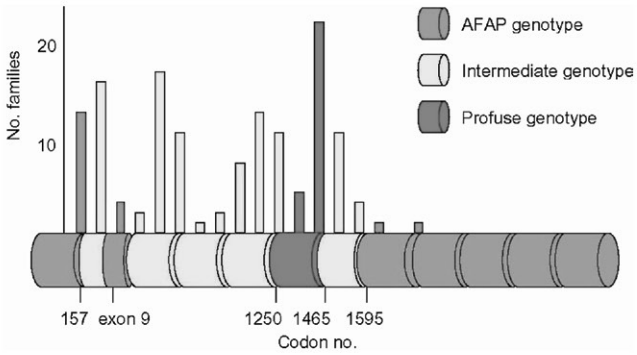

Figure 1. Distribution of APC mutations in 138 Dutch FAP families.

IRA in 3 subgroups of FAP patients, classified according to the APC genotype.

Methods

In 1985 the Netherlands Foundation for the Detection of Hereditary Tumours was established. From 1985–2005, 315 FAP families were enrolled in this Dutch Polyposis Registry. The main objective of the registry was to promote surveillance of the gastrointestinal tract in FAP families.

For the present study, all patients who had a colectomy and an IRA were selected from the FAP families with a known APC mutation. Data were collected on the location of the mutation, age at diagnosis of FAP, number of rectal polyps at the time of IRA, age at surgery, age at diagnosis of colorectal carcinoma, duration of follow-up, and the number of patients with rectal carcinoma and rectal excision after IRA, because of uncontrollable polyps or rectal cancer. Uncontrollable polyps includes conditions in which endoscopic polypectomy is very difficult or impossible, for example, large numbers of adenomas more than 5 or 10 mm in diameter, the presence of high-grade dysplasia in several adenomas, and the presence of high-grade dysplasia in a sessile adenoma that is difficult to remove.

The APC-positive patients who underwent IRA were subdivided into 3 groups according to the site of mutation in the APC gene.[4] In group 1, patients with mutations before codon 157, beyond codon 1595, and in the alternatively spliced site of exon 9 (codons 312–412) were included. These mutations are correlated with the AFAP phenotype.[4] In group 2, patients with mutations from codon 158–1249 and codon 1465–1594 were included. This region is reported to be associated with intermediate polyposis.[4] Patients with mutations between codons 1250–1464, correlated with a severe phenotype,[4] were included in group 3. If the mutation was a large deletion or a splice site defect, the patient was excluded from analysis. In these cases, remaining protein function and subsequent phenotype cannot be predicted.

For risk assessment, patients who underwent an IRA were studied with respect to their risk of developing rectal cancer or requiring excision of their rectum. The Kaplan-Meier estimate was chosen to calculate the cumulative risks of rectal excision and rectal cancer. Observation time was from the time of primary surgery (IRA) up to the date of last contact, death, date of diagnosis of rectal cancer, date of rectal excision, or closing date of the study (January 1, 2005). Differences among groups were tested by using the log-rank test. Statistical significance was considered at the $P < .05$ level.

Results

In the Dutch Polyposis Registry, data collection was complete on 315 FAP families. APC mutations were detected in 138 (43.8%) families. In Figure 1, the distribution of mutations in the APC gene is shown.

The study group comprised 174 patients who had an IRA between 1956–2004. The mean duration of follow-up after IRA was 13.8 years (range, 0–48 years). On the basis of the site of APC mutation, 26 patients were included in group 1, 121 in group 2, and 27 in group 3. Mean age at diagnosis and mean age at first surgery for these groups are displayed in Table 1. In addition, Table 1 shows the number of patients requiring rectal excision and the number of rectal cancers after IRA per mutation group. A total of 68 (39%) patients needed rectal excision because of rectal cancer or uncontrollable polyps. Twelve (7%) patients developed rectal cancer after IRA.

The cumulative risks of rectal excision after IRA are shown in Figure 2. For group 1, cumulative probability of rectal excision was 9.5%. For group 2, the risks of rectal excision 5, 10, 15, and 20 years after IRA were 8.5%, 20%, 34%, and 43%. For group 3, these risks were 15%, 38%, 61%, and 74%, respectively. The cumulative risk of rectal excision by years of follow-up after surgery was significantly higher in group 3, compared with group 1 and group 2 ($P = .0007$).

Figure 3 shows the risk of rectal cancer after IRA. At 5 and 15 years after IRA the cumulative risks were 0% and 5.9% for group 1, 2.5% and 3.5% for group 2, and 0% and 8.3% for group 3, respectively ($P = .2397$).

Table 1. Number of Patients and Mean Age (Range) at Diagnosis of FAP, First Surgery, Rectal Excision, and Rectal Cancer for Each Mutation Group and the Total Study Group

Mutation group, genotype	Group 1,[a] attenuated	Group 2,[b] intermediate	Group 3,[c] severe	Total
No. patients included	26	121	27	174
Age at diagnosis FAP	43.7 (23–68)	23.9 (10–49)	16.6 (6–35)	25.8 (6–68)
Age at first surgery	44.7 (23–68)	24.5 (10–56)	17.0 (6–32)	26.4 (6–68)
No. rectal excisions	2	48	18	68
Age at rectal excision	55.5 (46–62)	36.8 (20–63)	29.6 (12–57)	35.5 (12–63)
No. rectal cancers	1	7	4	12
Age at rectal cancer	62	51.7 (35–63)	34.3 (31–36)	46.7 (31–63)

[a]Codons 1–157, 312–412, 1596–end.
[b]Codons 158–1249, 1465–1595 excluding splice site mutations exon 9.
[c]Codons 1250–1464.

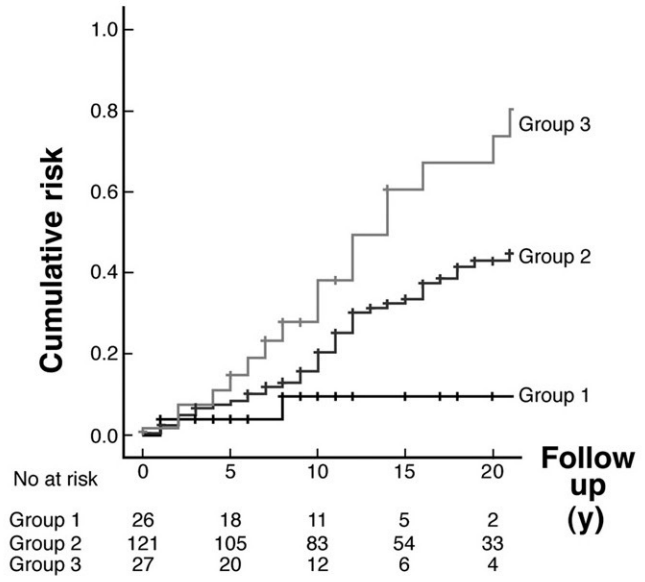

Figure 2. Cumulative risk of rectal excision until 20 years after IRA, per mutation group. Log rank $P = .0007$.

In Table 2, for patients with attenuated and severe genotypes the rectal phenotype at the time of primary surgery as well as the age at primary surgery is displayed. We found that most patients from group 1 (AFAP gentoype) had indeed a mild rectal polyposis with no or a few adenomas, and a minority (4 of 26) had multiple adenomas or carpeting of the rectum. None of the latter 4 patients needed a secondary proctectomy 31, 15, 15, and 3 years after IRA. In the patients from group 3 (severe genotype), 9 patients had carpeting of adenomas in the rectum. The remaining patients had multiple adenomas (4 cases) or only a few adenomas (8 cases) in the rectum. Eight of these 12 cases required a secondary proctectomy 5-26 years after primary surgery.

Discussion

The surgical choice between IRA and IPAA is a major dilemma in the management of FAP. In this study, we demonstrated that the risk of rectal excision after IRA is largely determined by the site of the APC mutation. Patients with a mutation between codons 1250-1464 are at high risk of rectal excision after IRA, even those patients with mild rectal polyposis preoperatively. In patients with the intermediate phenotype the rectal cancer risk is relatively low. However, 43% of these patients required rectal excision until 20 years after the primary IRA. Only 2 patients with the AFAP phenotype needed secondary rectal excision because of rectal cancer or uncontrollable polyposis.

Among the surgical options for patients with FAP, the most attractive option seems to be an IRA. This is a relatively simple procedure with a low complication rate and little disturbance of bowel function.[15,16] However, adenomas will almost always develop in the remaining rectum, and these might eventually become malignant. The alternative surgical option is an IPAA, which is considered to be safe, because the rectal cancer risk is virtually eliminated by nearly complete removal of the rectal mucosa. However, postoperative complication rate is considerable,[17] and functional outcome is less compared with an IRA procedure.[8] In more than 5% of the cases, the pouch has to be removed and replaced by an ileostomy as a result of complications.[12] Moreover, follow-up of the pouch is needed because adenomas and even carcinomas might develop.[18,19] On the basis of these considerations we would reserve the IPAA procedure for patients with severe rectal polyposis and a high rectal cancer risk.

In the present study, patients were categorized according to the site of the APC gene mutation. We found that in patients with a severe genotype (group 3), the ages at diagnosis of FAP and the first surgery were about 27 years earlier compared with those of group 1 (attenuated genotype). The patients of group 3 were also at high risk of rectal excision after IRA. Eighteen of 27 patients needed secondary proctectomy, 8 of them despite a relatively mild rectal phenotype before surgery. Most of these patients underwent 2 operations at a young age (age <30 years), which had undoubtedly interfered with their social lives and careers. For these reasons, an IPAA is advised as the primary procedure in patients with the severe FAP genotype. On the other hand, the majority of patients of groups 1 and 2 have retained their rectum until 20 years after IRA. Also the risk of rectal cancer was low in both groups. For most of those patients, an IRA seems to be a safe option. However, 43% of the patients with the intermediate genotype (group 2) will need rectal excision, on average 11 years (range, 0-40 years) after IRA. If patients do not accept the perspective of secondary surgery, an IPAA should be considered as primary surgery.

In previous studies, the use of genetics in surgical decisions has been discussed.[13,14,20,21] Almost a decade ago, we[13] proposed to perform an IRA in patients with mutations before codon 1250 and an IPAA in those with mutations after this codon. This view was criticized by Evans et al.[22] They argued that because of variable degrees of severity of polyposis in patients with mutations beyond codon 1440, patients with these mutations should be distinguished from those with mutations be-

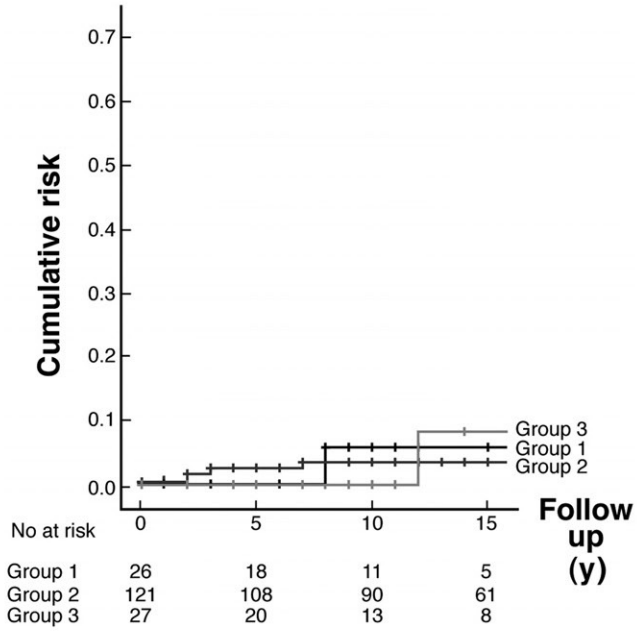

Figure 3. Cumulative risk of rectal cancer until 15 years after IRA, per mutation group. Log rank $P = .2397$.

Table 2. Severity of Rectal Polyposis at the Time of Surgery and the Need for Rectal Excision in Patients From the AFAP and Severe Genotype

AFAP genotype group				Severe genotype group			
Patient no.	No. rectal polyps*	Age IRA (*y*)	Age rectal excision (*y*)	Patient no.	No. rectal polyps*	Age IRA (*y*)	Age rectal excision (*y*)
1	Few	68		1	Few	24	30
2	None	39		2	na	15	19
3	Few	44		3	Carpeting	14	35, CA
4	Few	53		4	na	12	12
5	None	34		5	Carpeting	22	38
6	None	50		6	na	9	
7	None	38		7	na	12	14
8	None	25		8	Few	31	57
9	Multiple	35		9	Multiple	16	30
10	Few	23		10	Carpeting	17	
11	None	42		11	na	8	32, CA
12	None	34		12	Carpeting	21	35
13	Few	62		13	Carpeting	17	24
14	None	64		14	Multiple	17	22
15	Multiple	45		15	Carpeting	7	
16	Carpeting	37		16	Few	12	
17	na	60		17	Few	16	
18	Few	31		18	Multiple	26	46
19	None	54	62, CA	19	Carpeting	21	31
20	Carpeting	55		20	Few	17	
21	Few	59		21	Carpeting	8	
22	Few	29		22	Few	18	28
23	None	48	49	23	na	18	
24	Few	45		24	Carpeting	19	27
25	Few	44		25	Multiple	6	18, CA
26	None	43		26	Few	24	36, CA
27				27	Few	32	

None, 0 polyps; Few, 1–5 polyps; Multiple, 6–15 polyps; Carpeting, >15 polyps; na, information not available; CA, rectal cancer.

tween codons 1250–1440. Since the first articles on this issue,[13] knowledge on genotype-phenotype correlations has been increased significantly. Most studies confirm that mutations from certain regions of the APC gene correlate well with a specific phenotype, and this has led to refining the boundaries within the APC gene.[4]

Although Friedl et al[6] showed consistent correlation between the site of mutation in the APC gene and severity of intestinal polyposis, they recommended not to use genetic information for the individual patient because of phenotypic variation, even among patients with identical germline mutations. We agree that intrafamilial variation might occur, but it can be confidently stated that as shown in the present study, on average, patients with mutations in the region between codons 1250–1464 have a higher risk of rectal excision than patients with a mutation elsewhere, and second, patients with the AFAP genotype have, on average, a very low risk of secondary surgery. Because making a decision between the 2 surgical options might be difficult in some patients, we believe that all information, including the results of genetic testing, should be used.

In conclusion, we propose to use the outcome of mutation analysis in FAP patients to support the surgical decision between IRA and IPAA. Regarding the high risk of secondary rectal excision after IRA in patients with a mutation between codons 1250–1464 of the APC gene, an IPAA is advised for patients with these mutations, which predict the severe FAP phenotype. An IRA will be a safe option for most patients with the intermediate and AFAP phenotypes, predicted by mutations in the remainder of the APC gene. Of course, after the patient has been fully informed about the natural history of the disease and the pros and cons of the main surgical options, the final decision lies with the patient.

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Chapter 4

Genotype predicting phenotype in familial adenomatous polyposis: a practical application to the choice of surgery

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ORIGINAL CONTRIBUTION

Genotype Predicting Phenotype in Familial Adenomatous Polyposis: A Practical Application to the Choice of Surgery

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PURPOSE: Genetic information may help preoperatively select patients with familial adenomatous polyposis for either colectomy with ileorectal anastomosis or proctocolectomy with ileal pouch–anal anastomosis. Although complicated, the latter procedure has a low long-term risk of rectal cancer.

METHODS: Data were obtained from four national polyposis registries. On the basis of previously described genotype-phenotype correlations, patients were divided into three genotype groups predicting attenuated, intermediate, and severe polyposis phenotypes. Cumulative risks of secondary proctectomy and rectal cancer after primary colectomy were calculated using the Kaplan-Meier method.

RESULTS: Four hundred and seventy-five polyposis patients with a previous colectomy were included. Cumulative risks of secondary proctectomy 20 years after primary colectomy were 10%, 39%, and 61% in the attenuated, intermediate, and severe genotype groups, respectively ($P < 0.05$, groups compared separately). Cumulative risks of rectal cancer after primary colectomy were 3.7%, 9.3%, and 8.3%, respectively, in the three groups ($P > 0.05$, groups compared separately).

CONCLUSION: Mutation analysis may be used to predict the risk of secondary proctectomy after primary colectomy in familial adenomatous polyposis. Patients with severe genotypes have a high risk of reoperation after primary colectomy and will benefit from primary proctocolectomy with ileal pouch–anal anastomosis. The risk of rectal cancer after primary colectomy was not significantly different between the three groups.

KEY WORDS: Adenomatous polyposis coli; Colorectal surgery; Proctocolectomy; Restorative surgery.

Familial adenomatous polyposis (FAP) is an autosomally dominant inherited disease, characterized by the development of hundreds to thousands of adenomatous polyps in the colorectum of affected patients. Without treatment, the risk of colorectal cancer is nearly 100% before age 50. Furthermore, in FAP patients extracolonic manifestations are observed, comprising benign tumors of connective tissue and bones, desmoid tumors, adenomas of the upper gastrointestinal tract, and duodenal cancer.[1,2]

The majority of patients harbor a causative mutation in the adenomatous polyposis coli (*APC*) gene, a tumor suppressor gene located on chromosome five.[3,4] Occasionally, mutations in the *MUTYH* gene (chromosome one) are found to cause a similar phenotype termed MUTYH-associated adenomatous polyposis. Since the detection of the *APC* gene, it has become clear that the site of mutation is correlated with the severity of colorectal polyposis. According to the literature, three degrees of polyposis severity can be distinguished: the attenuated, intermediate, and severe phenotype, which are correlated with genotypes as

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follows: Mutations at the 5′and 3′ ends of the gene and the alternatively spliced site of exon 9 are correlated with attenuated FAP, defined as less than 100 polyps in the colorectum. Mutations between codons 1250 and 1464 predict a severe polyposis phenotype, with very young patients developing thousands of colorectal polyps. Mutations in the remainder of the *APC* gene correspond with the intermediate FAP phenotype, characterized by the development of hundreds of colorectal adenomas, generally from the second decade of life.[5] Recently we reviewed all large studies describing genotype-phenotype correlations and proposed a classification of FAP genotypes and corresponding phenotypes, based on above-mentioned information.[5] This classification is shown in Table 1.

Management of FAP includes surveillance of FAP patients and their family members. Mutation analysis can be used to identify carriers of an *APC* gene mutation. Screening of the colorectum by biannual sigmoidoscopy is recommended from early puberty.[6] To prevent the development of colorectal cancer, a prophylactic colectomy has to be performed, generally before age 25. The two main surgical options are a subtotal colectomy with ileorectal anastomosis (IRA) and a proctocolectomy with ileal pouch–anal anastomosis (IPAA).[7] An IRA is a relatively simple and straightforward procedure compared with IPAA; complications occur rarely, and functional outcome is generally good.[8] However, multiple adenomas or even rectal carcinoma may develop in the remaining rectum, requiring a secondary proctectomy. After an IPAA the risk of carcinomas derived from remaining rectal mucosa or from ileal mucosa is very low. However, adenomas may develop in the pouch.[9] Furthermore, for the IPAA procedure more extensive surgery is needed, posing a risk of serious complications like pelvic sepsis and fistula, leading to a high risk of reoperation,[10] fecal incontinence,[10] and reduced fertility.[11] Also, functional outcome after IPAA is inferior to that after IRA.[12]

In practice, patients suffering from severe colonic polyposis with many rectal adenomas will opt for an IPAA. For patients with mild rectal polyposis, the surgical decision is difficult. Moreover, the choice has to be made by young adults in a critical period of life. Several authors have previously suggested the use of genetic information to triage patients preoperatively according to their risk of developing rectal cancer.[8,13] However, the studies dealing with this issue comprised only small series of patients, until now.[14–16]

In the present study, we investigated the possibility of applying genetic knowledge to support surgical decision-making in a large cohort of FAP patients from the Dutch and three Scandinavian polyposis registries.

TABLE 1. Classification of adenomatous polyposis coli genotypes with the site of mutation and corresponding familial adenomatous polyposis phenotypes[5]

Genotype	*Codon no.*	*Estimated no. of polyps*	*Age of onset*
Attenuated	1–157 312–412 1596–2843	<100	Fourth and fifth decades
Intermediate	158–311 413–1249 1465–1595	Hundreds	Second and third decades
Severe/profuse	1250–1464	Thousands	First and second decades

PATIENTS AND METHODS

Information was obtained from the National Polyposis Registries of The Netherlands, Denmark, Finland, and Sweden. Over the past decades, data were collected prospectively and processed comparably by those registries, and results have been published previously.[17]

FAP patients with a known *APC* mutation (or with an *APC* mutation identified in the family) who had had a colectomy and an IRA were selected for this study. Patients with splice-site defects other than the alternatively spliced site of exon 9 or large deletions of the *APC* gene were excluded from analysis because genotype-phenotype correlations could not be clearly determined in these groups.

Mean ages of patients at the time of primary IRA, secondary proctectomy, and diagnosis of rectal cancer were calculated. The cohort was subdivided into three groups according to the site of mutation (classification in Table 1). This subdivision was based on a previous report, in which genotype-phenotype correlations in FAP were reviewed and classified.[5] For each group cumulative risks of secondary proctectomy and rectal cancer after primary IRA were calculated using the Kaplan-Meier method. End points were defined as either a secondary proctectomy, rectal cancer, death, or end date of the study. Differences in risk were determined by the log-rank test. The threshold of statistical significance was set at $P < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 12.0.1 (SPSS Inc., Chicago, IL).

Calculations were made separately for the periods before and after January 1, 1990, because the IPAA procedure was introduced around 1989. Studies have shown that after 1989, patients with less severe polyposis were selected for colectomy and ileorectal anastomosis with a lower risk of reoperation and rectal cancer.[18]

RESULTS

Four hundred and seventy-five patients from the Dutch (239), Danish (103), Finnish (88), and Swedish (45) polyposis registries met the inclusion criteria. Characteristics of the three genotype groups, predicting attenuated, inter-

TABLE 2. Number of patients and mean age (range) at primary ileorectal anastomosis, secondary proctectomy, and diagnosis of rectal cancer, by mutation group

	Mutation group[a]			
	1	*2*	*3*	*Total*
IRA				
n	58	362	55	475
Age (yr)	46 (17–76)	27 (7–69)	21 (6–56)	29 (6–76)
Proctectomy				
n	4	135	29	168
Age (yr)	58 (46–62)	40 (13–70)	29 (7–46)	39 (7–70)
Diagnosis of rectal cancer				
n	1	29	4	34
Age (yr)	62	49 (34–68)	35 (27–43)	48 (27–68)

IRA = ileorectal anastomosis.
[a]Group 1 (attenuated) = codons 1–157, 312–412, and 1596–2843; Group 2 (intermediate) = codons 158–311, 413–1249, and 1465–1595; Group 3 (severe) = codons 1250–1464.

mediate, and severe polyposis, are shown in Table 2. The 58 patients in the attenuated group had their primary IRA, on average, at age 46. Four patients (6.8%) of this group required a secondary proctectomy at a median age of 58 years. One rectal cancer (1.7%) was diagnosed in this group, at age 62. In the intermediate genotype group, 362 patients were included. They had their first surgical procedure at 27 years, and 135 (37%) needed a secondary proctectomy at a mean age of 40. Twenty-nine patients (8.0%) developed rectal cancer. Twenty-nine of 55 patients (53%) with the severe genotype had undergone two surgical procedures before age 30. Four patients from this group (7.3%) developed rectal cancer, all of them under age 43.

Figure 1 represents the cumulative risk of a secondary proctectomy after primary IRA. Twenty years after primary surgery the risks of a secondary proctectomy were 10%, 39%, and 61% in Groups 1 (attenuated), 2 (intermediate), and 3 (severe), respectively (Group 1 *vs.* 2, $P = 0.0106$; Group 1 *vs.* 3, $P = 0.0001$; Group 2 *vs.* 3, $P = 0.0051$). Figure 2 shows the cumulative risks of rectal carcinoma after IRA. Twenty years after IRA these risks were 3.7%, 9.3%, and 8.3% for Groups 1, 2, and 3, respectively ($P > 0.05$, calculated for each group separately).

Data were computed separately for the periods before and after January 1, 1990, and led to the same results.

DISCUSSION

In this study we demonstrate a practical approach to applying genetic information to the treatment decision in patients with FAP. To prevent the development of colorectal cancer, a colectomy has to be performed in FAP patients. Young and often asymptomatic patients have to choose one of the two main surgical options: an IRA, which has a relatively low risk of complications but the risk of a secondary proctectomy later in life, or an IPAA procedure, which has the risk of serious complications. Genetic information may be used to objectively support this complex

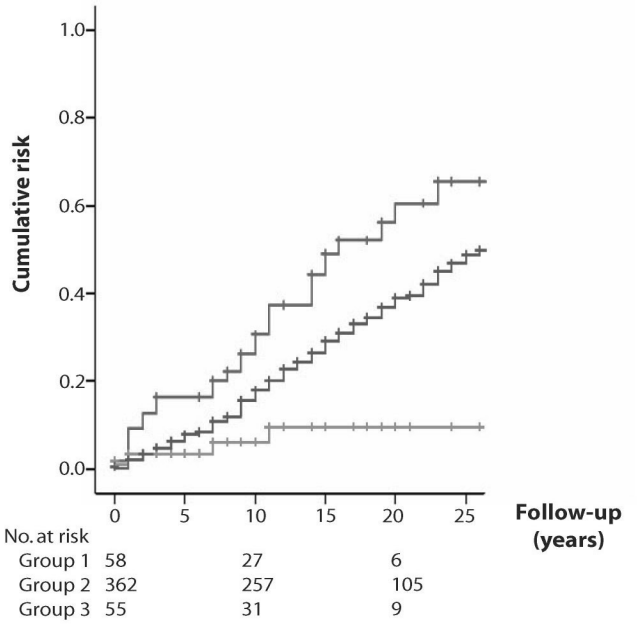

FIGURE 1. Cumulative risk of a secondary proctectomy after primary ileorectal anastomosis in patients with familial adenomatous polyposis with a genotype predicting an attenuated (Group 1, green), intermediate (Group 2, blue), or severe (Group 3, red) phenotype.

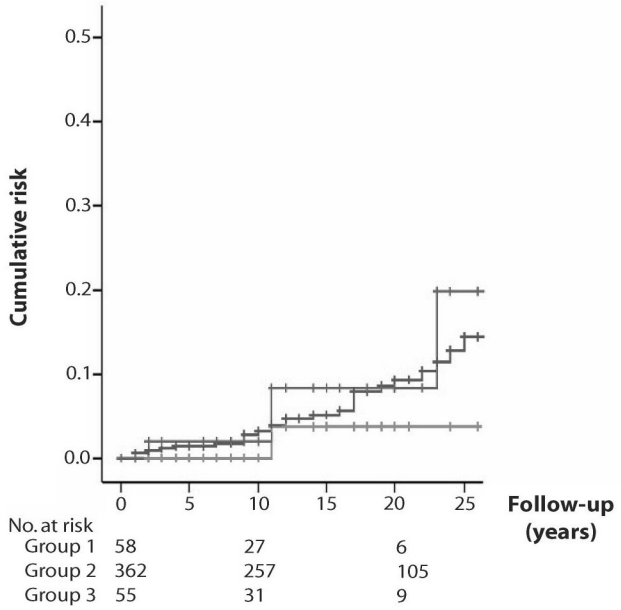

FIGURE 2. Cumulative risk of rectal cancer after a primary ileorectal anastomosis in patients with familial adenomatous polyposis with a genotype predicting an attenuated (Group 1, green), intermediate (Group 2, blue), or severe (Group 3, red) phenotype.

surgical decision. In the present international multicenter study, we show that patients with mutations predicting attenuated polyposis have a low risk (10%) of a secondary proctectomy after IRA, in contrast to patients with the severe genotype, who run a substantial risk of reoperation (61%) after IRA.

In 1996 Dutch investigators proposed the use of genetic information as a guide in the treatment decision for FAP.[14] However, at that time knowledge of genotype-phenotype correlations was limited.[19] With increasing genetic knowledge, further studies have been conducted,[15,16] although in relatively small cohorts of patients. The present study involved a large study cohort and patient data from the national polyposis registries of four countries.

The surgical choice for patients with FAP has been a subject of ongoing controversy in the literature. Several authors argue that an IPAA should be the standard surgical procedure for the majority of FAP patients.[20] Although functional outcome after IRA seems better than after IPAA,[10,12] no difference in quality of life was detected in a meta-analysis comparing these two surgical procedures.[10] However, the risk of serious complications like reduced fertility should be taken into consideration, especially since most FAP patients are young at the time of operation.[11] Moreover, after this procedure patients are still at risk for neoplasia, either arising from remaining rectal mucosa or in the pouch.[9] Current guidelines recommend an IRA in patients with no or only a few rectal polyps. For patients with severe colorectal polyposis, the IPAA procedure is the most attractive option.[7,17,18]

In practice, the rectal phenotype is not always conclusive, and the fate of the rectum after surgery cannot be predicted reliably. Ideally, patients at risk for a secondary proctectomy after IRA should be identified and advised to undergo IPAA as the primary procedure to avoid two surgical procedures. In the present study, we show that patients of diverse genotype groups run significantly different risks of a secondary proctectomy after IRA. Using this information, patients at high risk for secondary proctectomy can be identified. Genetic information never will substitute for major parameters such as the number of colonic adenomas and the rectal phenotype in determining the surgical choice, but it may add useful information. The combination of clinical and genetic parameters may help doctors and patients to make a well-defined surgical decision.

CONCLUSIONS

In conclusion, we have shown that for the majority of FAP patients with the attenuated genotype, an IRA is a safe option. Because of the high risk of a secondary proctectomy after IRA in patients with the severe genotype, an IPAA is advised as the primary procedure in those patients. Almost 40% of patients with the intermediate genotype needed reoperation. If IRA is chosen for a patient with the intermediate risk genotype, the patient should be well aware of the possibility that the rectum will have to be excised 20 to 25 years later. Therefore, the final choice of surgical procedure in the intermediate group should be based on a combination of clinical and genetic data, family phenotype, and patient preference.

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Chapter 5

Female fertility after colorectal surgery for familial adenomatous polyposis: A nationwide cross-sectional study

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Female Fertility After Colorectal Surgery for Familial Adenomatous Polyposis

A Nationwide Cross-sectional Study

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Background: Information on postoperative fertility problems in female patients with familial adenomatous polyposis (FAP) is scarce. Previous studies in FAP or colitis patients almost uniformly describe a reduction in fertility after ileal pouch-anal anastomosis, compared with ileorectal anastomosis.

Objective: To describe fertility problems in female FAP patients after colectomy and to investigate the relationship between self-reported fertility problems and the type of operation and other surgery-related factors (eg, comorbid conditions).

Methods: A questionnaire addressing surgery, fertility problems, and desire to have children was sent to a nationwide sample of FAP patients. Medical data were verified in the FAP-registry of the Netherlands Foundation for the Detection of Hereditary Tumors. Differences between women with and without fertility problems were investigated.

Results: Of 138 patients, 23 (17%) reported current or past fertility problems. The prevalence of fertility problems was similar among those who had undergone ileorectal anastomosis, ileal pouch-anal anastomosis, and proctocolectomy with ileostomy. None of the other surgery-related factors, nor desmoid tumors or cancer were associated significantly with the development of fertility problems. Patients reporting fertility problems were significantly younger at diagnosis of FAP (mean, 20 vs. 27 years, $P < 0.05$) and at the time of the first surgical procedure (mean, 22 vs. 28 years, $P < 0.05$).

Conclusions: The risk of developing postoperative fertility problems is not associated significantly with the type of surgery, indication for surgery, complications, or other comorbid conditions. Postoperative fertility problems are more common among women who had their first surgical procedure at a younger age.

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In familial adenomatous polyposis (FAP), patients develop multiple (>100) adenomas in the colon, beginning in the second decade of life. A subset of FAP patients also develops extracolonic manifestations including duodenal and gastric adenomas, duodenal cancer, desmoid tumors, osteomas, and rare malignancies.[1] Without treatment, there is a 100% risk of developing colorectal cancer. To prevent cancer, a prophylactic colectomy is performed at a mean age of 26 years.[2,3] The two main surgical options are a subtotal colectomy with ileorectal anastomosis (IRA) or a proctocolectomy with ileal pouch-anal anastomosis (IPAA).[4] The IRA is a relatively simple procedure with a good functional outcome. However, many patients need a secondary proctectomy later in life as a result of development of polyps or cancer in the remaining rectal mucosa. By performing an IPAA, the need for reoperation because of rectal polyps or rectal cancer is virtually eliminated.[5,6] However, compared with IRA, the IPAA procedure is a more complicated operation with worse functional outcome.[7] Moreover, sexual problems and reduced fertility rates have been reported after IPAA.[8–13] These are most often attributed to postoperative anatomic changes in the female pelvis.[12,14,15] However, most studies concerning postoperative fertility have focused on patients with inflammatory bowel diseases rather than FAP patients.

The aims of the present study were to describe postoperative fertility problems in female FAP patients and to investigate the association with the type of operation and various surgery-related factors.

METHODS

Data Collection

Participants were drawn from the FAP-registry of the Netherlands Foundation for the Detection of Hereditary Tumors. The results presented here are part of a larger study on the psychosocial effect of FAP.[16]

Invitation letters were sent to a contact person within a family. This was typically a family member (with FAP) who had assisted in drafting the family pedigree at the time of registration, and was often a key figure within the family with regard to counseling issues. The contact person was asked to (1) complete a self-report questionnaire; and (2) assist in inviting other family members by mail to participate in the study. In some families, more than one contact person was recruited because of the large number of family members and branches within the family.

Questionnaires were mailed between October 2005 and January 2007, with a reminder letter sent to all potential participants after 2 weeks. In total, 530 FAP family members participated (64% response rate), among which 341 patients with a genetic or endoscopic established diagnosis of FAP. The questionnaire assessed a range of sociodemographic, clinical, and psychosocial variables. The questionnaire comprised study-specific questions about type and number of surgical procedures, the actual desire for children, and whether fertility problems because of surgery for FAP had been experienced. If the patient reported having experienced fertility problems, she was asked to indicate whether she had had difficulty becoming pregnant, or had failed to become pregnant. There was space in the questionnaire to describe the nature of the fertility

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problems. Self-reported clinical data were confirmed by medical record audits whenever possible.

The study was approved by the ethics committee of the Netherlands Cancer Institute and the advisory board of the Netherlands Foundation for the Detection of Hereditary Tumors.

Patients

Women with a genetic or endoscopic established diagnosis of FAP, who had undergone colorectal surgery, and who had returned a completed questionnaire, were included in the current analysis.

Data Analysis

Continuous variables were compared using the Student's t test for independent samples. The χ^2 statistic and Fisher exact test were used to investigate the influence of categorical variables on reported fertility problems. A $P < 0.05$ was considered to be statistically significant. Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL).

RESULTS

A total of 341 FAP patients completed the questionnaire, 179 of which were female. Of these women, 138 met the inclusion criteria, of whom 23 patients (17%) reported current or past fertility problems. Self-reported problems included difficulty becoming pregnant (n = 14) and failure to become pregnant (n = 9). In 7 cases, fertility problems could be confirmed through medical record audit. Problems included tubal occlusion and ovarian dysfunction because of adhesions.

Table 1 displays the characteristics of the study sample. The mean age, education level, and marital status of those with and without fertility problems were comparable. Slightly less than half of the women who reported having had fertility problems had one or more children, compared with approximately two-thirds of those without fertility problems. Patients reporting fertility problems were on average 2 years older at the time of their first pregnancy than women without fertility problems (29 vs. 27 years, $P = 0.28$) The desire for offspring was significantly more often fulfilled in the group without fertility problems. In both groups, approximately 10% indicated that they did not currently wish to have (more) children.

As shown in Table 2, the frequency of fertility problems was not associated significantly with the type of surgery (ie, an IRA, IPAA, or proctectomy with ileostomy procedure). The data in the table refer to the last surgical procedure; similar results were obtained when analyzing "prior surgical procedures" (data not shown in tabular form). Similarly no significant associations were observed between the indication for surgery, the occurrence of desmoid tumors, cancer, or other comorbid conditions and the prevalence of fertility problems.

Patients reporting fertility problems were significantly younger at diagnosis of FAP and at the time of the first surgical procedure (Table 2). The mean age at primary IRA was 27 years, compared with 24 years at primary IPAA ($P = 0.16$, data not shown in tabular form).

TABLE 1. Sociodemographic Data, Number of Children and Desire to Have Children of Patients With and Without Fertility Problems due to Colorectal Surgery (n = 138)

	With Fertility Problems (n = 23) n (%)	Without Fertility Problems (n = 115) n (%)	P
Marital status			
Partner	20 (87)	97 (84)	0.39
Single	0 (0)	9 (8)	
Divorced	2 (9)	4 (4)	
Widow	1 (4)	5 (4)	
Children			
Yes	11 (48)	78 (68)	0.07
No	12 (52)	37 (32)	
	n = 11	n = 78	
Age at first pregnancy			
Mean (range)	29 (20–37)	27 (18–39)	0.28
Desire to have (more) children			
Yes	10 (44)	27 (24)	0.05*
No	13 (56)	88 (76)	
Reason			
Desire fulfilled	5 (22)	61 (53)	
I don't want children	2 (9)	12 (10)	
Don't know/no partner	6 (26)	15 (13)	
Level of education			
Primary school	6 (26)	39 (34)	0.61
High school	14 (61)	67 (58)	
College/university	3 (13)	9 (8)	
	n = 23	n = 115	
Current age			
Mean (range)	41 (30–68)	44 (21–78)	0.24

*Significant at 0.05 level (2-tailed).

DISCUSSION

In this study, we assessed fertility problems in women who had undergone surgery for FAP. Most remarkable was the comparable numbers of women reporting fertility problems either after IRA, IPAA, or proctocolectomy with ileostomy. Also, neither the indication for surgery, the number of operations and the number of procedures with complications, nor the occurrence of desmoid tumors, cancer, or other comorbid conditions were found to be associated significantly with self-reported fertility problems. However, women who reported fertility problems after surgery were substantially younger when diagnosed with FAP and at the time of first colectomy than women who did not experience fertility problems. The women with fertility problems had their first child at a later age, suggesting that early surgery has a negative influence on fertility.

Previous reports on the effect of surgical procedure on fertility almost uniformly describe a reduction in fertility after IPAA.[9,10,16–20] However, most of these studies were on ulcerative colitis patients. Only two studies described female fertility after surgery for FAP.[8,21] The study of Johansen et al found that 10% of the women had an unfulfilled desire to become pregnant, corresponding with the estimated population infertility rate.[21]

Olsen et al[8] compared fecundity, defined as the probability of becoming pregnant per month by unprotected intercourse, in 162 women who had undergone IRA or IPAA and a reference population including 914 women from the general population. Patients after IRA had a greater fecundity than the reference population, but fecundity after IPAA was severely reduced. Contrary to our study, in which the ages at IPAA and IRA did not differ significantly, in the study of Olsen et al, patients who underwent IPAA were significantly older. This may explain, in part, the decreased fecundity rates in the study of Olsen et al among those who had undergone IPAA. A further difference from our study was the way of assessing reproductive function.

TABLE 2. The Frequency of Fertility Problems in Relation to Surgery and Comorbidity and Mean Ages at Diagnosis of FAP and at Primary and Secondary Surgery (n = 138)

	With Fertility Problems (n = 23) n (%)	Without Fertility Problems (n = 115) n (%)	*P*
Type of last surgery			
IRA	9 (39)	49 (43)	0.56
IPAA	9 (39)	51 (44)	
Proctocolectomy and ileostomy	5 (22)	15 (13)	
Indication first operation			
Prophylaxis	22 (96)	110 (96)	1.00
Cancer	1 (4)	5 (4)	
No. operations			
1	16 (70)	90 (78)	0.37
>1	7 (30)	25 (22)	
Complications (adhesions, bleeding, abscess)			
Yes	12 (52)	44 (38)	0.22
No	11 (48)	71 (62)	
Desmoid tumour			
Yes	4 (17)	14 (12)	0.50
No	19 (83)	101 (88)	
Cancer (colorectal, thyroid, skin, cervix, non-Hodgkin lymphoma)			
Yes	3 (13)	13 (11)	0.73
No	20 (87)	102 (89)	
Comorbidity (Cardiovascular or pulmonary diseases, cerebrovascular accidents, diabetes, osteoarthritis, kidney failure, malignant tumors, psychological complaints)			
Yes	12 (52)	62 (54)	0.81
No	11 (48)	53 (46)	

	n	Mean (Range)	n	Mean (Range)	
Age at diagnosis of FAP	23	20 (6–36)	115	27 (9–58)	0.01*
Age at first operation	23	22 (10–36)	114	28 (10–59)	0.01*
Age at second operation	7	36 (26–54)	18	39 (17–59)	0.67

Pearson χ^2, Fisher exact test was performed for Desmoid tumour and Cancer, because of small numbers.
*Significant at 0.01 level (2-tailed).
IRA indicates ileorectal anastomosis; IPAA, ileal pouch-anal anastomosis.

A major strength of our study is the large number of participating FAP patients and the availability of detailed information about surgery, complications, and comorbidity. Furthermore, we were able to verify part of the self-reported problems with medical data.

A potential weakness of the study is the lack of detailed information on the "time to pregnancy," something that is difficult to assess accurately in a retrospective study.[8,22] Also, no information on fertility problems before surgery was available.

Reduced fertility after colorectal surgery is most often attributed to postoperative anatomic changes in the female pelvis.[11,14,15] As IPAA is a more complicated procedure than IRA, more tissue damage and postoperative adhesions would be expected after IPAA and multiple operations.[13] However, we found a similar rate of fertility problems after IRA and IPAA. The higher incidence of fertility problems after IPAA reported in earlier studies may be explained, at least in part, by the inclusion of ulcerative colitis patients.

We found that women with fertility problems were significantly younger at the time of the first surgical procedure, compared with women without fertility problems. Women with fertility problems who were able to get children had their first child on average 7 years after the first surgical procedure. Patients with children who reported no fertility problems had their first child on average 1 year before their first operation. These findings suggest that a colectomy early in life may lead to subfertility. However, patients may have postponed pregnancy for other reasons. Possibly, women who reported no fertility problems and had their first child before surgery did not perceive themselves as having fertility problems because their family was already complete. Because of the cross-sectional study design and because part of our population has no children at all we are unable to correct for this variable.

In our study, 1 of 6 female FAP patients indicated having had reduced fertility because of surgery. In the general Dutch population, 1 of 10 of the couples have subfertility complaints at least once during their lifetime.[23] However, these latter figures include both male and female fertility problems, making comparison with our results difficult.

In our study, the risk of developing fertility problems could not be attributed to the IPAA procedure exclusively, as patients after IRA reported the same frequency of fertility problems as those who had undergone other surgical procedures. For primary surgery, an IRA procedure is preferred because of the lower complication risk. The IPAA procedure should be considered the primary surgery of choice for polyposis patients with extensive rectal involvement. Based on the present study, concerns about fertility problems after IPAA may be of less importance than previously thought.

Further studies are needed to investigate the effect of less invasive surgical (laparoscopic) methods and to clarify the nature of fertility problems in FAP patients in more detail. The best way to evaluate subfertility would be a prospective analysis of the "time to pregnancy."

In conclusion, for female FAP patients, no association was found between fertility problems and type of surgery, other surgical-related factors, desmoid tumors, cancer, and other comorbidity. Women reporting postoperative fertility problems had their first surgical procedure earlier in life than women not reporting such problems. Female FAP patients should be well informed about the pros and cons of both procedures and the risk of reduced fertility later in life after both IRA and IPAA.

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Chapter 6

Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: A nationwide retrospective cohort study

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Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: A nationwide retrospective cohort study

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Background. *Duodenal cancer is a major cause of mortality in patients with familial adenomatous polyposis (FAP). The clinical challenge is to perform duodenectomy before cancer develops; however, procedures are associated with complications. Our aim was to gain insight into the pros and cons of prophylactic duodenectomy.*

Methods. *Patients with FAP from the nationwide Dutch polyposis registry who underwent prophylactic duodenectomy or were diagnosed with duodenal cancer were identified and classified as having benign disease or cancer at preoperative endoscopy. Surveillance, clinical presentation, surgical management, outcome, survival, and recurrence were compared.*

Results. *Of 1,066 patients with FAP in the registry, 52 (5%; 25 males) were included: 36 with benign adenomatosis (median: 48 years old; including two (6%) cancer cases diagnosed after operation), and 16 with cancer (median: 53 years old). Cancer cases had been diagnosed with colorectal cancer more often (6% vs 44%;* $P < .01$*). Forty-three patients underwent duodenectomy (35 benign/eight cancer): 30-day mortality was 4.7% (*$n = 2$*), and in-hospital morbidity occurred in 21 patients (49%), without differences between patients with benign adenomatosis and cancer. Adenomas recurred in reconstructed proximal small bowel in 14 of 28 patients (50%, median time to recurrence: 75 months), and one patient developed cancer. Median survival of all 18 cancer cases in the registry (1.7%; 12 ampullary/six duodenal) was 11 months.*

Conclusion. *Prognosis of duodenal cancer in patients with FAP is poor, which justifies an aggressive approach to advanced benign adenomatosis. Strict adherence to recommended surveillance intervals is essential for a well-timed intervention. Given the substantial morbidity and mortality of duodenectomy, patients' individual characteristics are to be critically evaluated preoperatively. As adenomas recur, postoperative endoscopic surveillance is mandatory. (Surgery 2012;■:■-■.)*

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FAMILIAL ADENOMATOUS POLYPOSIS (FAP) is an autosomal-dominant disease caused by germline mutations in the tumor suppressor gene *APC* (*adenomatous polyposis coli*).[1] Classically, FAP is characterized by the development of hundreds to thousands of adenomatous polyps in the colorectum.[2] Unless a prophylactic colectomy is performed, virtually all patients will develop

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colorectal cancer before the age of 50 years. In the past, surveillance and prophylactic colorectal surgery for patients at risk improved prognosis substantially by preventing colorectal cancer.[3-6] As a result, duodenal cancer is now the main cancer-related cause of death in patients who underwent prophylactic colectomy.[7-9]

Although the lifetime risk of duodenal adenomas approaches 100% in patients with FAP,[10] in contrast to colorectal polyps, duodenal polyps do not inevitably transform to cancer. Approximately 3–4% of patients eventually develop duodenal cancer.[11,12] The relative risk of duodenal adenocarcinoma and ampullary carcinoma in patients with FAP was estimated at, respectively, 331 and 124 times greater than in the general population in which duodenal carcinoma is rare.[13]

The clinical challenge is to identify the patients at high risk of developing duodenal cancer because duodenal cancer has been associated with a poor prognosis.[11,14-16] The Spigelman stages of duodenal disease severity assessed by surveillance endoscopy have been shown to correlate with the risk of developing duodenal cancer, with a risk of 36% during a 10-year period for the most advanced stage IV.[17] Endoscopic surveillance is recommended to start when the patient is 25–30 years of age, and frequency of surveillance and further management are determined on the basis of the Spigelman classification (Table I).[10,18]

Local treatment of duodenal polyposis with polypectomy or ampullectomy, endoscopically as well as surgically, is a relatively safe option, but high rates of adenoma recurrence up to almost 100% have been reported.[19-22] The relief of cancer threat, therefore, seems only temporary, and ongoing endoscopic surveillance is mandatory. When local treatment is no longer deemed possible, more extensive operative procedures such as classical pancreatoduodenectomy, pylorus-preserving pancreatoduodenectomy (PPPD), or the more recently introduced pancreas-sparing duodenectomy (PSD) need to be considered.[23] These interventions, however, bring about substantial risk of morbidity and mortality.[24-26] Furthermore, although these extensive surgical procedures offer the chance of a prolonged disease-free interval, the recurrence of adenomas[15,27] and even cancer arising from the remaining duodenal mucosa have been reported.[28]

To gain insight into the pros and cons of prophylactic duodenectomy, we reviewed data retrospectively of patients from the nationwide Dutch polyposis registry. Our primary aim was to analyze characteristics of all patients who underwent prophylactic duodenectomy for duodenal adenomatosis and all patients diagnosed with duodenal cancer. In addition, we compared both groups on features including surveillance and clinical presentation, surgical management and outcome, survival and causes of death, and recurrence.

Table I. Spigelman classification for duodenal adenomatosis with recommendations for management[10,18]

	Criterion points		
	1	*2*	*3*
Number	1–4	5–20	>20
Size (mm)	1–4	5–10	>10
Architecture	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0 (0 points) and stage I (1–4 points): endoscopic surveillance every 5 years; stage II (5–6 points): endoscopic surveillance every 2–3 years; stage III (7–8 points): endoscopic surveillance every 1–2 years with consideration for surgery; stage IV (9–12 points): surgery should be considered.

PATIENTS AND METHODS

Dutch polyposis registry. In 1985, the Netherlands Foundation for Detection of Hereditary Tumours (NFDHT) started a registry of patients with FAP. The main objectives of this nationwide polyposis registry are coordination of lifelong surveillance of at-risk patients and promotion of early detection of cancer in high-risk families.[29] Patients with FAP are referred to this national registry by gastroenterologists, surgeons, or clinical geneticists. At the time of registration, written informed consent is obtained from the patient for collection of personal and medical data, including endoscopic, surgical, and histopathology reports. To date, 1,066 patients with a genetically and/or clinically confirmed diagnosis of FAP are registered.

Study population. For this study, we searched the FAP database of the Dutch Polyposis Registry to identify and include for analysis: (1) patients who underwent a classic pancreatoduodenectomy with antrectomy (Whipple), PPPD, or PSD for advanced benign duodenal adenomatosis; and (2) patients who presented with duodenal cancer, irrespective of whether duodenal surgery was performed. Patients were classified in 2 groups according to tumor status at preoperative endoscopy, as patients with benign duodenal adenomatosis or patients with duodenal cancer.

Definitions and description of variables. Available medical data were evaluated, including clinical correspondence and endoscopic, surgical, and histopathology reports. The following data were recorded: type and indication of previous colorectal resection, APC mutation status, and details on

endoscopic assessments, in particular on the assessment before duodenal surgery and follow-up assessments after duodenal surgery. Cancers were classified as either ampullary or duodenal; duodenal cancers were those that arose from non-ampullary duodenum. Moreover, the mode of presentation was reviewed, assessing whether cancers were detected at surveillance endoscopy or whether cancer patients presented with disease signs or symptoms. The recommendations as depicted in Table I were generally used as standard for endoscopic surveillance in the Netherlands.

Complications after duodenectomy were classified as either in-hospital morbidity or long-term morbidity. Postoperative mortality was defined as 30-day mortality. Data on causes of death were collected, and causes were grouped as either related or unrelated to duodenal disease.

The recurrence of adenoma was defined as the appearance of new adenomas after duodenectomy (Whipple, PPPD, PSD) in the reconstructed proximal small bowel involving the residual duodenal mucosa (after PPPD or PSD) and the proximal jejunum used for reconstruction. Patients with adenomas at the first postoperative follow-up endoscopy were excluded, because these adenomas might have been present before duodenectomy was performed. Time to adenoma recurrence was measured from date of resection until date of first endoscopic surveillance showing the recurrence of adenomas or the date of last endoscopic surveillance without recurrence. Any carcinoma arising in the reconstructed proximal small bowel was also recorded.

Statistical analysis. Statistical analysis was performed using SPSS statistical software version 16.0 (SPSS, Chicago, IL). Frequency tables were provided for description of baseline characteristics. A group comparison was performed, primarily on the basis of tumor status at preoperative endoscopy. In addition, comparisons included groups defined by type of duodenectomy, surveillance status, and cancer localization. Differences on continuous variables including age at duodenal surgery were examined using Mann-Whitney U test. The Fisher's exact test was used to compare discrete variables, including those representing complications after duodenectomy, and causes of death. Survival and adenoma recurrence data were analyzed by Kaplan-Meier survival analysis and Log Rank test. A P value of $<.05$ (2-sided) was considered statistically significant.

RESULTS

Description of the study population. Of the 1,066 patients with FAP in the registry database, 53 patients (5%; 26 male, 27 female) met the criteria for inclusion. One male patient with duodenal cancer was excluded from all analyses because of missing clinical data. Subsequently, the study population comprised 52 patients (25 male, 27 female) from 44 FAP families. The presence of a germline APC mutation had been confirmed by genetic testing in 44 patients (85%). Patient characteristics of the total study population and the subgroups classified by tumor status at preoperative endoscopy as either benign duodenal disease ($n = 36$) or duodenal cancer ($n = 16$), are summarized in Table II. Patients' tumor status, surgical approach, and outcome are shown in Fig 1.

All operative procedures were performed in large regional teaching hospitals or specialized university centers between 1975 and 2008. The following procedures were performed: Whipple ($n = 13$), PPPD ($n = 8$), PSD ($n = 22$), duodenotomy with ampullectomy ($n = 1$), and laparotomy with or without palliative intervention because of unresectable and/or metastatic cancer ($n = 7$). In one patient, an operation was not performed because of unresectable ampullary cancer. Nearly all PSDs were performed in the most recent decade (Fig 2). Operative therapy for benign duodenal adenomatosis was performed at a median age of 48 years and duodenal cancer surgery at a median of 53 years (Mann-Whitney U test, $P = .23$).

Compared with patients with benign disease at preoperative endoscopy, patients with duodenal cancer at endoscopy had been diagnosed with colorectal cancer at primary colorectal surgery more often (6% vs 44%, respectively; Fisher's exact test, $P < .01$).

Patients with benign duodenal adenomatosis at preoperative endoscopy. The 36 patients with benign duodenal adenomatosis at preoperative endoscopy were graded as follows: Spigelman II disease with high-grade dysplasia around the neopapilla 9 years after ampullectomy ($n = 1$), and Spigelman III disease ($n = 6$) or Spigelman IV disease ($n = 29$). All patients were under surveillance except for one who underwent endoscopy for dyspepsia and was found to have Spigelman IV disease. Three patients previously had undergone surgical treatment for duodenal adenomatosis, including duodenotomy with polypectomy ($n = 2$) and ampullectomy with bile and pancreatic duct reconstruction ($n = 1$).

Two patients (6%) with preoperative benign duodenal adenomatosis were diagnosed with cancer after a previous operation, including 1 ampullary carcinoma found at postoperative histopathology and 1 locally advanced ampullary tumor with liver metastasis found during laparotomy.

Table II. Characteristics of the study population consisting of FAP patients with benign duodenal adenomatosis and duodenal cancer at endoscopy

	Total study population	*Cases with benign disease at endoscopy*	*Cases with duodenal cancer at endoscopy*
Number of patients, *n* (% male)	52 (48)	36 (47)	16 (50)
Median age at primary CR surgery, years (range)	28 (12–63)	28 (12–49)	32 (15–63)
Type of primary CR surgery, *n* (%)			
IRA	31 (60)	21 (58)	10 (62.5)
IPAA	12 (23)	10 (28)	2 (12.5)
Ileostomy	9 (17)	5 (14)	4 (25)
Cases with cancer at primary CR surgery, *n* (%)	9* (17)	2 (6)	7* (44)
Rectum	3	—	3
Colon	8	2	6
Median age at duodenal surgery, years (range)	49 (31–69)	48 (31–69)	53 (32–67)
Spigelman stage at preoperative endoscopy			
II	1	1	—
III	6	6	—
IV	29	29	—
Cancer	16	0	16
Duodenal cancer			
Ampullary	12	2	10
Duodenal	7	0	6
Type of duodenal surgery, *n* (%)			
Whipple	13 (25)	8 (22)	5 (31)
PPPD	8 (15)	5 (14)	3 (19)
PSD	22 (42)	22 (61)	—
Duodenotomy with ampullectomy, *n* (%)	1 (2)	—	1 (6)
Laparotomy with/without palliative intervention, *n* (%)	7 (14)	1 (3)	6 (38)
No surgery, irresectable cancer, *n* (%)	1 (2)	—	1 (6)

*In 2 cases, synchronous cancer of colon and rectum was present at primary colorectal surgery.
CR, Colorectal; *IRA*, ileorectal anastomosis; *IPAA*, ileal pouch-anal anastomosis; *ileostomy*, proctocolectomy with ileostomy; *Whipple*, classical Whipple's pancreaticoduodenectomy; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *PSD*, pancreas-sparing duodenectomy.

Patients with duodenal cancer at preoperative endoscopy. The characteristics of 16 patients with duodenal cancer diagnosed at preoperative endoscopy are included in Table III. Six of 16 patients were under surveillance: in 2, cancer was identified by endoscopic surveillance, and 4 presented with signs or symptoms of disease. Two patients presented with symptoms 12 and 22 months after scheduled endoscopic surveillance, when their duodenal adenomatosis was graded as Spigelman III and IV disease, respectively. In the latter patient, the recommended surveillance interval was not followed because of additional morbidity. The other 2 symptomatic patients who underwent duodenotomy with ampullectomy and palliative laparotomy, respectively, previously were not considered candidates for prophylactic surgery because of a desmoid tumor and severe jejunal adenomatosis.

Ten of 16 patients were not under surveillance and had no upper gastrointestinal endoscopy performed for at least the previous 5 years: 8 patients presented symptomatically, 1 patient underwent his first surveillance endoscopy, and for 1 patient the mode of presentation was unknown.

Twelve patients presented with clinical signs or symptoms of duodenal cancer, including jaundice and/or cholestasis ($n = 6$), anemia ($n = 4$), abdominal pain ($n = 3$), vomiting ($n = 2$), weight loss ($n = 2$), syncope ($n = 1$), and melena ($n = 1$). All patients presenting with jaundice and/or cholestasis had ampullary cancer, whereas all cases presenting with abdominal pain had duodenal cancer.

Complications after duodenectomy. Postoperative mortality and morbidity was evaluated for all patients who underwent duodenectomy ($n = 43$, 35 for benign disease, 8 for duodenal cancer). Overall 30-day mortality was 5% ($n = 2$). One patient died as the result of pericarditis with multiorgan failure 12 days after PSD for Spigelman IV disease (histopathology: ampullary cancer), and one had an anastomotic leak with abdominal sepsis and died 19 days after Whipple for Spigelman IV disease. A third patient died 7 months after undergoing the Whipple procedure for Spigelman IV disease.

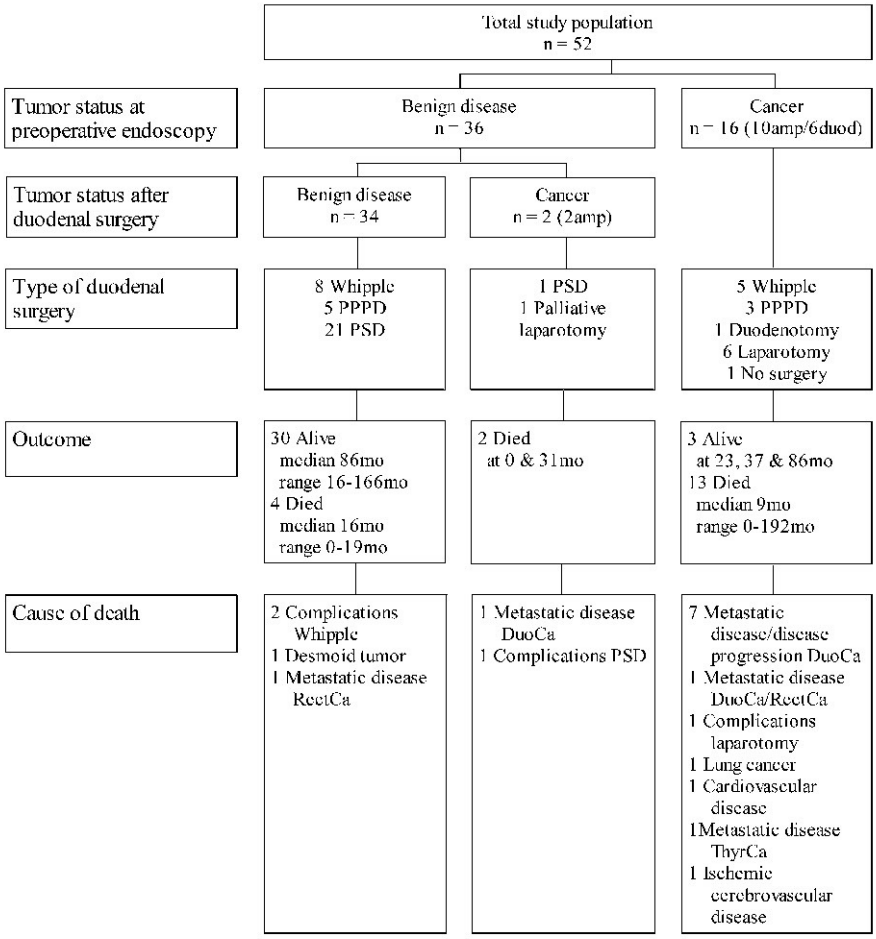

Fig 1. Flow diagram of tumor status at preoperative endoscopy, tumor status after duodenal surgery, type of duodenal surgery performed, outcome, and cause of death. *n,* Number of patients; *amp,* ampullary; *duod,* duodenal; *Whipple,* classical Whipple's pancreaticoduodenectomy; *PPPD,* pylorus-preserving pancreaticoduodenectomy; *PSD,* pancreas sparing duodenectomy; *RectCa,* rectal cancer; *DuoCa,* duodenal cancer; *ThyrCa,* cancer of thyroid gland.

The postoperative course was complicated by necrotizing pancreatitis, enterocutaneous fistula formation, and thrombosis of the superior caval vein. All in 3 instances of mortality, patients were surgically treated for what was considered to be benign duodenal disease.

An overview of all postoperative complications is shown in Table IV. A total of 33 in-hospital complications in 21 patients (49%; 17 benign disease, 4 cancer) were reported. There was no significant difference found in number of patients experiencing in-hospital complications when we compared patients with benign disease and patients with cancer at preoperative endoscopy (Fisher's exact test, $P = .62$), and when we compared the 3 types of duodenectomy (Fisher's exact test, $P = .20$).

Seven patients (16%; 5 benign disease, 2 cancer) needed unplanned relaparotomy because of

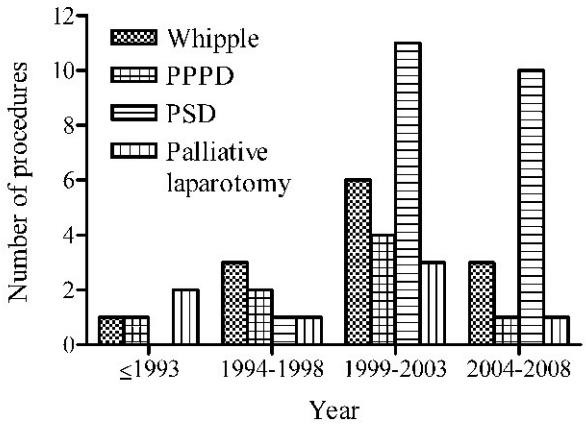

Fig 2. Number and type of surgical procedures performed in 5-year periods. *Whipple,* Classical Whipple's pancreaticoduodenectomy; *PPPD,* pylorus-preserving pancreaticoduodenectomy; *PSD,* pancreas-sparing duodenectomy.

Table III. Characteristics of 18 patients with duodenal cancer

		Mutation		*Primary CR surgery*			*Duodenal cancer and surgery*						
Case no.	*Sex*	*Exon*	*Codon*	*Type*	*Age, years*	*CRC*	*Mode of presentation*	*Site*	*TNM*	*Type of surgery*	*Age, years*	*Survival, months*	*Cause of death*
1*	F	15	1209	Ileostomy	27	—	Surveillance (Spigelman IV)	A	HGD, TxNxM1‡	Lapar, no intervention	59	31	Metastatic disease, liver
2*	F	5	178	IRA	29	—	Surveillance (Spigelman IV)	A	T1NxMx	PSD + antrum resection	60	0	Complications of surgery: multi-organ failure
3	F	15	685	IRA	33	—	Cholestasis	A	T1NxMx	Whipple	57	Alive 86	—
4	M	*n.k.*	*n.k.*	Ileostomy	29	Rectum	Anaemia, syncope, melaena	D	T3NxM1	Lapar, GJS	62	9	Progression of disease, peritonitis carcinomatosis
5	F	11	499	Ileostomy	63	Colon	Cholestasis	A	T3NxMx	Whipple	67	133	Metastatic disease from cancer of thyroid gland
6	M	11	516	IPAA	40	—	*n.k.*	A	T3N1Mx	PPPD	48	15	Metastatic disease
7	M	*n.k.*	*n.k.*	IRA	40	—	Anaemia, vomiting, weight loss	D	T4NxM1‡	Lapar, GJS	57	9	Metastatic disease, retroperitoneum and psoas
8	F	15	728	IRA	17	—	Jaundice	A	TxN1M1‡	Lapar, GJS	32	8	Metastatic disease, liver
9	M	14	630	IRA	32	—	Abdominal pain	D	T2N1Mx	Whipple	58	48	Lung cancer
10	F	4	150	IRA	42	Colon	Jaundice, vomiting	A	TxNxMx‡	*No surgery*	53	4†	Progression of disease
11	M	13	554	IRA	25	—	Surveillance (cancer)	A	T3N1Mx	PPPD	53	76	Cardiovascular disease
12	M	13	554	IRA	25	—	Surveillance (cancer)	A	T1N0M0‡	Duodenotomy with ampullectomy	59	Alive 37	—
13	F	12	541	IRA	36	Colon	Jaundice, anaemia	A	TxNxMx	Lapar, placement of billiary T-drain	47	3	Progression of disease
14	F	14	622	IRA	22	—	Abdominal pain	D	T4NxM1	Lapar, repositioning of intra-abdominal herniation	48	7	Metastatic disease, liver and lung
15	M	*n.k.*	*n.k.*	IRA	15	—	First surveillance endoscopy	D	T2NxMx	PPPD	49	192	Ischemic cerebrovascular disease
16	M	13	564	IPAA	18	Colon	Jaundice	A	T1N0Mx	Whipple	39	Alive 23	—
17	F	15	1464	Ileostomy	40	Colon, Rectum	Anaemia, weight loss	A	T4N0Mx	Whipple	40	11	Metastatic disease from synchronous CR and duodenal cancer
18	F	15	1062	Ileostomy	36	Colon, Rectum	Abdominal pain	D	TxN1M1	Lapar, GJS, partial resection of small bowel	56	0	Complications of surgery: sepsis, bile leakage, bleeding

*Patients who underwent prophylactic duodenectomy but were diagnosed with cancer after surgery.

†Patient died 4 months after diagnosis at endoscopy and radiologic assessment of irresectable ampullary cancer.

‡No material for histopathological evaluation was obtained during duodenal surgery, TNM-classification based on histopathological examination of biopsy material from preoperative endoscopy, clinical observations and/or additional radiologic evaluation.

A, Ampullary; *CR*, colorectal; *CRC*, colorectal cancer; *D*, duodenal; *HGD*, high-grade dysplasia; *IPAA*, ileal pouch-anal anastomosis; *IRA*, ileorectal anastomosis; *ileostomy*, proctocolectomy with ileostomy; *PSD*, pancreas-sparing duodenectomy; *TNM*, tumor node metastasis classification; *Whipple*, classical Whipple's pancreaticoduodenectomy; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *Lapar*, laparotomy; *GJS*, gastrojejunostomy; *n.k.*, not known.

Table IV. Patients with complications after duodenectomy for benign duodenal disease or cancer at preoperative endoscopy

Group	n	*Total morbidity*, n (%)	*In-hospital morbidity*, n (%)*	*Long-term morbidity*, n (%)†
Benign disease at endoscopy	35	23 (66)‡	17 (49)‡	7 (20)‡
Whipple	8	6	5	1
PPPD	5	3‡	3‡	1‡
PSD	22	14	9	5
Cancer at endoscopy	8	5 (63)	4 (50)	1 (13)
Whipple	5	4	4	0
PPPD	3	1	0	1
Overall	43	28 (65)	21 (49)	8 (19)

*In-hospital morbidity: intra-abdominal abscess (n = 6), fistula formation (n = 5), anastomotic leakage (n = 6), pancreatitis (n = 2), sepsis (n = 4), postoperative hemorrhage (n = 4), surgical site infection (n = 2), trombo-embolism of superior caval vein (n = 2, in 1 case with pulmonary embolism), occlusion of branches of the hepatic artery with local ischemia of liver tissue adjacent to the falciform ligament (n = 1), and pericarditis with multi-organ failure (n = 1).

†Long-term morbidity: (chronic) pancreatitis (n = 3), incisional hernia (n = 1), stenosis of the enterobiliary anastomosis (n = 2, in 1 case with cholangitis), cutanous fistula and abscess formation resulting in sepsis induced by migrated mesh into the jejunum (n = 1), anastomotic erosions/ulcer (n = 3).

‡Includes 1 patient with both in-hospital and long-term morbidity.

Of note: 1 patient can have more than 1 complication.

n, Number of patients; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *PSD*, pancreas-sparing duodenectomy; *Whipple*, classical Whipple's pancreaticoduodenectomy.

intra-abdominal infection (n = 3), hemorrhage (n = 2), or anastomotic leakage (n = 1). In 1 patient, no abnormalities were found, and the patient was treated for pancreatitis. A total of 10 long-term complications in 8 patients (19%; seven benign disease, 4 cancer) were reported, including 1 patient who previously suffered in-hospital morbidity.

Survival and causes of death. As shown in Fig 1, 4 of 36 patients (11%) with benign duodenal disease at endoscopy died of causes related to their duodenal disease, including metastatic duodenal cancer (n = 1) and postoperative mortality after duodenectomy (n = 3); 2 other patients (6%) died of unrelated causes.

Nine of 16 patients (56%) diagnosed with cancer at preoperative endoscopy died of causes related to duodenal cancer, including metastatic disease or progression of disease (n = 7), metastatic disease originating from either duodenal or synchronous rectal and colonic cancer (n = 1), and postoperative morbidity after palliative laparotomy (n = 1). Four patients (25%) died of unrelated causes, and 3 patients (19%) were alive at time of study closure.

The observed differences in distribution of causes of death for patients with benign duodenal disease or cancer at preoperative endoscopy, as either related or unrelated to duodenal disease, were not significant (Fisher's exact test, P = .14). Survival of patients with cancer at preoperative endoscopy was less than the survival of patients who underwent prophylactic surgical resection for benign disease (Fig 3; log-rank test, $P < .001$).

When we considering all 18 patients with cancer, the prognosis of duodenal cancer was deemed poor; the Kaplan-Meier estimated median survival was 11 months. There was a difference in estimated median survival of patients who underwent duodenectomy and patients who underwent palliative intervention (76 vs 8 months, log-rank test, $P <$ .05). Estimated median survival rates for cancer patients under surveillance versus cancer patients not under surveillance were 9 and 11 months, respectively (log-rank test, P = .54). The difference in estimated median survival after duodenal surgery between patients with ampullary cancer and duodenal cancer (15 vs 9 months, respectively) was not significant (log-rank test, P = .77).

Recurrence. Data on endoscopic follow-up were available in 32 patients. Adenomas were seen during follow-up endoscopy in 18 patients. Four patients (13%) with adenomas at the first postoperative follow-up endoscopy were excluded because these adenomas might have been present before duodenectomy was performed. Hence, in 14 of 28 patients (50%) adenomas recurred with a Kaplan-Meier estimated median time from surgery to recurrence of 75 months. Recurrence of adenomas was seen in 3 of 7 patients after the Whipple procedure (43%), 4 of 6 after PPPD (67%), and 7 of 15 after PSD (47%), with estimated median time from surgery to recurrence of 103, 53, and 66 months, respectively (log rank test, P = .28). The median score in points by Spigelman stage at recurrence was 5 (range, 3–7), with 7 cases of Spigelman I, 6 cases of Spigelman II, and 1 case of Spigelman III disease. One

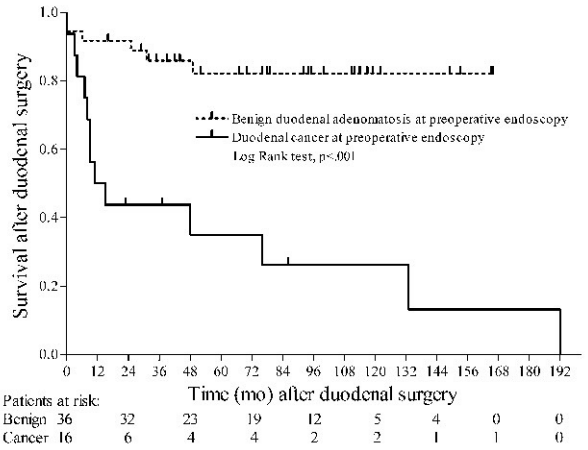

Fig 3. Kaplan-Meier curve: survival after duodenal surgery stratified for tumor status at preoperative endoscopy: benign duodenal adenomatosis or duodenal cancer. (Duodenal surgery includes classical Whipple's pancreaticoduodenectomy; pylorus-preserving pancreaticoduodenectomy; pancreas-sparing duodenectomy; laparotomy with or without palliative intervention, and duodenotomy with ampullectomy.) Of note: in 1 cancer patient no duodenal surgery was performed and survival (4 months) was measured from diagnostic endoscopy.

patient was diagnosed with cancer at the hepaticojejunostomy 156 months after PPPD for duodenal cancer.

DISCUSSION

In the present study, 18 patients of 1,066 patients with FAP in the Dutch registry (1.7%) were diagnosed with duodenal cancer between the years 1975 and 2008. Recently, a comparable rate of 1.9% was reported on the basis of 20 cases of cancer diagnosed in the St. Mark Hospital Polyposis Registry between 1969 and 2005.[16] Both studies suggest that the prevalence of duodenal cancer might be less than the 4.5% reported in the late 1980s.[11] It is unclear whether this difference in prevalence reflects a true decrease in duodenal cancer prevalence that subsequently might be attributed to improved management of duodenal disease in FAP patients.

Our results support previous findings on the poor prognosis of duodenal cancer in patients with FAP.[11,14-16] Notably, in almost one-half of the patients presenting with duodenal cancer at endoscopy, the cancer stage was too advanced to perform a curative resection. The aim of surveillance programs is to identify patients with advanced duodenal adenomatosis *before* cancer develops. In the majority of our cancer cases, either no surveillance was performed or the recommendation on surveillance interval was not followed. In contrast, nearly all patients with benign disease were under surveillance. The survival of patients who underwent prophylactic duodenectomy was far better. Our findings imply that if appropriate surveillance intervals were followed, nearly one-half of the cancers could have been diagnosed at a treatable stage or could even have been prevented by timely prophylactic intervention. Interestingly, patients with duodenal cancer had been diagnosed with colorectal cancer at previous initial colorectal surgery more often compared with patients with benign disease. All patients with FAP, but particularly patients diagnosed with cancer previously at initial colorectal surgery, should be motivated to follow strictly the recommended surveillance intervals.

Notwithstanding this recommendation, limitations in the sensitivity of endoscopic surveillance should be kept in mind. Two patients (6%) who underwent surgery for benign duodenal adenomatosis were diagnosed with cancer on the basis of histopathologic examination of the resected tissue. This finding illustrates that the presence of cancer may be underestimated by taking endoscopic biopsies of adenomas, most probably because of sampling error and the small size of the biopsies taken.[30,31] Moreover, although the Spigelman classification has been shown to correlate with the risk of developing cancer,[17] it seems inadequate to assess the individual patient's risk of cancer accurately. The classification focuses primarily on nonampullary duodenal disease, and the evaluation of ampullary disease should be taken into account separately.[16] In patients with advanced duodenal adenomatosis, endoscopic ultrasonography may provide additional information on malignant invasion.[32,33] Fludeoxyglucose positron emission tomography has been shown to differentiate between adenomas and carcinomas, detecting all cancer cases in patients with FAP with duodenal adenomas.[34] Although the role of fludeoxyglucose positron emission tomography at present has not been established firmly, it represents a promising modality in guiding treatment decisions concerning duodenectomy that warrants further attention.

Ideally, a prophylactic procedure should carry no risk of death and have low morbidity while preventing future disease. The 30 patients alive after extensive duodenectomy for benign duodenal adenomatosis could be considered as beneficiaries of prophylactic duodenectomy. Overall postoperative morbidity and mortality, however, is substantial. All 3 cases or mortality in our series occurred in procedures that were intended as prophylactic. In addition, postoperative in-hospital morbidity occurred in one-half of the patients, either after

prophylactic resection or cancer treatment. In previous studies authors have revealed comparable rates of postoperative morbidity of 38–60% and mortality of 0–12% after duodenectomy (PSD and PPPD) in patients with FAP.[25,35-37] It has been suggested that patients with FAP might be at greater risk of complications compared with patients without FAP because of more demanding operative conditions related to more technically demanding anastomotic reconstruction of a soft pancreas with a nondilated biliary and pancreatic ductal system, and adhesions caused by previous colorectal surgery.[25,37] Furthermore, a preoperatively undetected nonfusion of the pancreatic duct (pancreas divisum) was the cause of postoperative complications in patients with FAP after PSD.[25,38] To prevent these complications, magnetic resonance cholangiopancreatography might be indicated in standard preoperative evaluation for PSD.

Recurrence of adenomas in the reconstructed proximal small bowel after duodenectomy occurred in one-half of all patients with available postoperative endoscopic follow-up data within just more than 6 years, and 1 patient developed cancer after PPPD at the hepaticojejunostomy. These findings are in line with previous reports of recurrence of adenomas after extensive surgery[15,39] and malignant degeneration in residual duodenal mucosa after duodenectomy.[28] As shown by our finding of 13% of patients with adenomas at the first postoperative endoscopy, adenomas may already be present in the jejunum used for construction, especially in patients with more advanced duodenal adenomatosis.[40] To avoid this possibility, preoperative inspection of the jejunum by single- or double-balloon enteroscopy is advised. Our findings support the recommendation that upper gastrointestinal surveillance should be continued after duodenectomy, because the risk of cancer is not entirely eliminated.[28,35,36,39]

The strength of our study is that we reviewed data covering the total Dutch population of patients with FAP who were receiving medical care in both regional hospitals as well as academic referral centers. We evaluated a considerably large cohort of patients with extensive follow-up, including not only patients with duodenal cancer, but also patients who underwent prophylactic duodenectomy for advanced duodenal adenomatosis. The number of cancer cases involved, however, is small, and power might therefore be inadequate to prove differences to be statistically significant. Study limitations include the retrospective study design, resulting possibly in a cohort effect. Missing data, although limited, might have biased the results, particularly where it concerns clinical follow-up data, resulting in less reported long-term postoperative morbidity rate and adenoma recurrence.

In conclusion, our study illustrates the poor prognosis of duodenal cancer, justifying in our opinion an aggressive prophylactic surgical approach to advanced benign duodenal disease, despite the substantial risk of morbidity and mortality. Strict adherence to the recommended surveillance intervals is essential for well-timed operative intervention. Treatment decisions are to be made by critically evaluating a patient's individual characteristics, taking into account age, history of colorectal cancer, previous abdominal surgery, course of the Spigelman classification over time, previous treatment of duodenal adenomatosis, and additional morbidity. Even after radical duodenal resection, patients have to bear the continuing burden of endoscopic surveillance and threat of cancer.

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Chapter 7

Clinical evidence for an association between familial adenomatous polyposis and type II diabetes

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Clinical evidence for an association between familial adenomatous polyposis and type II diabetes

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Dear Editor,

Recent genome wide association (GWA) studies suggested that type II diabetes (T2D) is associated with TCF7L2 (or TCF4) polymorphisms.[1] TCF7L2/TCF4 is a transcription factor involved in the Wnt-signaling pathway, which plays an important role in colorectal carcinogenesis. Familial adenomatous polyposis (FAP) is a syndrome caused by germline mutations in the *APC* gene. *APC* gene defects lead to nuclear accumulation of β-catenin, and formation of β-catenin/TCF4 complexes, which enhances the expression of the Wnt-target genes.[2] Recent studies reported activation of the Wnt-signaling pathway in pancreatic cells in T2D patients, as well as in mice on a high-fat diet.[3] On the basis of these observations, we hypothesize that FAP patients are at increased risk of T2D.

To evaluate the prevalence of T2D in FAP, we used the Dutch Polyposis Registry Database and the outcome of a recent cross-sectional study on the psychosocial impact of FAP.[4] Eligible participants were those with a clinically and/or genetically proven FAP diagnosis. A questionnaire that addressed psychosocial issues and clinical variables, including questions about the presence of diabetes, was mailed in 2006. The study was approved by the ethical committees of both the Netherlands Cancer Institute and the Netherlands Foundation for the Detection of Hereditary Tumours. The prevalence of T2D in the study group was compared with that reported for the Dutch general population.[5] The standardized morbidity ratio (SMR) was calculated to evaluate whether the prevalence in the study group differs from that in the general population. The 95% confidence interval was calculated using the program confidence interval analysis, version 1.

Information was received on 341 FAP patients. Seventeen patients reported to have diabetes (16 T2D and 1 diabetes type I). All cases were confirmed by medical records and/or the general practitioner. One patient was excluded because of Whipple surgery for duodenal polyposis. The mean age of the remaining 15 T2D patients was 55.3 years (range: 35–75 years). The prevalence of T2D in the study group and in the general population is shown in Table 1. The prevalence of T2D in FAP patients was significantly higher than expected (SMR: 2.22; 95% confidence interval: 1.24–3.65).

Recent studies suggested that variants of TCF7L2/TCF4 are associated with the development of T2D.[1,6,7] Also laboratory studies suggested that the Wnt-signaling pathway is involved in T2D. FAP is caused by *APC* gene defects, which lead to the activation of this pathway. This is the first clinical study that demonstrated a significantly increased prevalence of T2D in FAP patients, which supports the role of the Wnt-signaling pathway in T2D. Future studies should explore the

Table 1. The prevalence of T2D in patients with FAP and in the general population

	Polyposis patients, $N = 339$		Zodiac study,[5] $N = 155{,}774$	Expected number of FAP patients with T2D based on population prevalence
Age range (years)	Number of patients with T2D/FAP patients	Prevalence	Prevalence T2D in general population	
16–19	0/14	0	0	0
20–29	0/44	0	0	0
30–39	4/92	4%	0.3%	0.276
40–49	1/69	1.4%	1.2%	0.828
50–59	2/75	2.6%	3.2%	2.400
60–64	4/26	15%	5.8%	1.508
65–69	3/13	23%	8.6%	1.118
70–79	1/6	17%	10.7%	0.642
Total number	15			6.772

mechanism of the development of T2D in the presence of an activated Wnt-signaling pathway.

Yours sincerely,
M.H. Nieuwenhuis
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Chapter 8

Desmoid tumors in a Dutch cohort of patients with familial adenomatous polyposis

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Desmoid Tumors in a Dutch Cohort of Patients With Familial Adenomatous Polyposis

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Background & Aims: **Desmoid tumors are a severe extracolonic manifestation in familial adenomatous polyposis (FAP). Identification of risk factors might be helpful in the management of FAP patients with such tumors. The aim of this study was to assess potential risk factors for the development of desmoids in a cohort of Dutch FAP patients.** ***Methods:*** **The medical records of 735 FAP patients were analyzed for the occurrence of desmoids. Relative risks and survival times were calculated to assess the influence of potential risk factors (female sex, family history, mutation site, abdominal surgery, and pregnancy) on desmoid development.** ***Results:*** **Desmoid tumors were identified in 66 of the 735 patients (9%). The cumulative risk of developing desmoids was 14%. No correlation was found between specific adenomatous polyposis coli mutation sites and desmoid development. Patients with a positive family history for desmoids had a significant increased risk to develop this tumor (30% vs 6.7%, $P < .001$). No association was found between female sex or pregnancy and desmoid development. Most desmoid patients (95%) had undergone previous abdominal surgery. In a substantial proportion of patients with an ileorectal anastomosis, it was impossible to convert the ileorectal anastomosis to an ileal pouch–anal anastomosis as a result of desmoid development.** ***Conclusions:*** **A positive family history of desmoids is an evident risk factor for developing desmoids. Most desmoids develop after colectomy. No correlation was found between desmoids and the adenomatous polyposis coli gene mutation site, female sex, and pregnancy. Ileal pouch–anal anastomosis is the appropriate type of surgery in FAP patients with a positive family history for desmoids.**

Familial adenomatous polyposis (FAP) is a hereditary disease, characterized by the development of multiple colorectal adenomas and a spectrum of extracolonic manifestations. Germline mutations of the adenomatous polyposis coli (*APC*) and *MUTYH* genes have been found to cause adenomatous polyposis.[1,2] Because of the large number of adenomas, patients almost inevitably develop colorectal cancer, usually before age 50. By performing a prophylactic colectomy, the colon cancer risk decreases and life expectancy increases. As a consequence, extracolonic manifestations have become relatively more important.

The clinically most important extracolonic manifestations of FAP are duodenal adenomas and desmoid tumors[1] because these may cause significant morbidity and mortality in FAP patients. Desmoid tumors are reported to be the second cause of death after colorectal cancer.[3]

The majority of desmoid tumors in FAP patients arise in the small-bowel mesentery and in the abdominal wall, with smaller numbers located on the extremities. Histologically, desmoid tumors are benign proliferations of myofibroblasts, arising in musculoaponeurotic tissues. Generally, the synonym *aggressive fibromatosis* is used if they are located in the mesenterium. Although desmoids do not metastasize, they are locally aggressive tumors, causing morbidity and mortality by local infiltration, impairment of circulation, and pressure on surrounding structures.[4]

Various management strategies have been described, including surgical excision, radiotherapy, and treatment with nonsteroidal anti-inflammatory drugs, anti-estrogens, and cytotoxic chemotherapy.[5–8] Evidence for the efficacy of these therapies is very limited because the treatment results reported in the literature all were based on small series of patients.[9]

In the general population desmoid tumors are rare, occurring in only 2 to 4 patients per million per year. In FAP patients, however, the prevalence of desmoids is 7% to 12%,[9] which suggests that the *APC* gene defect plays a role in the development of desmoid tumors.[10–12] However, the cause of desmoid tumors still is unknown. Several risk factors are suggested to be associated with desmoid development: female sex,[10,11] pregnancy,[5] exposure to oral contraceptives,[5] surgical trauma,[13] a positive family history for desmoids,[10,11,13] and the position of the *APC* germline mutation, either 5′ or 3′ of codon 1444.[10,11,14,15]

Abbreviations used in this paper: APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis.

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The identification of risk factors for desmoid development could result in rational treatment recommendations for these tumors. The aims of this study were to analyze the influence of potential risk factors on the development of desmoid tumors in a cohort of Dutch FAP patients.

Methods

Since the establishment of the Netherlands Foundation for the Detection of Hereditary Tumours in 1985, 735 patients from 315 families with a clinically verified diagnosis of FAP were registered.

We retrospectively analyzed the clinical, surgical, and pathologic records of all patients in this cohort to assess the presence of desmoid tumors or mesenteric fibromatosis. Cases were defined as those patients having clinically evident lesions, irrespective of the extent of the tumor. From the clinical records, information also was obtained on several potential risk factors, including sex, site of *APC* mutation, family history of desmoids, previous abdominal surgery, and pregnancy. The course of desmoid disease in women who became pregnant was described.

The overall cumulative risk of developing desmoids was calculated by survival analysis (Kaplan–Meier). In addition, cumulative risks were calculated separately for both sexes, for patients with and without a family history of desmoids, for patients with and without surgery, and for patients with *APC* mutations 5′ or 3′ of codon 1444.

Observation time was from birth until the age of diagnosis of the desmoid tumor, death, or closing date of the study (January 7, 2005), whichever came first. Differences between groups were tested using the log-rank test. Statistical significance was considered at P values less than .05. Statistical analysis was performed using SPSS version 12.0.1 (SPSS, Chicago, IL).

Results

Overall, desmoid tumors were diagnosed in 66 of the 735 FAP patients (9%). Patient characteristics are shown in Table 1. Two thirds were located intra-abdominally (in the mesenterium), with the remainder in the abdominal wall or on the extremities. Most patients received treatment, either a nonsteroidal anti-inflammatory drug (sulindac), tamoxifen, or a combination of these drugs. Nineteen of the 66 desmoid patients had died; 9 of them died (13.6%) from complications of mesenterically located desmoids, causing obstruction and perforation of the small intestine.

Table 1. Characteristics of 66 Patients With Desmoid Tumors in 735 Dutch FAP Patients

Sex, n (%)	
Male	34 (52)
Female	32 (48)
Age at diagnosis of first desmoid tumor, *y*	
Mean (range)	33 (14–58)
Location of desmoid tumor, n (%)	
Intra-abdominal/mesentery	44 (67)
Extra-abdominal/abdominal wall	14 (21)
Extremities	6 (9)
Unknown	2 (3)
Cause of death, n	
Complications of desmoid	9
Other	10

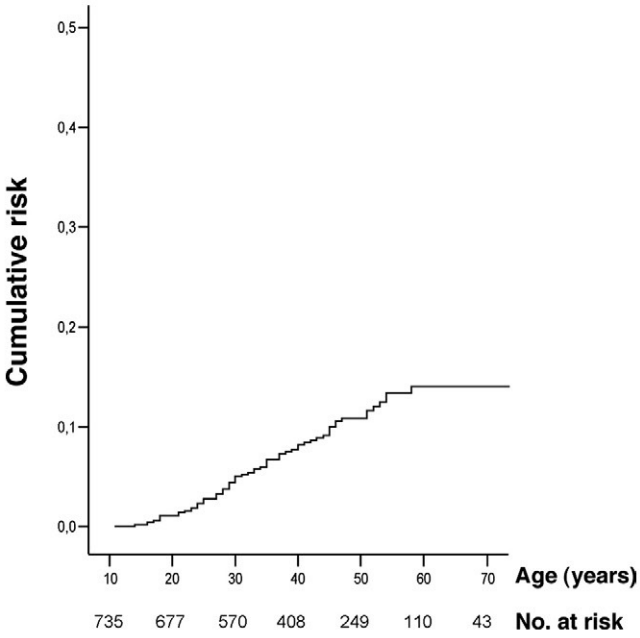

Figure 1. Cumulative risk of desmoid development.

Sex

The cumulative risk of developing a desmoid tumor was 14% at age 60 and did not significantly increase subsequently (Figure 1). The risk was shown to be the same for both sexes (13% for males and 15% for females; log rank $P = .6250$; no Kaplan–Meier curve shown).

Mutation Analysis

APC mutations were detected in 492 of the 735 (66.9%) patients. Desmoids developed in 49 of 448 (10.9%) patients with a mutation 5′ of codon 1444 and in 4 of the 44 (9.1%) patients with a mutation 3′ of codon 1444. The cumulative risk of developing desmoids for patients with a mutation before codon 1444 was not significantly different when compared with those patients with mutations beyond codon 1444 (18% and 12%, respectively; log rank $P = .5370$; no Kaplan–Meier curve shown). *MUTYH* mutations were detected in 43 of *APC* mutation-negative FAP patients; no desmoid tumors were observed in this group. In 60 of the 66 patients with a desmoid tumor, *APC* mutation analysis was performed. Fifty-three (88%) were found to have an *APC* mutation.

Family History

In Figure 2, for desmoid patients, the number of patients per family in relation to the mutation sites are shown. Thirty-one patients were the only desmoid patient in their family. Twelve families had 2 desmoid patients, and in 2 families 3 relatives were affected. In 1 family, 5 patients had desmoid tumors. In this family, a mutation in codon 150 of the *APC* gene was detected and the members had a phenotype of hundreds of colorectal adenomas.

Forty-six (15%) of the 315 FAP families had at least 1 patient with a desmoid tumor. A total of 638 patients had at least 1

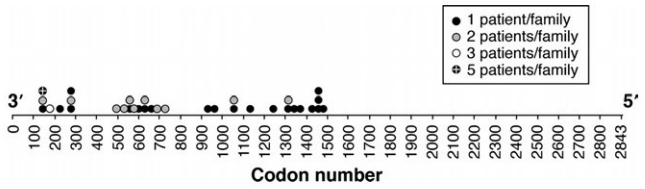

Figure 2. Representation of the *APC* gene and the distribution of mutations of families with a desmoid tumor. The number of dots corresponds with the frequency of mutations at one particular site.

relative with FAP. The cumulative risk at age 60 years of developing desmoids for patients with a positive family history for desmoids was 30%, compared with 6.7% if patients did not have relatives with desmoid tumors (log rank $P < .001$; Figure 3).

Surgery

A total of 612 patients underwent colorectal surgery; 63 (10.3%) of them developed desmoids after surgery between 1 and 30 years after surgery, most (65%) of them within 5 years after primary surgery. Three (2.4%) of 123 patients who had not undergone colorectal surgery developed desmoids as well. These desmoids were found either during primary surgery or became clinically manifest before surgery at ages of 22, 32, and 30 years, respectively. The cumulative risks of developing a desmoid tumor for patients with and without previous abdominal surgery are 15% and 4.6%, respectively (log rank $P = .0789$; figure not shown). The type of surgery did not seem to be a significant factor in the risk of developing desmoids; after ileorectal anastomosis (IRA), ileal pouch-anal anastomosis (IPAA), and ileostomy approximately 10% of patients developed desmoids (Table 2).

Forty patients with desmoids had an IRA as the primary surgical procedure. A second surgery was required in 23 of them: in 21 patients because of polyposis and in 2 patients because of carcinoma of the rectum. In 7 of these patients an ileostomy had to be performed because an IPAA procedure had

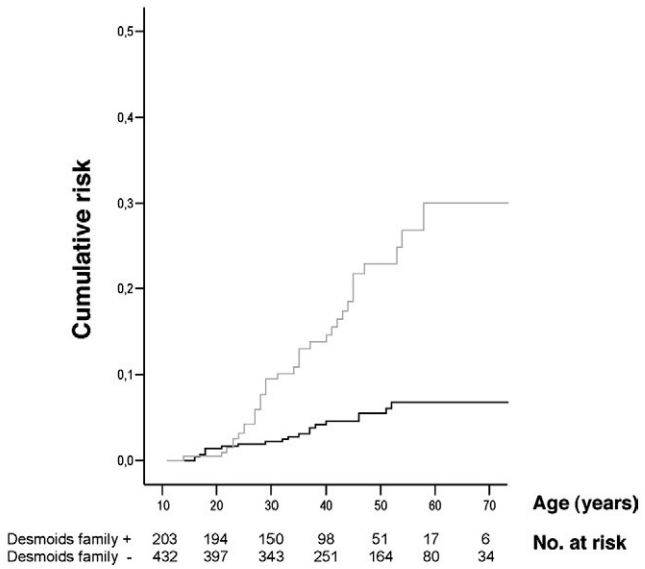

Figure 3. Cumulative risk of desmoid development for patients who have minimal 1 family member with a desmoid tumor (*grey*), compared with patients without desmoids (*black*) in the family history.

Table 2. Number of Patients Developing Desmoid Tumors After Colorectal Surgery

Type of primary surgery	Number of patients	No. (%) of patients developing desmoids
IRA	330	40 (12.1%)
IPAA	226	19 (8.4%)
Ileostomy	46	4 (8.7%)
Unknown	10	0

become impossible as a result of extensive desmoid development. In 4 other patients, secondary colorectal or gynecologic surgical procedures were seriously complicated as a consequence of desmoid tumors or fibromatous strictures.

Pregnancy

Thirteen of the 32 women with desmoid tumors in our series had been pregnant. Table 3 shows the age at pregnancy and the age at diagnosis of the desmoid tumor. Desmoids were distributed evenly intra-abdominally and extra-abdominally, and developed on average 13 years (range, 1–27 y) after pregnancy. Two women had desmoids before they became pregnant. One of them had a desmoid tumor in the abdominal wall that developed 1 year after IRA. After surgical excision her convales-

Table 3. Characteristics of Desmoids in Patients Who Had Been Pregnant

Patient no.	Age at pregnancy, *y*	Age at diagnosis of desmoid, *y*	Location of desmoid tumor
1	27	29	Mesenterium
2	18	22	Abdominal wall
	21	33	Abdominal wall
3	23	52	Mesenterium
	25		
4	34	25	Abdominal wall
	37		
5	21	37	Abdominal wall
	24		
	29		
6	26	44	Unknown
	30		
7	23	40	Mesenterium
	27		
8	26	46	Mesenterium
	28		
9	28	58	Extremities
	31		
	35		
10	24	33	Abdominal wall
		34	Abdominal wall
		40	Abdominal wall and mesenterium
11	25	24	Abdominal wall
	29	24	Abdominal wall
	31	26	Abdominal wall
12	32	37	Mesenterium
13	26	46	Mesenterium

NOTE. Patients 4 and 11 had desmoids before pregnancy, the other women developed desmoids an average of 13 years after pregnancy (range, 1–27 y).

cence was good. Nine years after excision of the desmoid tumor she became pregnant; no complications occurred during pregnancy. The other patient had an IRA at age 17 and an IPAA at age 22. One year after the IPAA procedure, a fast-growing tumor in the abdominal wall muscles was detected, which was shown to be a desmoid tumor after excision. Within 3 months after excision, she had a recurrence that again was removed surgically. Two years later she once more reported recurrence of the tumor. Six months previously she had delivered a baby. No complications were reported with regard to the combination of pregnancy and desmoid tumor. Three and 5 years later, she became pregnant again. No further desmoid tumors were reported.

Discussion

Desmoid tumors are a severe extracolonic manifestation in FAP, usually developing in young patients. In our series, desmoids were distributed equally between both sexes. The cumulative risk of developing desmoids was 14%, with most of the tumors being located in the small-bowel mesentery. They caused death in 9 of 66 desmoid patients. No correlation was found between the location of *APC* gene mutations and desmoid development; mutations were scattered over the gene. A positive family history for desmoids proved to be a strong predictor for desmoid development. Most desmoid tumors developed after abdominal surgery, although this was nonsignificant and in some cases desmoids were found before or at the time of primary surgery. The type of abdominal surgery showed no evident correlation with desmoid occurrence.

The prevalence, age at diagnosis, and the distribution of locations of desmoids in our series resemble those reported by others.[5,8,10,11,13,16] In our cohort, 9 patients (14%) died from complications of desmoids, confirming the observation of Arvanitis et al,[3] who found desmoids to cause significant mortality in FAP patients. A remarkable result of our study was the distribution of *APC* mutations among desmoid patients. Previous studies have shown that desmoids were linked to specific mutations in the *APC* gene, particularly those beyond codon 1444.[10,11,14,15] Other studies also have described families with *APC* gene mutations in codons 1924 and 1962 who had multiple desmoid tumors in the absence of the colonic features of FAP.[17,18] In contrast, the majority of mutations seen in our desmoid patients were distributed evenly over the 5′ part of the *APC* gene (Figure 2). In our series, a large family with 5 desmoid patients had a mutation in codon 150 of the *APC* gene. In this family, a severe colorectal phenotype was found. Also, other extracolonic manifestations were found in this family (adenocarcinoma of the papilla of Vater).

An evident predictive factor of developing desmoid tumors is the occurrence of desmoids in several members of 1 family. A positive family history of desmoids showed a significantly increased risk of developing desmoids; this also has been reported in previous studies, in which odds ratios varied between 3 and 12.[10,11,13]

We could not confirm an association between desmoids and female sex, which was reported for FAP-related[10,11] and sporadic[19] desmoid tumors. In contrast, in our cohort there was no evident sex difference, which is consistent with the findings in 2 other studies.[5,13]

In the past, pregnancy was suggested to enhance desmoid development because of the role of estrogens in desmoid growth.[5,9] In contrast, Church and McGannon[20] reported a milder course of intra-abdominal desmoid tumors after previous pregnancy. In our patients, pregnancy seemed not to elicit desmoid development. In current practice, pregnancy is discouraged in patients with desmoids. Regarding the good outcome of our pregnant patients with previous desmoids, we would propose to evaluate the outcome of pregnancy in a large number of patients.

It generally is assumed that desmoid development is induced by surgical trauma.[9] If desmoids develop, they often occur in the surgical scar and within 10 years after surgery. Those factors indeed suggest a relation between tissue defects and desmoid development. However, in the present study, 3 of 123 patients had developed desmoids or mesenteric fibromatosis before abdominal surgery. Also, in previous reports, desmoids were found in patients who had not undergone surgery.[5,13]

It should be noted that this issue is very difficult to evaluate. Nearly all FAP patients have a colectomy before age 30 to prevent colorectal cancer development; in 10% to 15% of young FAP patients, desmoids are observed. This raises the question: would these tumors have developed without surgery? The majority of FAP patients underwent prophylactic colectomy, but did not develop desmoid tumors, suggesting that other factors play a role in desmoid develoment.

Because of the supposed tendency of desmoids to develop after surgical intervention, Friedl et al[15] advised postponing elective colectomy in patients with mutations that predict desmoid tumors. However, we could not detect specific mutations strongly associated with desmoid development. The surgical options in FAP are either a colectomy with IRA or a total colectomy with IPAA procedure. Although an IRA is safer in terms of complications, one third of these patients will need secondary proctectomy because of unmanageable rectal polyposis or rectal cancer.[21] If desmoids have developed after an IRA, secondary proctectomy may be impeded or even become impossible,[16,22] as was the case in 7 of our patients. We would advise performing an IPAA as the primary procedure in patients with an increased risk of desmoid tumors. Based on our results, those patients with a family history of desmoids are candidates for IPAA because of their increased risk of desmoid development. Furthermore, if mesenteric fibromatosis is detected during the IRA procedure, conversion to an IPAA, if possible, should be considered, to avoid secondary proctectomy later in life, which then may have become impossible.

Finally, we recommend clustering of patients with desmoids in specialized centers to increase knowledge on desmoid disease and predicting factors. This will benefit the management of desmoid patients.

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Chapter 9

A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses

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A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses

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Desmoid-type fibromatoses are neoplasms of fibroblastic origin, occurring sporadically or associated with familial adenomatous polyposis (FAP) coli. By comparing sporadic and FAP-associated desmoid-type fibromatoses, we tried to identify clinical characteristics, which may indicate FAP. Histopathology data of all Dutch patients with desmoid-type fibromatoses diagnosed between 1999 and 2009 were retrieved from PALGA, the nation-wide network and registry of histopathology in the Netherlands. For calculation of incidence rates, person-years from the general matched population were used. Based on polyp counts in pathological records, the cohort was divided into a FAP group and a non-FAP group. Patient- and tumor characteristics were compared between the two groups. A total number of 519 patients older than 10 years with a confirmed diagnosis of desmoid-type fibromatoses were included. Thirty-nine (7.5%) desmoid patients were documented of having FAP. The incidences of sporadic and FAP-related desmoid-type fibromatoses were 3.42 and 2,784 per million person-years, respectively. The majority of FAP patients developed desmoid-type fibromatoses after the diagnosis of FAP. Having FAP was associated with male gender [odds ratio (OR) 2.0, $p = 0.034$], desmoid diagnosis at an earlier age (mean 36 *vs.* 42 years, $p = 0.031$), and desmoid localization intra-abdominally (OR 18.9, $p \leq 0.001$) or in the abdominal wall (OR 4.8, $p \leq 0.001$), compared to extra-abdominal desmoid localization. In conclusion, patients with desmoid-type fibromatoses are at risk of underlying FAP. Especially cases with desmoid localization intra-abdominal or in the abdominal wall, and all patients younger than 60 years, have a substantial increased risk and should be referred for colonoscopy.

Desmoid-type fibromatoses, previously known as aggressive fibromatoses, musculoaponeurotic fibromatoses or desmoid tumors, is a rare neoplastic disorder with an unpredictable disease course. Histologically, these neoplasms are benign fibroblastic tumors consisting of spindle cells and fibroblasts with a low mitotic rate. Differentiation from other soft tissue tumors, for example low grade fibromyxoid sarcomas, can be difficult.[1] Clinically, desmoid-type fibromatoses either presents as a solid tumor, located in muscles, or as diffuse fibromatoses in the mesenterium. Despite the histological bland morphology, desmoid-type fibromatoses show locally aggressive features such as infiltration in surrounding tissue, and a tendency to recur after resection. Desmoids lack metastatic potential. The etiology of desmoid-type fibromatoses is thought to be multifactorial.[1] Supposed risk factors are exposure to estrogens, trauma (associated with surgery or pregnancy), and a positive family history of desmoid-type fibromatoses.[2 5]

Desmoid-type fibromatoses are rare in the general population with estimated incidence rates of two to four per million individuals per year.[6] However, in patients with familial adenomatous polyposis (FAP), desmoid-type fibromatoses are reported in 10–30%,[2 4,7,8 10] whereas about 10–20% of all patients with desmoids have FAP.[11] FAP is a dominantly inherited colon cancer predisposition syndrome, caused by a germline mutation in the *APC* gene.[12] FAP patients develop hundreds to thousands of colonic adenomas from a young age of onset. Without treatment, virtually all patients develop colorectal carcinoma by the age of 40–50 years.[1,13]

Given their risk to develop colonic cancer, it is important to identify patients at high risk for FAP, and refer them for colonic examination. By this strategy, development of colorectal cancer can be prevented in patients and in their family members, by including them in screening programs.

Key words: desmoid-type fibromatoses, familial adenomatous polyposis, epidemiology, risk factors
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The aims of this study were (*i*) to calculate incidence rates of sporadic and FAP-related desmoid-type fibromatoses and (*ii*) to compare clinical characteristics of sporadic and FAP-related desmoid-type fibromatoses, to identify specific clinical features which are associated with FAP.

Material and Methods

Patients and data collection

Pathology records of patients who were diagnosed with a desmoid-type fibromatoses between January 1, 1999 and January 1, 2009 were retrieved from the PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands, which has nationwide coverage since 1991.[14] In this database, summaries of all histopathology and cytopathology reports of Dutch patients are collected and coded similar to the Systematized Nomenclature of Medicine Classification of the College of American Pathologists.[15] This database offers unique possibilities for studying true-pathology based incidence rates[16] or associations between biopsy-proven disease types.[17] Handling of samples and data retrieval was according to the ethical guidelines "Code for proper secondary use of human tissue in The Netherlands" established by the Dutch Federation of Medical Sciences.

To obtain information on all Dutch patients with desmoid-type fibromatoses, a search was performed with the search terms "desmoid" and "aggressive fibromatoses." The retrieved data included information on sex and age, place of birth, year of desmoid discovery and additional pathological diagnoses. The retrieved pathologic reports also included the indication for the examination, *i.e.*, information on the endoscopic findings. Inclusion criteria were (*i*) a diagnosis of desmoid-type fibromatoses between January 1, 1999 and January 1, 2009, and (*ii*) age above 10 years. Cases suffering from superficial fibromatoses of the hands or feet (Dupuytren's disease), and juvenile fibromatoses were excluded. The database was corrected manually for obvious miscoding. Records with a doubtful diagnosis of desmoid-type fibromatoses were discussed by the authors, one of which is an experienced soft tissue pathologist, and included if the diagnosis was revised to desmoid-type fibromatoses. Based on the information on colorectal polyps in pathology records of any date, and clinical background information given by the request to the pathologists, patients were divided into a "confirmed FAP" or a "non-FAP" group. "Confirmed FAP" was defined as more than 10 colonic adenomas and/or duodenal polyps detected under the age of 60 years.

Desmoid localizations were categorized into three groups, defined as (*i*) at least mesenterial (*ii*) abdominal wall and (*iii*) extra-abdominal sites, including head, neck, trunk, back, gluteal region, arms and legs. Further variables were retrieved from the database, including sex, age at primary desmoid-type fibromatoses, desmoid size and recurrence of desmoids. It was impossible to distinguish between recurrent and new primary desmoid-type fibromatoses by pathological records only. All other pathology records were categorized into one of the following groups of comorbidity: colorectal cancer, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), benign diseases of the skin (lipomas, epidermoid cysts and fibroadenomas), malignant diseases of the skin (melanoma, basal cell carcinoma and squamous cell carcinoma), benign diseases of the genitourinary tract (prostate hypertrophy, uterine fibroids), malignant diseases of the genitourinary tract (cancer of the bladder and prostate, cancer of female reproductive organs), breast cancer and hematological cancers.

Statistics

Incidence rates were calculated using data of the Dutch National Statistics Service to estimate Dutch population numbers. In this database, population numbers are reported stratified per decade, sex and different age groups. To calculate incidence rates, the time period 1999–2009 was used to calculate the denominator. Based on previous reports, the prevalence of FAP was set at 1/10,000 persons per year.[18] This FAP prevalence was used to estimate incidence rates of desmoid-type fibromatoses in FAP patients. Clinical and tumor related characteristics were compared in patients with and without FAP by univariate analysis using chi-square and Fisher's Exact Test for categorical variables, and the unpaired t-test for numerical variables. Logistic regression was used for multivariate analysis. Statistical significance was set at a p-value < 0.05. Statistical analysis was performed using SPSS version 16.0.0 (SPSS, Chicago, IL).

Results

Incidence of desmoid-type fibromatoses

A total of 519 patients met the inclusion criteria of this study. The Dutch population above 10 years of age comprised on average 14,015,356 persons between 1999 and 2009. Four hundred and eighty patients had sporadic desmoid-type fibromatoses, leading to an incidence of 3.42 per million person-years and a mean of 48 newly diagnosed patients per year in The Netherlands.

Assuming the FAP prevalence being 1/10,000, the FAP population comprised 1,400 patients older than 10 years between 1999 and 2009. Thirty-nine patients developed desmoid-type fibromatoses, leading to an incidence of 2,784 per million person-years and four diagnoses per year in The Netherlands FAP-population.

Compared to the general population, FAP patients have a more then 800-fold risk of developing desmoid-type fibromatoses.

Variables associated with FAP-related desmoid-type fibromatoses

Among the 519 desmoid patients, 39 (7.5%) FAP patients were identified. Thirty-three of these patients were diagnosed with FAP before the diagnosis of desmoid-type fibromatoses, whereas six patients developed FAP after a diagnosis of desmoid-type fibromatoses.

Table 1. Patient characteristics compared for FAP and non-FAP groups, respectively

	FAP yes *N* (%)	FAP no *N* (%)	Odds ratio	95% CI-interval	*p*-value
Total	39	480			
Sex					
Male	18 (46)	143 (30)	2.0	1.05–3.91	0.034
Female	21 (54)	337 (70)	1 (ref)		
Age at diagnosis of 1st DT (years)					
Mean (SD)	36.0 (12.9)	41.6 (15.8)		0.52–10.70	0.031
Age 1st DT, 10 years categories (years)					
11–20	4 (10)	23 (5)	1 (ref)		
21–30	10 (26)	94 (20)	0.61	0.18–2.13	0.436
31–40	13 (33)	156 (32)	0.48	0.14–1.60	0.222
41–50	5 (13)	85 (18)	0.34	0.08–1.36	0.113
51–60	6 (15)	58 (12)	0.60	0.15–2.30	0.448
61–70	1 (3)	33 (7)	0.17	0.02–1.66	0.161[1]
71–80	0	22 (4)	N.E.	0.73–0.997	0.117[1]
81–90	0	9 (2)	N.E.	0.73–0.997	0.553[1]
Localization 1st DT					
At least intra-abdominal	19 (51)	61 (13)	18.87	6.17–58.82	<0.001
Abdominal wall	14 (38)	175 (37)	4.76	1.54–14.71	0.003
Extra-abdominal	4 (11)	238 (50)	1 (ref)		
Size of first desmoid (cm)					
Median (min–max)	7.0 (5–16)	7.0 (1–35)		−5.36–5.64	0.950
Mean (SD)	9.0 (4.5)	9.1 (6.6)		−5.84–6.12	0.963
Recurrent/new primary DT					
No	36 (92)	424 (88)	1.59	0.47–5.32	0.604[1]
Yes	3 (8)	56 (12)	1 (ref)		
Age of recurrent/new primary DT					
Mean (SD)	42.7 (10.7)	41.0 (14.0)		−18.2–14.8	0.837
Comorbidity					
Colorectal carcinoma	7 (18)	14 (3)			<0.001
IBD	2 (5)	42 (9)			0.763[1]
Benign skin disease	11 (28)	99 (21)			0.265
Malignant skin disease	0	28 (6)			0.256[1]
Benign GU-tract disease	2 (5)	59 (12)			0.297[1]
Malignant GU-tract disease	0	10 (2)			1.00[1]
Breast cancer	0	15 (3)			0.618[1]
Hematological cancer	0	4 (0.8)			1.00[1]

[1]Fisher's exact test.
Abbreviations: FAP, familial adenomatous polyposis; CRC, colorectal cancer; DT, desmoid tumor; IBD, inflammatory bowel disease; GU-tract, genitourinal tract; Ref, reference; N.E., not estimable.

The comparison of patient characteristics between the FAP and non-FAP group is shown in Table 1. Overall, more female than men were affected by desmoid-type fibromatoses. In the group with sporadic desmoids, 70% were female, and in the group with FAP-related desmoids, 54% were female. An evaluation of the available pathology reports per patient showed FAP patients more often having colorectal cancer, compared to non-FAP patients. No statistical association was found between desmoid-type fibromatoses and other comorbid conditions.

Patients with FAP were significantly younger at the diagnosis of primary desmoid-type fibromatoses (mean age 36 *vs.*

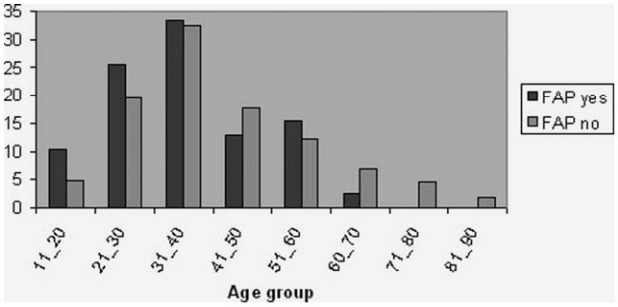

Figure 1. Proportion of patients per age group (10-year categories) having a primary diagnosis of desmoid type fibromatoses, showing a mainly congruent age distribution between FAP and non-FAP patients.

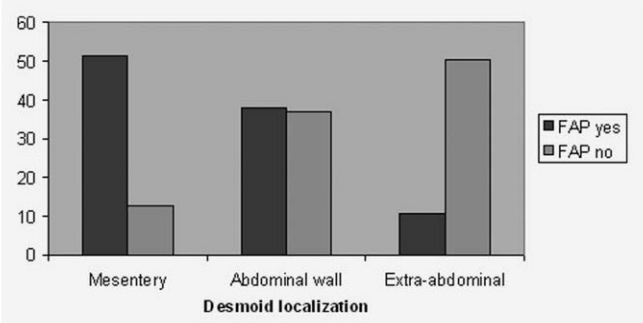

Figure 2. Proportion of patients per desmoid localization, for FAP and non-FAP patients.

42 years, $p = 0.031$). Figures of age distribution of primary diagnosis of FAP-related and sporadic desmoids follow the same pattern, as shown in Figure 1. FAP-related desmoids were found most often intra-abdominally (51%), whereas 50% of sporadic desmoids was located extra-abdominally. The odds ratio (OR) for a localization in the abdominal wall compared to extra-abdominal localizations was 4.76, whereas the OR was 18.87 for intra-abdominal desmoid-type fibromatoses. In both the FAP and non-FAP groups, 38 and 37% of desmoid-type fibromatoses was located in the abdominal wall, respectively. In Figure 2, the proportion of patients per desmoid localization is shown.

As desmoid localization, sex, and age showed statistical significance at univariate analysis, these variables were put into a logistic regression model (Table 2). After adjustment, the OR for FAP was still statistically increased in male (OR 3.25). Importantly, after adjustment for age and sex, the OR for FAP in abdominal desmoid-type fibromatoses was much higher than for extra-abdominal desmoids, with an OR of even 23 for intra-abdominal desmoid-type fibromatoses.

Discussion

Desmoid-type fibromatoses are rare neoplasms, occurring either sporadically or in the context of FAP. In our study, at least 7.5% of desmoid-type fibromatoses were associated with FAP. The calculated incidence of sporadic desmoids was 3.42

Table 2. Multivariate analysis with the risk of having FAP as dependent variable, and age of diagnosis of desmoid, localization of desmoid and sex as covariates

Variable	Odds ratio	*p*-value	95% confidence interval
Age (continuous)	0.95	0.002	0.92–0.98
Sex			
Male	3.25	0.007	1.38–7.67
Female	1 (ref)		
Localization desmoid			
At least intra-abdominal	23.22	0.000	7.21–74.75
Abdominal wall	6.70	0.002	2.00–22.43
Extra-abdominal	1 (ref)		

per million person-years, whereas for the FAP population, the incidence was 2,784 per million person-years. This shows that the risk to develop desmoid-type fibromatoses for a FAP patient is more than 800-fold increased. However, most of these neoplasms seen by surgeons and pathologists are sporadic ones, due to the relative low incidence of FAP. Factors which we found to be associated with FAP-related desmoids were male sex, age of desmoid development younger than 60 years, and desmoid localization intra-abdominally.

The incidence rates of sporadic and FAP-related desmoid-type fibromatoses, calculated in our cohort, resemble that of previous reports.[6,9]

One previous study compared characteristics of sporadic and FAP-related desmoid-type fibromatoses,[11] reporting 70 of 447 (16%) desmoid patients having FAP. In our study, a lower percentage (7.5%) of desmoid patients were found to have FAP. This difference may be explained by different ways of data collection. We used data from all Dutch hospitals, collected in a national pathology registry. Fallen *et al.*[11] retrieved data from the Mayo Clinic, which is a tertiary care institution, to which generally the more complicated cases (mesenterial desmoids) are referred. Moreover, we may have under-estimated the incidence of FAP-related desmoid-type fibromatoses. First, there might be patients with an as yet undiagnosed FAP, presenting with sporadically appearing desmoid-type fibromatoses. Furthermore, we might have missed FAP patients who have had colectomy before 1991, whose pathological records on colonic polyps were recorded incompletely.

Both in Fallens' study as in our study, women were more often affected by desmoid-type fibromatoses than men. This might be attributed to the influence of estrogens.[4] However, as the sex difference in FAP patients was considerably smaller than in non-FAP patients, hormonal influences may be less important in FAP-related desmoids.

Although Fallen detected no significant differences in ages between development of desmoids in FAP and non-FAP settings, we found desmoid development on average 6 years earlier in FAP patients, compared to non-FAP patients. However, the age distributions of FAP-related and non-FAP-

related desmoids show great similarity, making age as a discriminating factor to identify FAP unreliable for individual patients.

Although we categorized desmoid localizations slightly different than Fallen, in both studies the majority of FAP-related desmoid-type fibromatoses were located intra-abdominally, whereas the majority of sporadic desmoids were located extra-abdominally.

We also assessed tumor size and desmoid recurrence, both showing no significant differences between FAP and non-FAP groups. As expected, colorectal cancer was more common among the FAP patients. Despite the spectrum of extracolonic manifestations in FAP, including multiple benign skin lesions, comparable numbers of such lesions were observed in both groups.

Strengths of this study were the large number of cases with complete data, which were retrieved from the nation-wide PALGA database. This nation-wide coverage enhances the generalizability of the study results.[19] A limitation of using this database was that only pathology reports and no colonoscopy reports were available. Information on *APC* mutation status and family history of desmoid-type fibromatoses and of colorectal cancer would have lead to a more exact estimation of the number of FAP patients.[2,12,20,21] Various other potential predictive factors were not taken into account since these could not be extracted from pathology reports and tracing of these data was not compatible with ethical considerations. For example, previous pregnancy, exposure to estrogens and surgical trauma are considered to be important risk factors for developing abdominal wall desmoids.[5] In addition, we may have underestimated the number of FAP-related desmoid-type fibromatoses, as biopsies are not always taken in these cases.

Identifying FAP patients has obvious clinical implications, not for the patient only but also for family members, who may be affected by FAP too. Due to hereditary cancer registrations, FAP is generally diagnosed early in life, and as shown in our study population, FAP is often diagnosed earlier than desmoid-type fibromatoses. However, about one-third of FAP patients has *de novo* mutations of the *APC* gene, being the first person in the family that is diagnosed with FAP. Furthermore, several previously published case reports show that there are still patients with apparently sporadic desmoid-type fibromatoses who were found to have FAP at further examination.[22–24]

In conclusion, as at least 7.5% of desmoid-type fibromatoses are associated with FAP, the possibility of FAP should be considered in each patient presenting with desmoid-type fibromatoses. Based on our results, colonic examination is highly recommended in patients younger than age 60 years and patients with intra-abdominal or abdominal wall desmoid localizations. Of course, all patients should be asked for clues pointing to FAP, including abdominal complaints, rectal blood loss and details of gastrointestinal disorders in the family. In the case of any suspicion of FAP, referral to a gastroenterologist is essential.

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Chapter 10

Family history, surgery, and *APC* mutation are risk factors for desmoid tumors in familial adenomatous polyposis: An international cohort study

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ORIGINAL CONTRIBUTION

Family History, Surgery, and *APC* Mutation Are Risk Factors for Desmoid Tumors in Familial Adenomatous Polyposis: An International Cohort Study

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BACKGROUND: Ability to identify patients with familial adenomatous polyposis who have a high risk of developing desmoid tumors may affect decisions in clinical practice.

OBJECTIVES: Our aim was to assess several risk factors for desmoid tumor development in an international cohort of patients with familial adenomatous polyposis and to evaluate the clinical relevance of risk factors.

DESIGN: This was a retrospective cohort study.

SETTING AND PATIENTS: Polyposis registries in The Netherlands, France, Denmark, Finland, and Italy provided information on familial adenomatous polyposis patients with desmoid tumors.

MAIN OUTCOME MEASURES: We used univariate and multivariable analyses of data from registries in The Netherlands, France, Denmark, and Finland to test whether gender, *APC* mutation site, previous colorectal surgery, colorectal cancer, and family history for desmoid tumors contribute to risk of developing desmoid tumors at any location, or specifically at an intra-abdominal location. The effect of family history was tested with a generalized linear mixed model.

RESULTS: Of 2260 patients with familial adenomatous polyposis from 912 families in The Netherlands, France, Denmark, and Finland, 220 patients (10%) had desmoid tumors (101 men). In 387 patients with desmoid tumors (including 167 patients from the Italian registry), the median age at diagnosis of the first desmoid tumor was 31 years (range, 4 months–74 years). Desmoid locations were intra-abdominal (53%), abdominal wall (24%), extremities (9%), and unknown sites or combinations of sites (14%). Multivariable analysis of risk factors for desmoids at any location showed surgery (OR, 2.58; $P = .0004$), an *APC* mutation 3′ of codon 1444 (OR, 3.0; $P < .0001$), and a positive family history ($P < .0001$) to be independently associated with desmoid development. When only intra-abdominal location was analyzed, *APC* mutation site was not associated with desmoid development.

LIMITATIONS: Selection bias may have occurred.

CONCLUSIONS: A positive family history for desmoid tumors, abdominal surgery, and *APC* mutation site are significant risk factors for development of desmoid tumors. The results may have implications for

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determining the optimal management of FAP patients and guide future studies.

KEY WORDS: Desmoid tumor; Familial adenomatous polyposis; Risk factors.

Desmoid tumors are a serious manifestation of familial adenomatous polyposis (FAP), occurring in about 12% of patients.[1,2] A germline mutation in the adenomatous polyposis coli gene (*APC*) in patients with FAP leads to development of hundreds of colorectal adenomas. Without prophylactic colectomy, colorectal cancer inevitably results. In addition to the development of colorectal adenomas, patients with FAP may display various other manifestations, with desmoid tumors as one of the most threatening.

Although desmoid tumors are histologically benign fibroblastic neoplasms, intra-abdominal desmoids in particular cause substantial morbidity and even mortality in patients with FAP. The etiology of desmoid tumors has not yet been elucidated. Several potential risk factors have been suggested, including surgical trauma, estrogens, pregnancy and female gender, a strong family history of desmoids, and mutations at the 3′ end of the *APC* gene.[1–11] However, some potential risk factors, for example female gender, a positive desmoid family history, and a 3′ *APC* mutation site, were not consistently found in previous studies.[5,7,8,10] Moreover, the clinical relevance of some risk factors is questionable.

The aim of the present study was to assess risk factors for desmoid tumor development in a large European database of FAP patients. A secondary aim was to evaluate the potential clinical implications of such risk factors.

METHODS

Data were retrieved from 5 European polyposis registries located in The Netherlands, France, Denmark, Finland, and Italy. Patients with either a genetically (germline *APC* mutation) or clinically (more than 100 colorectal adenomas) confirmed diagnosis of FAP were included in the analysis. The Italian, Dutch, and French data had been used in previous studies on desmoid risk factors.[2,7,8] Because the Italian registry included only data on patients with desmoid tumors, these data were not included in the risk factor analysis. All patients in the registries had given informed consent for use of their data for research, and all patient data were handled anonymously.

For all patients, information was obtained on gender, age at first colorectal surgical procedure, type of colorectal surgery, and colorectal cancer at any time in life. For the patients with desmoid tumors, additional data were collected including age at diagnosis of the desmoid tumor and desmoid location.

Results are reported as median (range) for continuous variables, and number (percentage) for categorical variables. The associations between 4 potential risk factors (gender, mutation site, surgery, colorectal cancer) and development of a desmoid tumor were first assessed by univariate analysis, using Student T test for continuous variables and the χ^2 test for categorical variables. All tests were 2-sided at a .05 significance level. Variables with a P value lower than .2 were included in a multivariable logistic regression model. Analyses were performed using StatView computer software (version 5, 1992–1998, SAS Institute, Cary, NC).

To assess the impact of belonging to a family affected by desmoid tumors, a generalized linear mixed model was fitted, with the occurrence of a desmoid tumor as the response variable, the family effect regarded as a random effect, and the location of the mutation as a covariate. These analyses were restricted to individuals belonging to families where data were available for at least 2 family members. This mixed-effect model was compared to a fixed logistic regression model with the same response variable and covariate (likelihood ratio test). Testing this random effect allowed us to determine whether belonging to a family affected by desmoid tumors would modify an individual's risk of displaying a desmoid tumor, while simultaneously allowing us to adjust for the site of a frameshift mutation. Analyses were performed using the R statistical package (R Development Core Team; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

RESULTS

Characteristics of Patients With FAP

Data available for patients with FAP registered in databases in Denmark, Finland, France, and The Netherlands (Table 1) included 912 families comprising 2260 patients (52% men). Most patients (61%) had undergone surgery once, at a median age of 30 years. In the majority of cases, a subtotal colectomy with ileorectal anastomosis (IRA, n = 740, 39%) or total colectomy with ileal pouch–anal anastomosis (IPAA, n = 806, 43%) was performed. Of all patients, 508 (22%) had had a diagnosis of colorectal cancer. *APC* mutations 5′ of codon 1444 were the most common, occurring in 62% of patients, whereas mutations 3′ of codon 1444 occurred in 9%. A total of 220 patients (10%) developed at least 1 desmoid tumor.

The total cohort of FAP patients with desmoid tumors consisted of 387 patients, including the 220 patients from

TABLE 1. Characteristics of FAP patients from 4 European registries

	Netherlands (n = 992)	*France (n = 434)*	*Denmark (n = 498)*	*Finland (n = 336)*	*Total (n = 2260)*
No. of families	289	315	187	121	912
Sex, n (%)					
Men	517 (52)	214 (49)	276 (55)	157 (47)	1164 (52)
Women	475 (48)	220 (51)	222 (45)	179 (53)	1096 (48)
APC mutations, n (%)					
5′ of codon 1444	674 (68)	266 (61)	252 (50)	214 (60)	1406 (62)
3′ of codon 1444	82 (8)	22 (5)	46 (9)	49 (15)	199 (9)
Large deletion	53 (5)	36 (8)	0 (0)	13 (4)	69 (3)
Whole gene deletion	2 (0.2)	1 (0.2)	25 (5)	8 (2)	36 (2)
No/unknown mutation	181 (12)	109 (31)	175 (36)	52 (15)	517 (23)
Age at first surgery, y					
Median (range)	28 (5–91)	30 (6–67)	31 (5–87)	31 (1–71)	30 (1–91)
Number of operations, n (%)					
No operation	243 (24)	1 (0.2)	76 (15)	58 (17)	378 (17)
One operation	572 (58)	378 (87)	227 (46)	199 (59)	1376 (61)
More than one	177 (18)	55 (13)	195 (39)	79 (24)	506 (22)
Type of first surgery, n (%)					
IRA	347 (46)	63 (15)	167 (40)	127 (45)	740 (39)
IPAA	272 (36)	340 (79)	156 (37)	74 (27)	806 (43)
Proctocolectomy + ileostomy	57 (8)	24 (6)	20 (5)	42 (15)	143 (8)
Other procedure	73 (10)	6 (1)	79 (19)	35 (13)	193 (10)
Colorectal cancer, n (%)					
Yes	141 (14)	90 (21)	183 (37)	94 (28)	508 (22)
No	851 (86)	344 (79)	315 (63)	242 (72)	1752 (78)
At least 1 desmoid tumor	83 (8)	59 (14)	33 (7)	45 (13)	220 (10)

FAP = familial adenomatous polyposis; IRA = subtotal colectomy with ileorectal anastomosis; IPAA = total colectomy with ileal pouch–anal anastomosis.

Denmark, Finland, France, and The Netherlands, plus 167 patients from the Italian registry. Characteristics of this cohort are shown in Table 2. The median age at diagnosis was 31 years (range, 4 months–74 years). Approximately half (53%) of the initial desmoids had an intra-abdominal location. Intra-abdominal desmoid tumors were diagnosed at a significantly later median age than tumors at other locations (35 vs 28 years, $P < .0001$). Of all 387 patients with desmoid tumors, 324 (84%) had an *APC* mutation, with 5′ mutations more common than 3′ mutations (65% vs 19%). In addition, a total of 63 patients (16%) had large deletions or unknown mutations.

TABLE 2. Characteristics of FAP patients with desmoid tumors from 5 European registries

	Netherlands (n = 83)	*France (n = 59)*	*Denmark (n = 33)*	*Finland (n = 45)*	*Italy (n = 167)*	*Total (n = 387)*
Age at 1st desmoid diagnosis, median (range), y	31 (8–58)	39 (16–68)	30 (17–74)	28 ([a]–69)	31 ([b]–67)	31 (0–74)
Location of 1st desmoid, n (%)						
Intra-abdominal (mesentery)	51 (61)	30 (51)	16 (48)	24 (53)	84 (50)	205 (53)
Abdominal wall	13 (16)	8 (13)	13 (39)	15 (33)	46 (28)	95 (24)
Extremities	5 (6)	1 (2)	4 (12)	6 (13)	18 (11)	34 (9)
Unknown/combination of sites	14 (17)	20 (34)	0	0	19 (11)	53 (14)
Desmoid without colorectal surgery, n (%)	22 (27)	9 (15)	7 (21)	15 (33)	56 (33)	109 (28)
Desmoid after colorectal surgery, n (%)	61 (73)	50 (85)	26 (79)	30 (67)	111 (66)	278 (72)
Time between surgery and desmoid, median (range), months	49 (1–474)	60 (1–261)	30 (13–318)	30 (5–262)	32 (1–366)	36 (1–474)
APC mutations, n (%)						
5′ of codon 1444	62 (75)	36 (61)	17 (52)	16 (35)	120 (72)	251 (65)
3′ of codon 1444	8 (10)	11 (19)	4 (12)	18 (40)	32 (19)	73 (19)
Large deletion	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	3 (1)
Whole gene deletion	0 (0)	0 (0)	2 (6)	4 (9)	1 (1)	7 (2)
No/unknown mutation	12 (14)	10 (17)	10 (30)	7 (16)	14 (8)	53 (13)

FAP = familial adenomatous polyposis; NA = not available.
[a]Minimum, 8 months.
[b]Minimum, 4 months.

TABLE 3. Univariate and multivariable analysis of risk factors for desmoid tumors at any location

	Univariate		*Multivariable*	
	Desmoid tumor, n/N (%)	*P*	*OR (95% CI)*	*P*
Sex		.08		NS
Women	119/1096 (10.9)			
Men	101/1164 (8.7)			
APC mutation site		<.0001		<.0001
5′ of codon 1444	133/1406 (9.5)		1	
3′ of codon 1444	41/199 (20.6)		3.0 (1.99–4.46)	
Age at first surgery		.003		NS
≤31 years	71/859 (8.3)			
>31 years	126/1007 (12.5)			
Previous abdominal surgery		.003		.0004
No operation	21/378 (5.6)		1	
Operation	199/1882 (10.6)		2.58 (1.53–4.35)	
Type of surgery		.53		
IRA	78/704 (11.1)			
IPAA	85/842 (10.1)			
Colorectal cancer		.45		
Yes	45/508 (20.4)			
No	175/1752 (9.9)			

N = number of patients with available data from registries in The Netherlands, France, Denmark, and Finland; OR = odds ratio; NS = not significant; IRA = subtotal colectomy with ileorectal anastomosis; IPAA = total colectomy with ileal pouch–anal anastomosis.

Desmoid tumors occurred without a history of abdominal surgery in 109 patients (28%) and after surgery in 278 patients (72%). Mutations 3′ of codon 1444 occurred more frequently in patients without a history of abdominal surgery than in those with a postoperative desmoid tumor (40% vs 15%, $P < .0001$). Analysis of available data on tumor location showed an intra-abdominal location in 49% (47 of 96) for preoperative desmoids and in 66% (158 of 238) for desmoids developing after surgery, $P = .0031$. Postoperative desmoids developed at a median of 36 months (range, 1–474 months) after surgery.

Risk Factor Analysis

Our analysis of data of patients from Denmark, Finland, France, and The Netherlands showed that location of an *APC* mutation 3′ of codon 1444 and previous abdominal surgery were significant risk factors for developing a desmoid tumor, regardless of tumor location (Table 3). Sub-

TABLE 4. Univariate and multivariable analysis of risk factors for intra-abdominal desmoid tumors

	Univariate		*Multivariable*	
	Intra-abdominal desmoid tumor, n/N (%)	*P*	*OR (95% CI)*	*P*
Sex		.88		
Women	62/1096 (5.7)			
Men	60/1164 (5.2)			
APC mutation site		.19		NS
5′ of codon 1444	80/1406 (5.7)			
3′ of codon 1444	16/199 (8.0)			
Age at first surgery		.05		NS
≤31 years	41/859 (4.8)			
>31 years	70/1007 (7)			
Previous abdominal surgery		.009		.0016
No operation	10/378 (2.6)		1	
Operation	112/1882 (6)		2.33 (1.21–4.49)	
Type of surgery		.50		
IRA	45/704 (6.4)			
IPAA	47/842 (5.6)			
Colorectal cancer		.32		
Yes	23/508 (4.5)			
No	99/1752 (5.7)			

N = number of patients with available data from registries in The Netherlands, France, Denmark, and Finland; OR = odds ratio; NS = not significant; IRA = subtotal colectomy with ileorectal anastomosis; IPAA = total colectomy with ileal pouch–anal anastomosis.

analysis specifically for intra-abdominal desmoid tumors (Table 4) showed abdominal surgery to be the only significant risk factor for desmoid development. Gender and previous colorectal cancer were not associated with desmoid development. Although age was a significant factor in univariate analysis, it was not an independent risk factor in the multivariable analysis.

Based on the likelihood ratio test, the mixed-effect model, with family regarded as a random effect variable, differed significantly from the fixed logistic regression model (difference of deviances = 69.8, $P < 10^{-5}$). This suggests that belonging to a family affected by desmoid tumors significantly increases the individual risk of displaying a desmoid tumor and that this effect is independent of the frame-shift mutation site.

DISCUSSION

In the present study in a large international cohort of FAP patients, an *APC* mutation 3′ of codon 1444, previous abdominal surgery, and a positive family history of desmoid tumors were independent risk factors for desmoid tumor development. As far as we know, this study used the largest desmoid database currently in existence. However, because of the retrospective design of the study, we must take into account the possibility of selection bias for desmoid cases. Moreover, there may be differences in registration methods in the different countries. Despite these caveats, we believe that our cohort provides a reliable representation of European FAP patients with clinically relevant desmoid disease.

Several previous studies of risk factors for desmoid tumor development have reported contradictory results. Only previous abdominal surgery has been consistently found to influence desmoid development.[1,9–12] Our current study confirms previous abdominal surgery as an evident risk factor for intra-abdominal desmoid development.

Familial clustering of desmoid tumors was reported as a risk factor in at least 3 studies,[2,5,10] but was not found in a French study.[8] Because FAP is a hereditary disease, analysis of the impact of familial clustering is complicated. We used robust statistical analysis, taking into account information on *APC* mutations, and our calculations provided strong evidence for familial clustering of desmoid tumors.

Since the first reports on genotype-phenotype correlations in patients with FAP, several investigators have shown a high risk of desmoid tumors in patients with 3′ *APC* mutations, particularly mutations 3′ of codon 1444.[2,4,8,9] However, the cutoff at this codon was arbitrary and other studies could not confirm this association.[8,10] Remarkably, in our study, a mutation site 3′of codon 1444 was a statistically significant risk factor for the development of desmoid tumors when we analyzed all tumor locations together, but not when we analyzed only intra-abdominal desmoids, which are clinically the most threatening ones.[8]

There is controversy about the influence of female gender on the risk of developing FAP-related desmoid tumors.[2,5,7–10] In a recent study, we showed that sporadic desmoid tumors were more common in female patients than in male patients, whereas FAP related desmoids were evenly distributed over both sexes.[13] Our current results confirm equal gender distribution for desmoids associated with FAP. We also investigated whether previous colorectal cancer was associated with desmoid development, but could not confirm such an association. Although this variable was not previously shown to be a risk factor, we wanted to exclude a possible relation between desmoids and colorectal cancer.

The increased risk of desmoid development after surgery can be explained by the function of fibroblasts, which are involved in repairing tissue damage. In a subset of FAP patients, the surgical procedure triggers uncontrolled growth of fibroblasts, resulting in a desmoid tumor. However, as this does not occur in all FAP patients, the question is which additional factors induce desmoid development. The role of the *APC* mutation site is unclear, because it does not influence the risk of development of intra-abdominal desmoids. However, other genetic modifiers may play an important role in desmoid development. The fact that intra-abdominal desmoids were found later than those at other locations may also be attributable to a need for additional somatic mutations/inactivation in order for such tumors to develop. Possibly, a combination of genetic changes and environmental factors causes desmoid development. Genetic modifiers would also explain the finding of a strong family effect, as family members share genetic variations.

For clinical practice, it is important to identify those FAP patients at high risk of desmoid tumors. Deferring colorectal surgery may be considered in cooperative patients in whom frequent surveillance is guaranteed, particularly if patients have a positive family history of desmoids.[14] If surgery is needed, there is a choice between IRA and IPAA. Elayi et al[11] proposed performance of minimally invasive surgery (i.e., IRA) in patients with a high risk of desmoid tumors. However, to avoid a situation in which the development of intra-abdominal desmoids precludes secondary proctectomy,[7] we advise consideration of primary IPAA in such patients. In addition to surgery, prophylactic treatment with antiestrogens and nonsteroidal anti-inflammatory drugs (NSAIDs) may be considered[15] in patients at high risk for desmoid development. Currently, information on the mutation site seems not to be very useful in clinical practice. Particularly for intra-abdominal desmoid tumors, the relevance of the mutation site is not evident. Further efforts should be made to find genetic modifiers.

CONCLUSION

A positive family history for desmoid tumors, abdominal surgery, and *APC* mutation site are significant risk factors for development of desmoid tumors. The results may have implications for determining the optimal management of FAP patients and guide future studies.

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Chapter 11

Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients

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Full Paper

Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients

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BACKGROUND: The optimal treatment of desmoid tumours is controversial. We evaluated desmoid management in Dutch familial adenomatous polyposis (FAP) patients.

METHODS: Seventy-eight FAP patients with desmoids were identified from the Dutch Polyposis Registry. Data on desmoid morphology, management, and outcome were analysed retrospectively. Progression-free survival (PFS) rates and final outcome were compared for surgical *vs* non-surgical treatment, for intra-abdominal and extra-abdominal desmoids separately. Also, pharmacological treatment was evaluated for all desmoids.

RESULTS: Median follow-up was 8 years. For intra-abdominal desmoids ($n = 62$), PFS rates at 10 years of follow-up were comparable after surgical and non-surgical treatment (33% and 49%, respectively, $P = 0.163$). None of these desmoids could be removed entirely. Eventually, one fifth died from desmoid disease. Most extra-abdominal and abdominal wall desmoids were treated surgically with a PFS rate of 63% and no deaths from desmoid disease. Comparison between NSAID and anti-estrogen treatment showed comparable outcomes. Four of the 10 patients who received chemotherapy had stabilisation of tumour growth, all after doxorubicin combination therapy.

CONCLUSION: For intra-abdominal desmoids, a conservative approach and surgery showed comparable outcomes. For extra-abdominal and abdominal wall desmoids, surgery seemed appropriate. Different pharmacological therapies showed comparable outcomes. If chemotherapy was given for progressively growing intra-abdominal desmoids, most favourable outcomes occurred after combinations including doxorubicin.

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Keywords: desmoid tumour; desmoid-type fibromatosis; familial adenomatous polyposis; management

Familial adenomatous polyposis (FAP) is a dominantly inherited cancer predisposition syndrome, caused by mutations in the adenomatous polyposis coli (*APC*) gene. Carriers of the mutated *APC* gene develop hundreds to thousands of adenomatous polyps in the colon and rectum, leading to a nearly 100% cancer risk by the age of 40 years (Lynch *et al*, 2008). By performing a prophylactic colectomy, the risk of death due to colorectal cancer is decreased. Among FAP patients, a spectrum of extra-colonic manifestations is often observed, including duodenal cancer and desmoid tumours. These manifestations are currently the most common causes of death after colorectal cancer (Arvanitis *et al*, 1990).

Desmoid tumours or aggressive fibromatoses are histologically benign proliferations of fibro-aponeurotic tissue (Goldblum and Fletcher, 2002). In the general population, the incidence of desmoids is about 3 per million per year, and the tumours are mainly located in the extremities or in the abdominal wall (Fallen *et al*, 2006). Of all patients presenting with a desmoid tumour, at least 7.5% has FAP or will develop FAP later in life (Nieuwenhuis *et al*, 2010, submitted for publication). In the total

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FAP population, desmoid tumours develop in about 10–30% and are usually located in the mesentery of the small bowel (Fallen *et al*, 2006). Desmoids range from small, indolent, or even regressive tumours to large and progressive growing neoplasms causing obstruction of vital organs. Desmoid tumours do not metastasise, although they can present as multifocal disease.

Treatment of FAP-related desmoid tumours is controversial (Sleijfer, 2009). As desmoid tumours are rare, and show a variable disease course, the effectiveness of treatment is difficult to determine. There are no randomised controlled trials. Usually, extra-abdominal and abdominal wall desmoid tumours are removed surgically, but two recently published reports argued a wait-and-see policy for patients in which surgery would result in major functional or cosmetic defects (Bonvalot *et al*, 2008; Stoeckle *et al*, 2009). For intra-abdominal desmoid tumours, surgery is not recommended because surgical resection is complicated or impossible in most cases, and because of high recurrence rates (Rodriguez-Bigas *et al*, 1994). Furthermore, there is evidence that tissue damage is a risk factor for desmoid development (Clark *et al*, 1999; Bertario *et al*, 2001). The most frequently used pharmacological therapies include non-steroidal anti-inflammatory drugs (NSAIDs), hormonal agents, biological agents, and cytotoxic chemotherapy (Janinis *et al*, 2003; Tolan *et al*, 2007). Currently, most guidelines recommend a stepwise approach, starting with NSAIDs (preferably sulindac). If this is not effective, hormonal therapy is added, most commonly consisting of tamoxifen or toremifene. Fast growing desmoid tumours not responsive to these agents are treated by cytotoxic chemotherapy or surgery (http://www.nccn.org; Janinis *et al*, 2003; Latchford *et al*, 2006; Melis *et al*, 2008; Casali and Blay, 2010).

In the present study, we retrospectively evaluated long-term outcome of Dutch FAP patients with desmoid tumours, undergoing surgical, and pharmacological therapies. First, we assessed the effectiveness of surgical *vs* non-surgical strategies for intra- and extra-abdominal desmoid tumours, and second, we assessed the effectiveness of various pharmacological modalities in desmoid tumour treatment.

MATERIALS AND METHODS

Patients

The FAP database of the Netherlands Foundation for the Detection of Hereditary Tumours was used for the study. This national database comprises medical data on over a thousand FAP patients. Patients gave written consent to register their personal and medical information. A total of 78 patients with desmoid tumours were identified. Patient characteristics, genetic data, and medical information were retrieved from the database. The study was approved by the Medical Ethics Committee.

Desmoid localisation was defined as 'at least intra-abdominal' or 'extra-abdominal and in the abdominal wall'. For all patients, the type of primary therapy for the first desmoid tumour was determined. If surgery was performed due to the severity of desmoid symptoms or with the aim of removing the desmoid tumour, patients were categorised into the 'surgery' group. All patients who received conservative treatment (wait-and-see or medication), and patients whose desmoid tumour was detected coincidentally during another surgical procedure, without resection, were categorised into the 'non-surgery' group.

Time from diagnosis of the desmoid tumour to progression of desmoid tumour growth was calculated. Progression of desmoid tumour growth was defined as tumour growth causing clinical symptoms. Also, for each patient, the status of desmoid growth at the end of follow-up was assessed and categorised into either 'regression or stabilisation of tumour growth' or 'progression of tumour growth'.

Data analysis

Baseline characteristics between the groups were analysed by univariate analysis (Student's *t*-test for numerical variables, χ^2-test for categorical variables). Progression-free survival (PFS) was calculated by the Kaplan–Meier method. Univariate analysis was performed using the log-rank test. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (Chicago, IL, USA).

RESULTS

Group description

Between January 1978 and January 2010, 78 FAP (34 males) patients had developed at least one desmoid tumour. Desmoid localisations were as follows: 49 (62.8%) intra-abdominal, 13 (16.7%) involving both the mesentery and the abdominal wall, 13 (16.7%) abdominal wall only, 2 (2.6%) trunk, and 1 (1.3%) head/neck. The median size of the desmoids was 7 cm, ranging from 1 to 24 cm. Fifty-six patients were treated at a tertiary referral centre, 22 in a local hospital. The median follow-up period from diagnosis of desmoid to the last observation was 8 years, ranging from 0 to 29 years (Table 1).

Table 1 Characteristics and follow-up data of FAP-related mesenterial desmoid tumours, according to primary surgical treatment *vs* non-surgical treatment

	Primary treatment		
	Surgery (*N* = 36)	**No surgery (*N* = 26)**	***P*-value**
Sex, male			
N (%)	16 (44)	13 (50)	0.665
Age at first DT (years)			
Median, min–max	30, 15–54	35, 14–51	0.396
Size first DT (cm)			
Median, min–max	9.5, 1–20	6.5, 2–24	0.568
DT progression, N (%)	26 (72)	13 (50)	0.074
Time to first DT progression (months)			
Median, min–max	13, 1–189	24, 2–229	0.913
Total follow-up from diagnosis of first DT to last observation (years)			
Median, min–max	8, 0–29	7, 0–28	0.762
Age at last follow-up (years)			
Median, min–max	41, 23–67	42.5, 18–79	0.606
Status at last follow-up, N (%)			
Alive	21 (58)	18 (69)	0.783
Lost to follow-up	1 (3)	1 (4)	
Dead due to DT	9 (25)	5 (19)	
Dead due to other cause	5 (14)	2 (8)	
DT status at last follow-up, N (%)			
Regression/stable	25 (69)	20 (77)	0.515
Progression/variable	11 (31)	6 (23)	

Abbreviations: DT = desmoid tumour; FAP = familial adenomatous polyposis.

Surgery *vs* non-surgical management for intra-abdominal desmoid tumours

The group with 'at least intra-abdominal' desmoid tumours consisted of 62 patients. In 36 patients, primary treatment consisted of surgery with the intention to remove the intra-abdominal desmoid tumour. Twelve of these patients received desmoid-targeted medication immediately after surgery. Primary treatment was non-surgical in 26 patients (17 wait-and-see policy and 9 medication). The surgery and non-surgery groups were comparable for sex, age at first desmoid, size of first desmoid tumour, and duration of follow-up (Table 1). None of the intra-abdominal desmoid tumours could be resected entirely. The probability of PFS for the surgery group was 63.9%, 43.8%, and 32.9% after 1, 5 and 10 years, respectively. In the non-surgical group, these percentages were 80.8%, 55.3%, and 49.1%, respectively (log-rank, $P = 0.163$) (Figure 1).

When considering desmoid status at the last observation, the majority of desmoid tumours had become stable or regressive in both the surgery and non-surgery groups (69% and 77%, respectively, $P = 0.515$). In the surgery and non-surgery groups, 25% and 19%, respectively, died from desmoid disease ($P = 0.783$) (Table 1).

Extra-abdominal and abdominal wall desmoid tumours

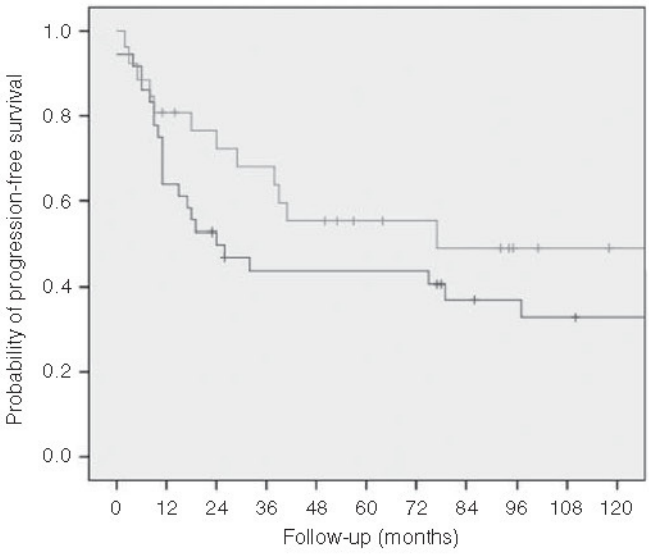
Sixteen patients had extra-abdominal desmoid tumours (Table 2). Thirteen patients had a desmoid tumour in the abdominal wall (3 male patients and 10 female patients), two male patients had desmoids at the thoracic wall and back, and one female patient had a desmoid tumour localised in the muscles of the neck. Fourteen (87.5%) of the tumours were treated surgically, with seven $R_{1/2}$ (microscopically/macroscopically irradical), six R_x (unknown surgical margin), and one R_0 (radical) excision. One, 5, and 10 years after primary surgery, 93.3%, 71.1%, and 63.2% of patients were free of progression. In most patients, progression was observed within 6 years after primary surgery (Figure 2). None of the patients died from desmoid disease. When considering desmoid status at the last observation, three quarter of the desmoid tumours had stabilised or regressed.

Effectiveness of pharmacological treatment

Various pharmacological agents were used, including NSAIDs (sulindac and celecoxib) and hormonal medications (tamoxifen, toremifene, LHRH-agonists, and anastrozole). For all patients who received medical treatment as primary therapy, irrespective of previous surgery, survival rates were calculated. After 5 years of follow-up, the PFS rates were similar after treatment with NSAIDs and hormonal medications including combination therapy, as shown in Figure 3 (log-rank, $P = 0.111$). A small subset of patients had received other drugs, including prednisone, interferon, and colchicines. After these medications, both positive as well as negative effects on desmoid tumour growth were reported, but patient numbers were too small to perform statistical analysis.

Cytotoxic chemotherapy and imatinib

Ten patients received cytotoxic chemotherapy, and three patients had treatment with imatinib. Effects and complications of these therapies are summarised in Table 3. The most frequently used chemotherapy was doxorubicin, in combination with other agents such as DTIC, carboplatin, and ifosfamide. Effects of chemotherapy were variable. Four patients eventually had regression or stabilisation of tumour growth, and five patients had progression of tumour growth. One patient died only a few days after the first session of chemotherapy due to a massive pulmonary embolism, caused by pressure of the desmoid tumour on the large veins.



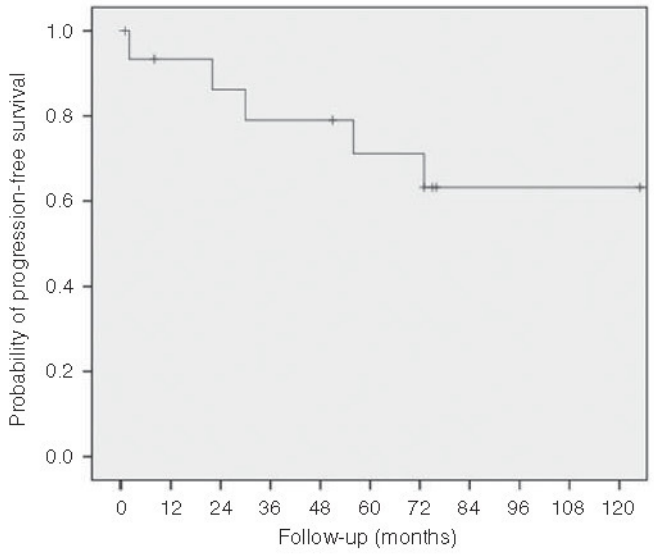
Time	0	12 (1 year)	60 (5 years)	120 (10 years)
N patients surgery	36	23	14	7
N patients non-surgery	26	20	10	3

Figure 1 Progression free interval after primary surgical (black line) and non surgical (grey line) treatment for mesenterial desmoid tumours in FAP patients (log rank test, $P = 0.163$).

Table 2 Characteristics and follow up data of extra abdominal and abdominal wall desmoid tumours

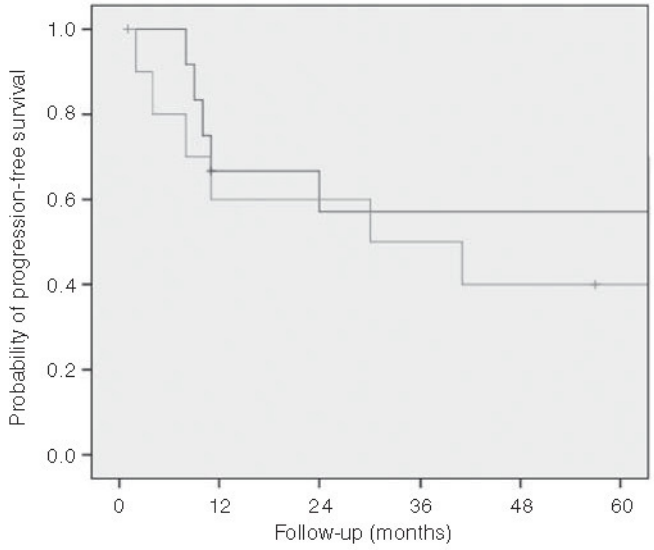
	Extra-abdominal and abdominal wall DT ($N = 16$)
Sex, male, N (%)	5 (31)
DT localisation, N (%)	
Abdominal wall	13 (81)
Trunk	2 (13)
Head/neck	1 (6)
Age at first DT (years)	
Median, min max	30.5, 8 57
Size of first DT (cm)	
Median, min max	5, 2 13
Primary treatment, N (%)	
Surgery	13 (81)
Surgery and medication	1 (6)
Medication	1 (6)
Wait-and-see	1 (6)
DT progression, N (%)	5 (31)
Time to DT growth months	
Median, min max	30 (2 73)
Status last follow-up, N (%)	
Alive	13 (81)
Dead due to DT	0
Dead due to other cause	3 (19)
Desmoid status at last follow-up, N (%)	
Regression/stable	12 (75)
Progression/variable	4 (25)

Abbreviation: DT = desmoid tumour.



Time	0	12 (1 year)	60 (5 years)	120 (10 years)
N patients	16	13	9	5

Figure 2 Progression free interval after primary treatment for extra abdominal and abdominal wall desmoid tumours in FAP patients.



Time	0	12 (1 year)	60 (5 years)
N NSAID	12	7	6
N hormonal therapy	11	6	3

Figure 3 Progression free interval after NSAIDs ($n = 12$, black line), and hormonal therapy or combination therapy ($n = 11$, grey line), irrespective of previous surgery (log rank test, $P = 0.111$).

Another patient bled to death due to fistulas and abscesses after chemotherapy. Furthermore, three patients developed severe complications as fistulas and abscesses (after 5, 18, and 60 months, respectively) besides the known spectrum of side effects associated with cytotoxic chemotherapy.

In the three patients receiving imatinib (of which two also had received chemotherapy), variable outcomes were seen, but the follow-up intervals were limited.

Radiotherapy and embolisation

A total of five patients were treated by radiation therapy. Three patients had radiation therapy for intra-abdominal desmoids. In one of them, the tumour size decreased, enabling surgery. The two other patients had stable desmoids during 6 years and progression within 1 year, respectively. Two patients had radiation therapy for extra-abdominal desmoid tumours: a patient with trunk desmoids had progression within a few months, and another patient had regression of an abdominal wall desmoid after irradiation; however, this patient developed serious radiation enteritis.

In two patients, the desmoid tumours were treated by embolisation. However, in both patients this treatment failed as the desmoids did not have large supplying vessels.

DISCUSSION

The present study demonstrates that for intra-abdominal desmoid tumours, similar PFS rates were observed after surgical treatment and a more conservative approach. None of the intra-abdominal desmoids could radically be resected by surgery, but at the end of the follow-up period, two thirds of the intra-abdominal desmoids showed regression or stabilisation of tumour growth. About one fifth of the patients died due to complications of an intra-abdominal desmoid tumour. Most patients with abdominal wall and extra-abdominal desmoid tumours were treated surgically. The PFS rates were greater than after surgery of intra-abdominal desmoids, and at the end of the follow-up period, in 75% of the patients the tumours had stabilised or decreased in growth. None of these patients died from desmoid disease. Evaluation of pharmacological agents showed comparable PFS probabilities after NSAIDs and hormonal agents including combination of both medicines. Effects of chemotherapy were variable, with doxorubicin-based regimens being most effective.

The optimal treatment of intra-abdominal desmoids is unknown. Previous studies reported high recurrence rates after surgery and a low success rate of radical removal of desmoid tumours (Rodriguez-Bigas *et al*, 1994; Heiskanen and Järvinen, 1996). On the other hand, favourable outcomes have been reported after surgery performed by experienced surgeons in carefully selected patients (Latchford *et al*, 2006). In our series, none of the desmoids could be radically resected and the PFS was similar after surgery compared to conservative treatment. Based on these findings, a conservative approach appears to be the preferred choice in patients with large stable or slowly growing desmoids. Only in cases of progressively growing desmoids, with complications such as obstruction of the small bowel, surgical treatment might be an option. In such patients, minimal surgery (intestinal bypass) could be performed. In patients with obstruction of the ureter, stenting of the ureter might be indicated. These conclusions support the current guidelines on the treatment of desmoid tumours (http://www.nccn.org) (Casali and Blay, 2010).

Extra-abdominal and abdominal wall desmoid tumours are generally more suitable for surgical therapy than mesentery desmoids. Previous studies reported mainly good outcomes after surgery, although recurrence was common after excision (Clark *et al*, 1999; Melis *et al*, 2008). Recent reports proposed a wait-and-see policy for patients in which major surgical defects are expected, because spontaneous regression or tumour stabilisation is not uncommon (Bonvalot *et al*, 2008; Fiore *et al*, 2009; Stoeckle *et al*, 2009). In our series, the majority of extra-abdominal and abdominal wall desmoids was resected, with overall favourable outcomes, despite only few radical resections. Based on this and

Table 3 Description of treatment outcome of patients who received cytotoxic chemotherapy and/or targeted agents as desmoid treatment

Sex	Site DT	Age (years)	Treatment	Effect on desmoid growth	Follow-up (months)
Male	Mesentery	45	Irresectable DT, etoposide and ifosfamide, tamoxifen tamoxifen and LHRH-agonist anastrozole	Quick regression DT, necrosis in DT Stabilisation, after 5 years progression Progression	5 70 5
Male	Head, abd. wall and mesentery	15–17	R_2 resection DT head, RT mes. DT, sulindac, toremifene doxorubicine and DTIC, R_2 resection mes. DT sulindac, toremifene, R_2 resection abd. wall DT all medication stopped	Progression mes. DT Stabilisation, after 2 years abd. wall DT Both periods of progression and regression, after 2 years growth DT head, DT mes. and abd. wall stable Stabilisation	35 38 100 36
Male	Mesentery	29	R_2 resection, sulindac, toremifene doxorubicine and carboplatin R_2 resection, sulindac, tamoxifen	Progression Regression < 25% Stabilisation	11 7 50
Male	Mesentery	29	R_2 resection, sulindac, tamoxifen, toremifene doxorubicine and ifosfamide, sulindac, toremifene imatinib	Progression Stabilisation, after 8 months progression Stabilisation, but fistulas and abscesses at DT	38 8 10
Female	Abd. wall, trunk, breasts, neck	25–40	Multiple R_2 resections, tamoxifen, sulindac, LHRH-agonists, anastrozole, radiotherapy imatinib	Progression and multiple new DT Progression Progression	11 10
Male	Mesentery	32	R_2 resection doxorubicine and DTIC	Progression Regression, death not due to DT	19 184
Male	Mesentery	30	Chemotherapy[a] and radiotherapy, R_2 resection colchicine, LHRH-agonists, anti-estrogens, prednison, IFN	Stabilisation for 4 years Progression; after colchicine multiple abscesses; death due to DT	51 58
Female	Mesentery and abd. wall	24	Naproxen, toremifene doxorubicine and DTIC	Progression Progression, death due to DT	16 3
Female	Mesentery	33–35	Sulindac, anti-estrogens, DT irresectable liposomal doxorubicine	Progression Death pulmonary embolism, due to compression of DT on the large veins	24 0
Female	Mesentery	35–37	Wait-and-see, sulindac, celecoxib, tamoxifen, toremifene carboplatin and doxorubicine imatinib fulvestrant	Progression Necrosis in DT, fistulas and abscesses Stabilisation, after 1 year progression Stabilisation, after 2 years progression and death due to DT	37 7 12 19
Male	Mesentery	47	Irresectable DT, sulindac, tamoxifen vinblastin and methotrexat	Progression Progression, death due to desmoid	4 18

Abbreviations: abd. wall = abdominal wall; DT = desmoid tumour; DTIC, dacarbazine; IFN = interferon; LHRH, luteinizing hormone releasing hormone; Mes. = mesenterial; RT = radiotherapy. [a]Details and type of chemotherapy are not available.

previous studies, surgery seems to be safe for extra-abdominal and abdominal wall desmoid tumours. In patients in which surgery would result in serious defects, a wait-and-see strategy should be considered.

Commonly used pharmacological agents are NSAIDs and hormonal agents. One systematic review showed favourable outcomes after using NSAIDs and hormonal agents, although the results might be confounded by successful case reports (Janinis *et al*, 2003). Another prospective study showed the effectiveness of high-dose tamoxifen (120 mg) and sulindac (300 mg) in 9 out of 13 patients (69%), compared to stabilisation after surgery and medication in only 1 out of 4 patients (25%) after 10 years of follow-up (Hansmann *et al*, 2004). Based on these results, the authors advised high-dose tamoxifen and sulindac as the primary treatment for FAP-related desmoid tumours. Recently, another retrospective study reported effective hormonal therapy for desmoid tumours (De Camargo *et al*, 2010). Our study showed no significant differences in PFS rates between NSAIDs and hormonal treatment including a combination of both medicines. The PFS was about 50% at 5 years of follow-up. However, patients in our study received various doses of hormonal agents. Possibly, hormonal treatment at higher doses would have led to significant better outcomes. Based on personal experience from our authors (H.G.), the optimal dose of tamoxifen is 40 mg 4 times a day, and for toremifene 60 mg 4 times a day. Based on this and previous studies, treatment with NSAIDs and/or hormonal agents seems to be the best option for large and/or progressive desmoids.

Recently, several studies reported successful treatment of desmoids with pegylated liposomal doxorubicin, with acceptable side effects (Gega *et al*, 2006; Bertagnolli *et al*, 2008; Constantinidou *et al*, 2009; De Camargo *et al*, 2010). All four patients in our study who reached stabilisation or regression after chemotherapy were treated with doxorubicin. Our findings and those of others suggest that (pegylated liposomal) doxorubicin-based chemotherapeutic regimens are effective for patients with progressive, symptomatic desmoid tumours. Inspite of previous promising reports (Heinrich *et al*, 2006; Wcisio *et al*, 2007), imatinib treatment had no evident positive effects in our patients. Long-term effects of targeted therapies are yet to be evaluated. Recently, a study to evaluate imatinib in desmoid tumours was initiated (NCT01137916).

In the past, radiotherapy alone or in combination with surgery was shown to be effective in sporadic, mainly extra-abdominal desmoid tumours (Ballo *et al*, 1999; Nuyttens *et al*, 2000; Lev *et al*, 2007; Guadagnolo *et al*, 2008). Radiotherapy enabled surgery in one of our patients, but in other patients disease progression after radiotherapy was observed. Recently, an EORTC study (EORTC-62991, EORTC-22998, and NCT00030680) was performed to evaluate moderate dose radiotherapy for inoperable desmoid tumours. Results of this study are not yet available. According to the American National Comprehensive Cancer Network guidelines, radiotherapy should be considered only in desmoid tumours located at the extremities (http://www.nccn.org). Embolisation showed not to be a reliable option for desmoid treatment.

In the current study, we evaluated the effectiveness of long-term treatment of desmoid tumours in FAP patients. Nationwide data, both from university hospitals as well as local hospitals were included, thus avoiding potential confounding by patient selection. However, because of the retrospective study design, we were not able to gain information about the selection of patients for certain treatment modalities. Nevertheless, this is a complete and informative series on desmoid treatment to date. For future studies, a prospective, randomised study design would be a more robust approach to this research question.

For clinical practice, we recommend surgery for patients with extra-abdominal and abdominal wall desmoid tumours, unless major surgical defects are expected. For patients with stable intra-abdominal desmoid tumours, both a wait-and-see strategy as well as pharmacological treatment are appropriate. Cytotoxic chemotherapy may be effective in patients with progressively growing desmoids. In the case of severe complications, including ileus, perforations, and abscesses, surgery is indicated.

In conclusion, desmoid disease is a heterogeneous disease entity, with various treatment modalities. Clustering of desmoid patients in some specialised referral centres will benefit treatment and follow-up, and enables further research into this controversial topic.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 12

Evidence for accelerated colorectal adenoma-carcinoma progression in *MUTYH*-associated polyposis?

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Evidence for accelerated colorectal adenoma–carcinoma progression in *MUTYH*-associated polyposis?

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ABSTRACT

Background and aim *MUTYH*-associated polyposis (MAP) is an autosomal recessive inherited disorder characterised by the development of polyposis in the upper and lower gastrointestinal tract and a high risk of colorectal cancer (CRC). We evaluated the natural history of the disease and the outcome of colorectal surveillance and management.

Methods A large Western European dataset of biallelic *MUTYH* mutation carriers comprising 254 patients was used. Detailed information was collected on polyp and cancer development in the colorectum, and the outcome of surveillance and surgery. Survival methods were used to calculate the risk of CRC development.

Results The mean follow-up was 9.8 years. Colorectal polyposis was diagnosed at a mean age of 44.8 years (range: 12–77 years). Most patients had <100 colorectal adenomas at diagnosis. CRC was diagnosed in 147 (58%) of the 254 patients (mean age at diagnosis: 48.5, range: 21–77 years). The cumulative lifetime risk of CRC was 63% at age 60 years. There was no correlation between the number of adenomas and the presence of CRC. The cumulative risk of CRC in patients presenting with polyps was 9% after 5 years of follow-up. Patients presenting with CRC had 11% risk of developing a metachronous CRC at 5 years after surgery. Thirty-seven per cent of patients with MAP with CRC who underwent partial colonic resection needed secondary surgery shortly afterwards.

Conclusions The high risk of developing CRC under surveillance in patients with MAP may suggest an accelerated carcinogenesis. Surveillance of these patients should therefore include colonoscopy at short intervals, for example, at 1–2-year intervals starting from the age of 18 to 20 years. If surgery for CRC is warranted, a (sub)total colectomy is recommended.

Significance of this study

What is already known about this subject?
- *MUTYH*-associated polyposis (MAP) is a recessive inherited polyposis syndrome caused by mutations in the base-excision repair gene *MUTYH*
- The MAP phenotype resembles that of attenuated familial adenomatous polyposis
- The MAP extracolonic tumour spectrum resembles that of Lynch syndrome

What are the new findings?
- In patients with MAP, colorectal cancer (CRC) risk is not associated with the number of colorectal polyps
- CRC development seems to be accelerated, as about 10% of the patients presenting with polyposis or CRC had developed a primary or a metachronous CRC within 5 years of follow-up
- After hemicolectomy, patients had a substantial risk of reoperation

How might it impact on clinical practice in the foreseeable future?
- Biallelic *MUTYH* mutation carriers should have regular colonoscopic surveillance independent of the number of polyps. If surgery is needed, a total colectomy is recommended

INTRODUCTION

The best known inherited form of gastrointestinal polyposis is familial adenomatous polyposis (FAP), an autosomal dominant syndrome caused by APC germline mutations. MAP is an inherited polyposis syndrome described for the first time in 2002 that is transmitted as an autosomal trait caused by biallelic germline mutations in the base-excision repair gene *MUTYH* (OMIM #608456), located on chromosome 1. The syndrome is characterised by the development of multiple colorectal adenomas and a high risk of CRC.[1] The frequency of monoallelic mutations in the Western European population is about 2%. Approximately, 0.3% of patients with CRC from population-based series are associated with biallelic *MUTYH* mutations.[2]

Usually, biallelic *MUTYH* mutation carriers present with a polyposis phenotype that strongly resembles that of AFAP, with onset in the fourth or fifth decade, and development of <100 colorectal polyps predominantly in the right colon.[3] Duodenal adenomas and carcinomas are reported in patients with FAP and those with MAP.[4 5] A recent study indicated that the overall incidence of extra-intestinal malignancies was increased. The reported tumour spectrum included cancer of the ovary, bladder and skin, which indicates an overlap with the Lynch syndrome.[4]

The risk of developing CRC is comparable to that in FAP, although the age at onset is delayed.[3] A population-based series showed high penetrance of biallelic mutations with a substantially elevated CRC risk, with estimated penetrances of 20% at

age 50 and 43% at age 60 years, respectively.[2] Compared to the general population, relative risks of CRC were estimated from 53 to 117.[6 7] For monoallelic mutation carriers, a trend of a slightly elevated CRC risk was suggested in most studies.[6 8 9]

Currently, limited information is available on the natural history of adenoma and carcinoma development in MAP. The outcome of surveillance and surgical management is also unknown. The question is whether MAP is simply an attenuated version of FAP or a distinct cancer susceptibility syndrome needing specific management guidelines.[10 11]

The aims of the present study were to evaluate the natural history of adenoma and carcinoma development and to assess the outcome of management of a large series of patients with MAP.

METHODS

Patients

For this study, clinical data were retrieved from three genetics institutes (Institute of Human Genetics, Bonn, Germany; Institute of Medical Genetics, Cardiff, UK; Centre for Human and Clinical Genetics, Leiden, The Netherlands) and The Netherlands Foundation for the Detection of Hereditary Tumours. Ethical approval was obtained from national and/or local review boards (The Multi-Centre Research Ethics Committee for Wales, ref. 06/MRE09/19; medical faculty of the University of Bonn Ethics Review Board, no. 063/04; Leiden University Medical Centre Ethics Review Board, no. P01.019). The methods for *MUTYH* mutation analysis in patients with adenomatous polyposis have been described previously.[3 12 13]

Patients with biallelic *MUTYH* mutations with available data on management and follow-up were selected. The study cohort consisted of patients with symptoms (75%) and call-up cases (25%) and overlaps with the cohort described in previous studies.[4 9 14]

Data and statistical analysis

The data collected include gender, mutation, date of birth and details on diagnosis, disease course of polyposis and CRC development. Available data on surgery were analysed. Data are presented as mean values (with ranges) for continuous variables and numbers (with percentages) for categorical variables. To calculate the risk of cancer development and the probability of secondary surgery, Kaplan–Meier methods were used. The observation time was from age at diagnosis of polyposis to event, death, loss to follow-up or end of the study (1 July 2009). Data were analysed and calculated with SPSS V.16.0.0 (SPSS Inc.). A p value of <0.05 was considered to be statistically significant.

RESULTS

Characteristics of the study cohort

Data were available on 254 biallelic *MUTYH* mutation carriers, of whom 141 (56%) were male. They presented between 1963 and 2009 with polyposis and/or a CRC, or were identified due to mutation analysis in the family. The mean duration of follow-up from diagnosis of polyposis to the last observation for this study was 9.8 years (range: 10 months–36 years). The mean age at diagnosis of polyposis was 44.8 years (range: 12–77 years). The majority of patients (63%) had <100 colorectal polyps at first diagnosis; 20% had more than 100 adenomas, and in 15% of patients, the exact number of adenomas was unknown. Four patients (2%) had no polyps at the time of diagnosis; two of them presented with CRC, and two underwent colonoscopy due to positive mutation analysis in the family.

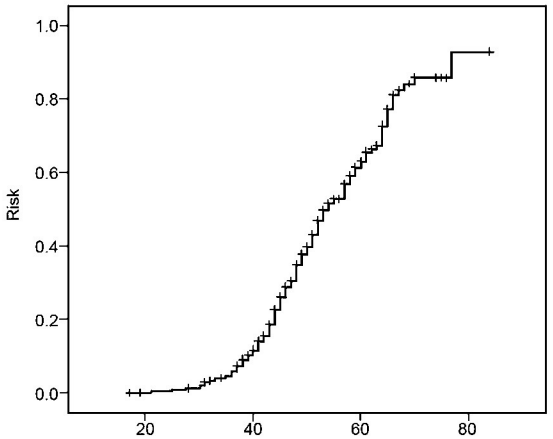
CRC development

A total of 147 (58%) of the 254 patients developed CRC at a mean age of 48.5 years (range: 21–77 years). Three patients (2%) were younger than 30 years at diagnosis of CRC. The lifetime cumulative risk of developing CRC is shown in figure 1. By the age of 60 years, 63% had developed CRC. Eighty (54%) of the 147 CRCs were right sided, whereas 56 (38%) were located in the left part of colon and rectum; for 11 CRCs, the location was unknown.

In 120 patients, CRC was diagnosed at the initial endoscopy at a mean age of 48 years (range: 21–77 years). Table 1 displays the number of colorectal polyps detected simultaneously with CRC.

About half of the patients had <50 adenomas. The risk of developing CRC was comparable for patients with <50 and those with >50 colorectal polyps (43% vs 46%, p=0.647). Histopathology analysis showed adenomas in 118 patients. Two patients who presented with CRC had no colorectal polyps. In 12 patients (10%), besides adenomas, hyperplastic polyps were also reported; in all cases, the majority of polyps was adenomatous.

The remaining group of 134 patients presented with 'polyposis only' at a mean age of 42 years (range: 12–68 years). The initial treatment of these patients was endoscopy and polypectomy in 70, surgery in 34 and unknown in 30 patients. Twenty-seven (20%) of these patients subsequently developed CRC during follow-up at a mean age of 52 years (range: 36–68 years). The cumulative risk of developing CRC during follow-up is shown in figure 2. Within the first year after diagnosis of polyposis, the risk of developing CRC was 5%, increasing to 9% after 5 years and to 31% after 15 years of follow-up. In addition, 16 of the 120 (13%) patients who presented with primary CRC developed a metachronous CRC under surveillance. The cumulative risk of developing a metachronous CRC is shown in figure 3. In the first year after primary CRC, 2% of the patients had developed a metachronous tumour, increasing to 11% after



Time (yrs)	0	20	30	40	50	60	70
N*	254	254	244	205	113	45	7
Risk	0%	0%	2%	12%	40%	63%	86%

*N = no. of patients at risk

Figure 1 Cumulative risk of developing CRC for biallelic *MUTYH* mutation carriers. CRC, colorectal cancer.

Table 1 Number of polyps at initial endoscopic examination in patients presenting with CRC (n=120)

N polyps	N patients (%)
0	2 (2)
1–20	26 (22)
21–50	18 (15)
51–100	24 (20)
>100	25 (21)
Unknown	25 (21)
Total	120 (100)

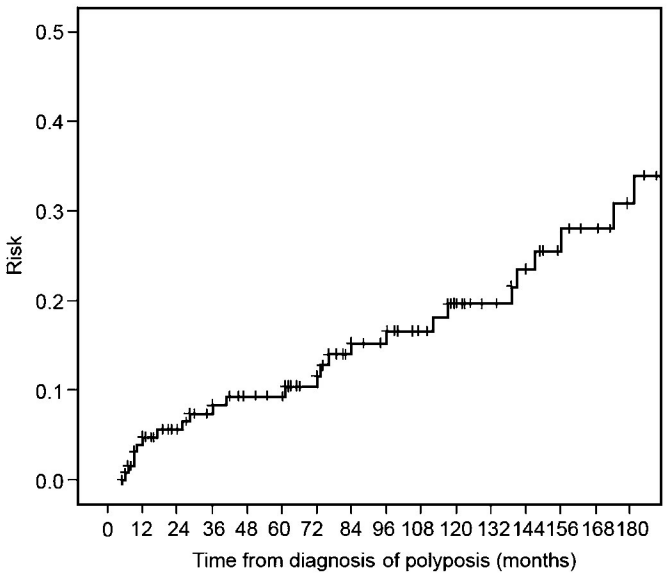
5 years and to more than 20% after 15 years. Features of patients with primary CRC and those with CRC detected under surveillance are shown in table 2.

Surgical management

Detailed information on surgical management was available for 87 of 120 patients with CRC at initial endoscopy. Fourteen (37%) of 38 patients who had had a partial colectomy needed reoperation, including seven because of cancer and seven because of uncontrollable polyps that could not be removed endoscopically. Only four (8%) of 49 patients undergoing a (sub)total colectomy needed reoperation, all because of polyps.

DISCUSSION

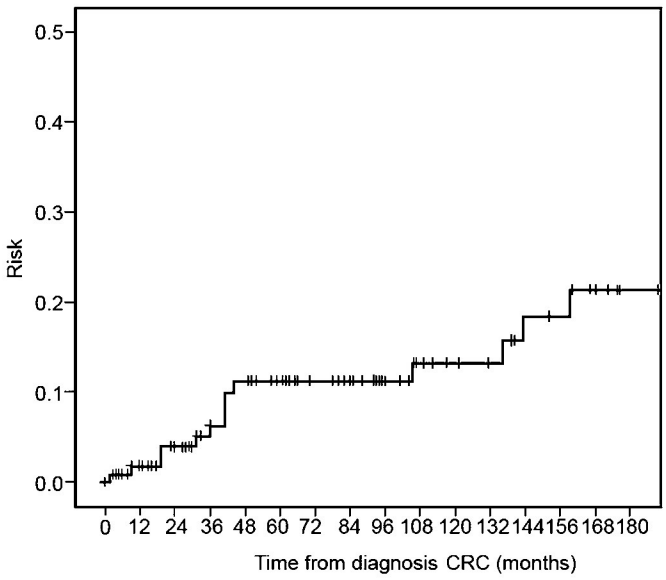
Previous studies have shown that the phenotypic expression of MAP resembles that of AFAP. The majority of patients with MAP and those with AFAP develop <100 colorectal adenomas and present with CRC at a more advanced age compared to those with classical FAP. However, the present study demonstrates that there are also remarkable differences between the two polyposis syndromes. In MAP, in contrast with (A)FAP, the risk of CRC appears not to be associated with the number of adenomas in the colorectum. Another clinically important



Time (mo)	0	12	60	120	180
N*	134	114	84	47	23
Risk	0%	5%	9%	20%	31%

*N = no. of patients at risk

Figure 2 Cumulative risk of developing CRC under surveillance after presenting with polyposis. CRC, colorectal cancer.



Time (mo)	0	12	60	120	180
N*	120	100	67	37	20
Risk	0%	2%	11%	13%	21%

*N = no. of patients at risk

Figure 3 Cumulative risk of developing metachronous CRC in patients presenting with CRC. CRC, colorectal cancer.

finding was that a substantial proportion of patients developed CRC within the first decade after primary diagnosis of polyposis or a primary CRC, an observation that suggests an accelerated adenoma-to-carcinoma progression. Regarding the surgical treatment of CRC, more than one third of the patients who underwent partial resection needed secondary surgery, often soon after primary treatment.

In classical FAP caused by an APC mutation, there is a strong correlation between the polyp burden and CRC risk. For example, patients with the codon 1309 mutation generally develop thousands of colorectal adenomas in the second decade of life, and these patients have a high risk of developing CRC before the age of 30 years.[15] In contrast, patients with attenuated FAP develop less adenomas and develop CRC on average in their 50s. A recent study on patients with AFAP showed that the median number of colorectal adenomas in patients with CRC was higher than that in patients without CRC (37 vs 20, p=0.05), suggesting that, also in the AFAP group, the cancer risk

Table 2 Characteristics of CRC in patients with biallelic *MUTYH* mutations, according to mode of diagnosis

	Symptomatic CRC	Screen-detected CRC
Number of patients	120	27
Mean age at CRC	48 years	52 years
Localisation CRC right-sided, N (%)	65 (54)	15 (65)
Stage of CRC, N (%)		
Dukes A	23 (19)	10 (37)
Dukes B	44 (37)	8 (30)
Dukes C	31 (26)	8 (30)
Dukes D	11 (9)	0
Unknown	11 (9)	1 (3)
Cause of death		
CRC	32/47	0/9
Other cause	15/47	9/9

CRC, colorectal cancer.

is related to the number of adenomas.[16] In our series of patients with MAP, the risk of CRC was not clearly associated with the number of adenomas. About 40% of the patients with CRC had <50 adenomas, and a similar proportion had >50 adenomas. Two patients even developed CRC in the absence of adenomas. A phenotype without polyps has also been observed in biallelic *MUTYH* mutation carriers identified in population-based CRC series. A substantial proportion (29%) of population-based patients with CRC with biallelic *MUTYH* mutations did not have adenomas.[2 17] These findings have important implications for clinical practice because they suggest that the polyp burden may not be a good guide for determining the surveillance interval in patients with MAP and that biallelic mutation carriers without colonic adenomas should also have colonoscopic examinations at short intervals. Furthermore, the absence of polyps does not exclude the diagnosis of a hereditary polyposis syndrome.

The most remarkable finding in our study was the high risk of CRC development in patients under surveillance. In patients presenting with polyposis as well as in patients presenting with CRC, the risk of developing a primary or metachronous CRC within 5 years of follow-up was considerable (9% and 11%, respectively). This risk is even higher than the risk of developing CRC under surveillance reported for Lynch syndrome, which was 6% at 10 years of follow-up.[18] Along with our observation of an advanced stage (regional metastases) in one third of the screen-detected CRCs, these findings may indicate the presence of an accelerated carcinogenesis in MAP that has also been reported for Lynch syndrome.[19] There are parallels between MAP and Lynch syndrome as defects in DNA repair function are involved in both syndromes, that is, base excision repair and DNA mismatch repair, respectively. In Lynch syndrome, the mismatch repair defect leads to rapid accumulation of mutations in genes that control cell growth and division, which may explain the accelerated carcinogenesis. The mechanism for an accelerated carcinogenesis in MAP is unclear. As suggested in recent studies, there may be a link between base excision repair and low-frequency MSI pathways.[17] Recently, it was suggested that the MLH1 gene can be a target of *MUTYH* transversions leading to MSI phenotype.[20] Another study showed some similarities of MAP-associated CRCs to microsatellite unstable cancers, such as a preferential right-sided location, mucinous histology type and increased presence of tumour-infiltrating lymphocytes.[21] Furthermore, as adenomas and hyperplastic polyps were found in patients with MAP, the serrated pathway is thought also to play a role in MAP tumourigenesis.[22]

The usual surgical treatment for FAP is a (sub)total colectomy with either an ileorectal anastomosis or an ileo-pouch anal anastomosis. In the present study, a substantial proportion of patients had undergone a hemicolectomy. In view of the high probability of reoperation after hemicolectomy in our series, ileorectal anastomosis seems to be the best surgical option in MAP, including patients with CRC and only a few colorectal adenomas. In patients with multiple adenomas in the rectum, an ileo-pouch anal anastomosis might also be an appropriate option. As CRC is rare before the fourth decade, the optimal timing for prophylactic colectomy may be later than in classic polyposis.[23] Colonoscopy at intervals of 1–2 years and polypectomy might be considered in patients with MAP with few adenomas without CRC.

The present study is based upon a large series of biallelic *MUTYH* mutation carriers identified via three polyposis registries in the UK (Cardiff), Germany (Bonn) and the Netherlands (Leiden). As a large proportion of patients with symptoms were referred to a geneticist, we have to keep in mind the possibility of bias towards cases with symptoms with multiple polyps and an overestimation of the risk of developing CRC in asymptomatic patients. This explains the finding of multiple polyps in 98% in our cohort (table 1) compared to 70% in biallelic mutation carriers identified in population-based CRC series.[2 17]

In polyposis registries, usually, annual or biannual colonoscopies are recommended in patients with multiple adenomas from polyposis families with either an *APC* defect or an *MUTYH* defect and also in families with an unknown gene defect. A limitation of our study is that we were not always informed whether such a protocol was consequently applied in all three registries or that we had no detailed information on management strategies. However, the fact that the risk of developing metachronous CRC after surgical treatment of CRC (after which a strict colonoscopic protocol is advised) was virtually the same as the risk observed in patients who presented with polyposis suggests that accelerated carcinogenesis is a true feature of MAP. Future prospective studies are needed to confirm our findings.

Another limitation is that we are not certain whether all metachronous lesions were real metachronous lesions and not missed synchronous adenomas or CRCs. Although colonoscopy is the gold standard for colonic examinations, studies have shown that even advanced lesions may remain undetected.[24] However, even if some of the lesions were missed lesions, the risk of developing CRC is still considerable.

In conclusion, the recently recognised syndrome of MAP appears to be a cancer susceptibility syndrome with a distinct phenotype with features associated with FAP and Lynch syndrome. MAP resembles (attenuated) FAP phenotypically with respect to numbers of adenomas and age at diagnosis of CRC. However, as shown recently, the tumour spectrum overlaps that of Lynch syndrome, and the accelerated CRC development observed in MAP is also a typical feature of Lynch syndrome. Based on these findings, we propose an intensive colorectal surveillance program for proven biallelic *MUTYH* mutation carriers consisting of regular colonoscopic screenings every 1–2 years independent of the number of adenomas. In patients with CRC, unmanageable polyps or adenomas with a high degree of dysplasia, a (sub)total colectomy is the most appropriate surgical option.

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Competing interests None.

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Chapter 13

Is colorectal surveillance indicated in patients with *PTEN* mutations?

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IS COLORECTAL SURVEILLANCE INDICATED IN PATIENTS WITH *PTEN* MUTATIONS?

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ABSTRACT

Background and aim: *Patients with germline phosphatase and tensin homologue (PTEN) mutations develop hamartomatous lesions in several organs and are at increased risk of various malignancies. We assessed the lifetime risk of benign and malignant gastrointestinal lesions in patients with a proven PTEN mutation.*

Method: *Data on sex, mutation, dates of birth, last contact, and diagnosis, location, and type of gastrointestinal lesions were collected from nine countries. The lifetime risk of gastrointestinal lesions was calculated by Kaplan-Meier methods.*

Results: *A total of 156 patients (67 males, 43%) from 101 families with a PTEN mutation were included. Patients were born between 1928 and 2008. Benign gastrointestinal polyps were reported in 49 patients (31%) at a mean age of 38 years (range 18-62 years) and were most often hamartomas. Twenty-two patients (44%) had upper as well as lower gastrointestinal lesions, 14 (29%) had only colonic lesions, and 13 (27%) had gastrointestinal lesions at unknown sites. The cumulative risk of developing benign gastrointestinal polyps was 70% at age 60. Four patients (two males) developed colorectal carcinoma (CRC) at 53, 57, 59, and 62 years, respectively. The cumulative risk of developing CRC was 18% at age 60. Except one carcinoid in the small intestine, no upper gastrointestinal cancers were observed.*

Conclusion: *Benign gastrointestinal lesions are common in PTEN mutation carriers. We show a three- to fourfold increased lifetime risk of CRC, compared to the general population. Colorectal screening of patients with germline PTEN mutations is recommended, starting at age 40 years.*

What is new in this paper?

Patients with a germline PTEN mutation have a significant risk of developing benign colorectal tumors (70% cumulative risk at age 60) and colorectal cancer (18% cumulative risk at age 60). Surveillance of the colorectum is recommended from age the age of 40 years.

INTRODUCTION

PTEN hamartoma tumor syndrome (PHTS) is the collective term for clinical syndromes caused by germline mutations in the tumor suppressor *P*hosphatase and *ten*sin homologue, deleted on chromosome *ten* (*PTEN*).

The *PTEN* gene is located at chromosome 10q23.31. *PTEN* acts as a tumor suppressor by counteracting the important cancer promoting PI3K/Akt signaling pathway. *PTEN* is also involved in regulation of genomic instability, DNA repair, stem cell self-renewal, cellular senescence, and cell migration/metastasis.[1]

Clinical syndromes caused by *PTEN* mutations include Cowden syndrome, Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome, and Proteus-like syndrome. A common characteristic of these syndromes is the development of hamartomatous tumors which can arise from all embryonal layers and therefore occur at various sites of the body. Although histologically benign, some lesions have serious consequences, for example Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma), a hamartomatous overgrowth of cerebellar tissue which can cause mass effects in the posterior fossa. Beside the benign tumors, PHTS patients have an increased risk of developing cancer, particularly cancer of the breast and thyroid.[2] Surveillance protocols have been established to allow timely detection of (pre)malignant lesions.[3]

Although colorectal hamartomas and other types of polyps in the gastrointestinal tract are common, there are no consistent guidelines for gastrointestinal surveillance in PHTS patients. It is notable that information on cancer risks in the *PTEN* hamartoma tumor syndrome are generally derived from studies of individuals who fulfill published clinical criteria for Cowden Syndrome but who do not necessarily have an identifiable *PTEN* mutation. In this type of study, several have reported increased risks of colorectal polyps and cancer in such patients.[2-5]

In the present study we assessed the lifetime risk of benign and malignant lesions in the gastrointestinal tract in a large international cohort of *PTEN* mutation carriers and discuss the need for colorectal surveillance in these patients.

PATIENTS AND METHODS

Clinical and genetic data on patients with a germline *PTEN* mutation were obtained from clinical genetic centers from nine countries (USA, France, Norway, United Kingdom, Germany, Switzerland, Australia, Denmark, The Netherlands). Patients had given informed

consent for using clinical data for research purposes and data were gathered anonymously. The data collected included information on date of birth, date of last contact, type of *PTEN* mutation, and details on gastrointestinal lesions, including year of diagnosis and type of the lesions. The *PTEN* mutations reported in the study cohort were considered to be deleterious based upon the type of the mutation (nonsense, frameshift, or splice site mutation), or upon existing literature on this mutation. For mutations that have not been described evidence for pathogenicity was obtained by mutation prediction software and/or co-segregation of characteristic phenotype within families. Patients with a *PTEN* and *BMPR1A* contiguous deletion, known to cause a different phenotype with early onset juvenile polyposis, were excluded. A minority of patients had a missense mutation with uncertain pathogenicity, therefore a second statistical analysis without the data of these patients has been performed to determine whether the results were different.

Descriptive results were reported as mean (range) for continuous variables and number (percentage) for categorical variables. The lifetime risk of benign and malignant gastrointestinal lesions was calculated by Kaplan-Meier methods. The observation time was from the date of birth until CRC, gastrointestinal polyps, death, or date of last contact, whichever came first. For the calculations, all patients were in the denominator, assuming that all patients had had gastrointestinal examinations. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (Chicago, Ill, USA).

RESULTS

A total of 156 patients with documented deleterious *PTEN* mutations from 101 families were included. Sixty-seven (43%) were male. The patients were born between 1928 and 2008. The mean age at the date of last contact was 33 years (range 1-73 years). Forty-three patients (28%) were younger than 18 years at the date of last contact. Four patients had died at a mean age of 48 years (range 42-68 years), all of them had cancer.

In 49 patients (31%), benign gastrointestinal lesions were reported. There was no familial clustering of polyps. The mean age at diagnosis of gastrointestinal lesions was 38 years (range 18-62 years). All patients were above age 18 at the first diagnosis of gastrointestinal polyps. The polyp types included hamartomas (n=42), ganglioneuromas (n=8), adenomas (n=6), juvenile polyps (n=4), hyperplastic polyps (n=3), leiomyomas (n=2), lipomas (n=2), and a neurofibroma (n=1). Twenty-two patients (45%) had both upper as well as lower gastrointestinal lesions, 14 (29%) had only colorectal polyps, and for 13 (27%) patients, the

location of the polyps in the gastrointestinal tract were unknown. Different mutation sites were distributed evenly among patients with and without polyps. In figure 1, the cumulative lifetime risk of developing benign gastrointestinal lesions for patients with a *PTEN* gene mutation is shown. The risk was similar for both sexes (log rank test, p=0.181, figure not shown).

Four patients (2.6%) developed colorectal cancer (CRC), all above age 50. Characteristics of these patients are shown in Table 1.

Table 1 Characteristics of the four patients with colorectal cancer (CRC)

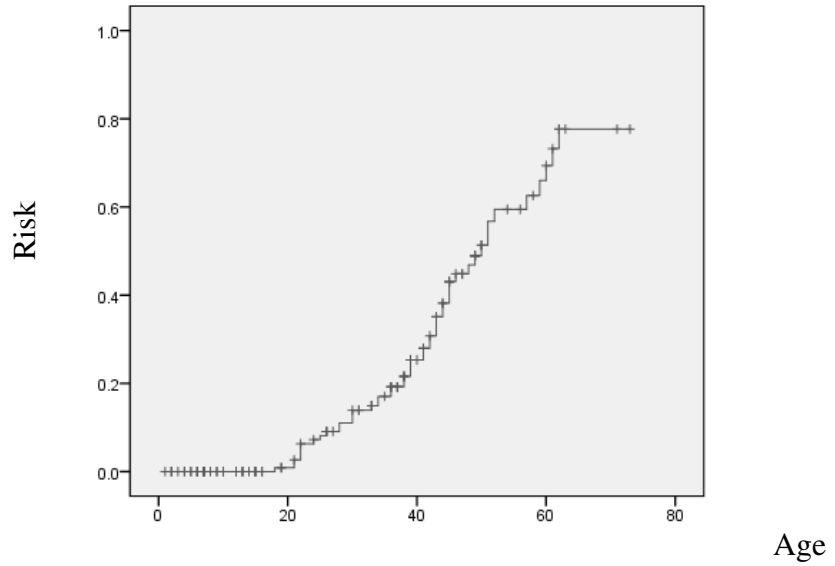
	Gender	Age CRC	Previous GI findings	Other cancer
1	Male	57	>100 hamartomas and adenomas whole GI tract	Carcinoid small intestine age 57 Melanoma, age unknown Basal cell carcinoma age 62 Renal cancer, age unknown
2	Female	59	Leiomyomas and lipomas upper GI tract	Carcinoid lung (at obduction) age 59 DCIS* and LCIS** breast age 50
3	Female	53	-	Breast cancer age 50 Thyroid cancer age 53
4	Male	62	Leiomyoma and neurofibroma colon	Clear cell renal carcinoma age 62

*DCIS: ductal carcinoma in situ ** LCIS: lobular carcinoma in situ

The patients with CRC had all a different *PTEN* mutation site. All patients had at least one other malignant tumor at the time of diagnosis of CRC, including intestinal carcinoid, lung carcinoid, breast cancer, renal cancer, melanoma, and basal cell carcinoma. The lifetime risk of developing CRC for patients with a *PTEN* gene mutation was 18% by the age of 60 years (Figure 2).

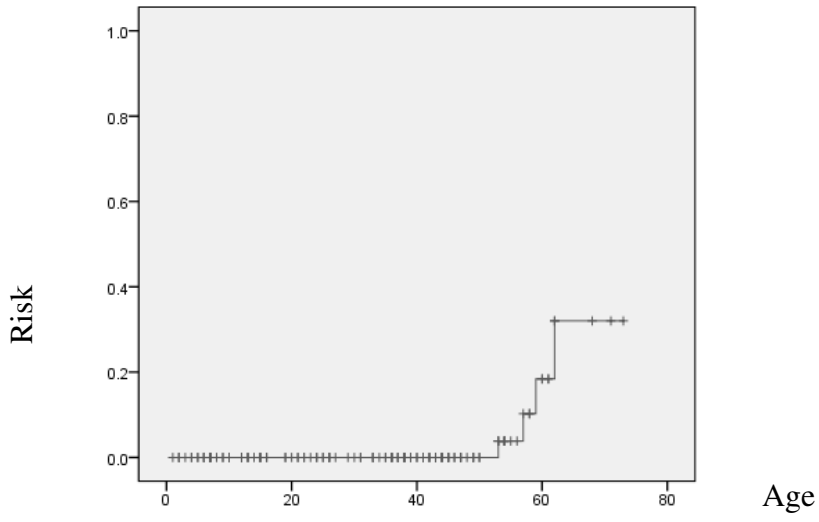
Thirteen patients had a missense mutation with uncertain pathogenicity. Statistical analysis without the data of these patients showed similar outcomes.

Figure 1 Cumulative lifetime risk of gastrointestinal polyps in patients with germline PTEN mutations



Age	0	10	20	30	40	50	60	70
Number left in analysis	156	126	110	88	57	18	8	2
Risk	0%	0%	0.9%	13.9%	25.3%	51.4%	69.4%	77.7%

Figure 2 Cumulative lifetime risk of colorectal cancer (CRC) in patients with germline mutations in the PTEN gene



Age	50	60	70
Number left in analysis	25	8	2
Risk	0%	18.4%	32%

DISCUSSION AND CONCLUSIONS

The present study demonstrates that benign gastrointestinal lesions are common in *PTEN* mutation carriers and can occur at various ages. The most frequent findings were colorectal hamartomas. In this study, for patients with a *PTEN* gene mutation a three- to fourfold increased risk of developing colorectal cancer by the age of 60 years was observed, compared with the general population. Except for one small intestinal carcinoid, upper gastrointestinal malignancies were not observed.

Two case reports describe Cowden patients with colorectal cancer at age 28, 39 and 56, respectively.[4,6] Furthermore, two recent studies have evaluated the occurrence of colorectal neoplasms in PHTS. A study from the USA reported nine CRC cases in 127 *PTEN* mutation carriers (7%), leading to an adjusted standardized incidence ratio (SIR) of 224.[5] In this study, all CRC diagnoses were between ages 35 and 49 years, but an age distribution was not provided in the article. Selection of patients was based on symptomatic Cowden Syndrome, or having gastrointestinal features. Another recent study evaluated CRC cases in Cowden syndrome patients in whom diagnosis was based on clinical criteria and not confirmed by DNA testing. Most of these cases were reported in the literature, and the authors added a small new patient series.[2] Five out of 211 patients (2.4%) developed CRC, with the earliest CRC diagnosis at age 43. A lifetime risk (by the age of 70 years) of CRC of 16% was calculated. These two cohort studies, and our study evidently show a three- to four times increased risk of CRC in PHTS patients, compared with the healthy population, as for people living in industrialized countries the cumulative lifetime risk of developing CRC is about 5%.[7]

Remarkably, in our series, we observed various types of polyps, but no cancers in the upper gastrointestinal tract, except one carcinoid of the small intestine. Reviewing the literature revealed three cases of gastric carcinoma, in PHTS patients at 67, 66 and 73 years old, respectively.[5,8,9]

The mechanism of colorectal cancer development in *PTEN* mutation carriers remains unclear. Although hamartomas are considered as benign polyps, in the past, a hamartoma-carcinoma sequence was suggested, caused by an abnormal microenvironment due to mutations, and leading to increased risks of neoplastic transformation.[10] A case study described a patient with a germline *PTEN* mutation who developed two independent CRCs at age 56. She had hamartomatous and hyperplastic polyposis throughout the gastrointestinal tract and the adenocarcinomas were shown to develop from the hyperplastic polypous lesions.[4] Of the three gastric cancers reported in the literature, two arose from a large

hyperplastic/hamartomatous polyp, but the other from an adenoma.[5,8,9] We were unable to determine whether the CRCs in our study arose from hamartomas or other types of colorectal polyps. A possible explanation for CRC development in *PTEN* mutation carriers was recently published. Huang et al. suggested that *PTEN* mutations seem not to be the single driving force for CRC development and that hMSH3 (mismatch repair) defects in nondysplastic epithelium may explain the increased risk of neoplastic progression of colonic hamartomas in PHTS patients.[11]

Our study comprises unique data of a large cohort of *PTEN* mutation carriers, and is distinguished from the earlier cohort studies in that it is based on mutation carriers only. Due to the retrospective design of the study, there may be a selection bias for symptomatic patients and patients with cancer. However, the selection bias might be limited, as many submitted patients did not even meet the Cowden syndrome diagnostic criteria.[12] On the contrary, the calculated risks of polyps are most likely underestimations, as not all patients had full endoscopic examinations and thus some may still have undetected polyps.

The most recent NCCN Guidelines for Cowden syndrome and other syndromes due to *PTEN* mutations do not provide specific recommendations for gastrointestinal surveillance in PHTS (0,13). Several investigators have suggested colorectal screening of PHTS patients. Some recommended biennial screening starting at age 15,[14] others proposed performing one baseline colonoscopy in asymptomatic patients at age 50,[15] or surveillance from the age of 25-30 years in a study setting.[6] The authors of the most recent studies recommend colonic surveillance starting at age 35, with follow-up examinations depending of the polyp burden,[5] and colonic surveillance starting at age 40 with 5-year intervals,[2] respectively. Based on our study and our review of the recent literature, for PHTS patients and patients with demonstrated *PTEN* mutations, we would propose performing surveillance colonoscopies every five years - or more frequently if polyps are discovered at baseline -, starting at age 40, or five years before the first CRC diagnosis in the family.

In conclusion, patients with *PTEN* germline mutations have an increased risk of developing CRC, which warrants colorectal surveillance. The risk of upper gastrointestinal cancer is not increased, so gastroduodenoscopy should only be performed when clinically indicated.

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Chapter 14

Summarizing discussion

The aim of this thesis was to describe clinical aspects of the hereditary polyposis syndromes familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), and *PTEN* hamartoma tumor syndrome (PHTS) to optimize the diagnosis, surveillance, and management of patients with these syndromes. In the Introduction (**Chapter 1**), we formulated several questions, which will be addressed below.

Part I Familial adenomatous polyposis (FAP)

Can genetic information be applied for management decisions in FAP?

In **Chapter 2**, genotype-phenotype correlations for FAP were reviewed. Since the detection of the adenomatous polyposis coli (*APC*) gene in 1991 (1), many reports described an association between location of the *APC* mutation and the number of colorectal polyps. Based on reported genotype-phenotype correlations we proposed to define three genotypic regions and associated phenotypes: First, mutations before codon 157, after codon 1595, and the alternatively spliced region of codon 9 (codons 312-412) generally cause an attenuated phenotype with less than 100 colorectal polyps. Second, if the mutation is located between codons 1250-1464, profuse polyposis with thousands of colorectal polyps is expected. Third, mutations from codons 158-311, 413-1249, and 1465-1594 are correlated with an intermediate phenotype, characterized by development of hundreds to thousands of colorectal polyps. For extracolonic lesions, genotype-phenotype associations were less obvious.

Using information on genotype-phenotype associations for clinical decisions was proposed in **Chapters 3** and **4**. The risk of rectal excision and rectal cancer after colectomy with ileorectal anastomosis (IRA) was assessed for patients with the attenuated, intermediate, and profuse genotype, respectively. As expected, in the groups with a genotype predicting a more severe polyposis phenotype the risk of rectal excision and rectal cancer was increased (61-74% versus 10% cumulative risk of rectal excision 20 years after primary IRA for profuse versus attenuated genotype groups, p=<0.05). Genetic information should never be the unique guide

for treatment decisions, as there may be intrafamilial phenotypic variation in FAP families. However, the combination of endoscopic and genetic data predicted the disease course, and can therefore be used to support clinical decisions. In a recent study, genotype-phenotype correlations were confirmed (2). Moreover, follow-up data for the different genotype groups were assessed, showing a reduced survival in the severe genotype group, compared to the milder genotype groups (2).

Can risk factors be identified for postoperative fertility problems?

Most FAP patients are in the fertile ages at the time of prophylactic colectomy. Information on the impact of IRA or IPAA on fertility in female FAP patients is scarce (3). We evaluated self-reported postoperative fertility problems in a cohort of 138 female FAP patients (**Chapter 5**). Seventeen percent reported fertility problems due to surgery, which seems to be higher than the estimated rate of 10% subfertility complaints in the Dutch population (4). Our results showed no significant surgery- or disease related risk factors (type of surgery, indication, number of surgical procedures, complications, desmoid tumor, cancer, other comorbidity) for developing postoperative fertility problems. Women who reported fertility problems were significantly younger at the time of primary surgery than women not reporting fertility problems (22 versus 28 years, p=0.01). This finding suggests that extended abdominal surgery at a young age may lead to reduced fertility. The mechanism is most likely anatomical changes and scarring due to surgery, although there may be other factors as impaired sexual function, psychological distress, and fear of pouch problems after pregnancy and delivery (5). One previous study showed increased time to pregnancy in female FAP patients who had undergone total proctocolectomy with ileal pouch-anal anastomosis (IPAA) (3). Our results showed no difference between type of surgery and postoperative problems. The differences between this observation and our findings can be explained by different study designs. In a meta-analysis the risk of fertility problems after IPAA was confirmed and options for prevention and management of post-IPAA infertility were suggested, including delay of IPAA, rectum-preserving surgery, embryo cryopreservation, and use of anti-adhesion products (5).

However, the studies included in this meta-analysis involved mainly ulcerative colitis patients. Therefore, further studies should focus on FAP patients. Furthermore, as publication bias cannot be excluded, future studies should preferably be prospective.

What is the outcome of patients with advanced duodenal adenomatosis or duodenal cancer?

Duodenal adenomatosis is very common in FAP patients (6). A subset of the patients develop duodenal cancer. To assess the clinical course of FAP patients with severe duodenal disease, all known cases with advanced duodenal adenomatosis (36/1066, 3.4%) and duodenal cancer (18/1066, 1.7%) were selected from the Dutch Polyposis Registry database (**Chapter 6)**. Patients with duodenal cancer had a poor prognosis with a median survival of eleven months. Prophylactic surgery in patients with advanced adenomatosis may prevent development of cancer, however, postoperative morbidity was considerable and even postoperative mortality was reported in three patients in our study. Furthermore, even after duodenectomy, fifty percent of the patients developed new adenomas in the neoduodenum. Nonetheless, the extremely poor prognosis of duodenal cancer justifies an aggressive surgical approach in patients with advanced duodenal adenomatosis. Patients should be under strict surveillance to control duodenal adenomatosis and to plan the optimal time for surgical intervention, if needed (7).

What are the implications of recent findings on the Wnt pathway and type II diabetes?

In the past years new techniques came available which enable rapid analysis of large amounts of genetic data. In genome wide analysis studies (GWAS) variants in the DNA sequence (single nucleotide polymorphisms, SNPs) are compared between cohorts of affected and non-affected persons. SNPs occurring more frequently in the affected patients are suspected to be associated with the disease. The recent detection of an association between type II diabetes and TCF7L2 (or TCF4) polymorphisms (8) led us to the question whether this type of diabetes is more common in FAP patients, as TCF7L2 is a transcription factor involved in the Wnt-

pathway, which is upregulated in FAP patients due to a germline *APC* mutation. In our study an increased prevalence of type II diabetes was found in FAP patients, compared with the general population **(Chapter 7)**. Our clinical study indeed confirmed the laboratory findings and supported the hypothesis of Wnt-pathway involvement in type II diabetes (9).

Part II Desmoid tumors

What are the characteristics of FAP patients with desmoid tumors? Can differences between FAP-related and sporadic desmoids be used to predict a FAP syndrome? What are risk factors for desmoid tumor development? What is the outcome of different treatment strategies for desmoid tumors?

In the **Chapters 8, 9, 10, and 11,** epidemiology-, etiology-, diagnosis-, and treatment issues on desmoid tumors are discussed. Desmoid tumors are a significant problem in FAP. FAP patients have a 14% lifetime risk of developing a desmoid tumor, and we found a substantial risk of 14% of dying from (complications of) desmoid disease in FAP patients with such a tumor (**Chapter 8**). Furthermore, secondary proctectomy was problematic or even impossible in seven patients.

Comparison of clinical characteristics of FAP-related and sporadic desmoid tumors showed that a substantial number (at least 7.5%) of all desmoid tumors were associated with FAP, particularly in case of intra-abdominal or abdominal wall tumor locations (**Chapter 9**).

Predicting the risk of developing a desmoid tumor may affect management decisions for FAP patients. Our study (**Chapter 10)** on 2260 European FAP patients, of which 220 had a desmoid tumor, showed that an *APC* mutation located 3' of codon 1444 and previous abdominal surgery were signifcant risk factors for desmoid development (regardless tumor location). If only the intra-abdominal desmoid tumors were taken into account, only previous abdominal surgery was a significant risk factor. Furthermore, a family history of desmoid tumors was a significant risk factor for desmoid development, as also observed by others (10). Further

assessed factors, including age of desmoid diagnosis, sex, and colorectal cancer, did not show to be independent risk factors for desmoid development.

In **Chapter 11**, we evaluated treatment modalities for FAP-related desmoid tumors including medical treatment (NSAIDs, anti-estrogens, other medication), surgery, and cytotoxic chemotherapy. For intra-abdominal desmoids, the progression-free survival was similar after surgery and a non-surgical approach (medicines, wait-and-see). In both groups, approximately two-thirds of tumors were stable or in regression, and about one fifth of patients died due to the desmoid tumor. For extra-abdominal and abdominal wall desmoids, surgery was the most common type of therapy with overall good outcome: three-quarter became stable or regressive, and no patients died in these groups. Evaluation of medical therapy showed similar progression-free survival in patients who received NSAIDs and hormonal therapy. Due to small numbers, effects of chemotherapy were difficult to interpret. Doxorubicin-based therapies seemed to be most effective.

The outcome of our studies on desmoid tumors emphasize the significance of particularly intra-abdominal desmoid tumors. Based on our studies, we recommend the following approach. First, in each patient presenting with a desmoid tumor, the possibility of an underlying FAP syndrome should be kept in mind (11,12). To exclude FAP, we recommended to perform colonoscopy in all patients with a desmoid tumor under age 60 years, and all patients with intra-abdominal or abdominal wall desmoids regardless of age. Second, in patients who already have a diagnosis of FAP, risk factors for developing desmoids should be taken into account. As previous abdominal surgery is an evident risk factor, in a subset of patients colorectal surgery may be postponed, if possible. Moreover, the fact that family history is a risk factor implicates that genetic modifiers may be involved in desmoid development, which would be an interesting focus for future research (10). Third, for management of intra-abdominal desmoid tumors we recommend watchful waiting or pharmacological therapy. Recent literature also shows a tendency to watchful waiting in patients with stable desmoid tumors (13). Cytotoxic chemotherapy and surgery should be reserved for progressively growing tumors, or tumors causing obstruction. For extra-

abdominal and abdominal wall desmoids, surgery seems to be safe, unless large postoperative defects are expected.

Part III Other polyposis syndromes

What is the natural course of MUTYH-associated polyposis?

About a decade ago, a new polyposis gene, *MUTYH*, was discovered (14). Since then, many studies described characteristics of patients with *MUTYH*-associated polyposis (MAP) (15,16). Generally, MAP patients develop between ten and a few hundred colorectal adenomas from the age of 46-48 years, and many of them present with CRC (15,16) However, information on the natural history of this type of polyposis was limited. We assessed this topic in a multicenter study, in which we included 254 MAP patients from three countries (**Chapter 12)**. Patients with a biallelic *MUTYH* mutation had a cumulative risk of developing CRC of 63% at age 60. Remarkably, among patients presenting with CRC, about half of the patients had less than 50 adenomas, and half of the patients had more than 50 adenomas. The number of colorectal polyps seems not to play an important role in CRC development. Another remarkable finding was that patients who presented with CRC had a considerable risk of developing a secondary CRC (11% after 5 years). Also, the patients presenting with colorectal adenomas had a substantial cumulative risk of CRC of 10% after 5 years of follow-up. These findings suggest accelerated adenoma to carcinoma development in MAP patients. Possibly, DNA repair genes involved in Lynch syndrome play a role in CRC development in MAP, which could explain accelerated tumor development. In other studies, a link between base excision repair and low-frequency MSI-pathways (17) and *MLH1* gene as a target of *MUTYH* transversions (18) were suggested. Although MAP in most cases displays an attenuated polyposis phenotype, our study showed rapid CRC progression. Therefore, intensive colorectal surveillance is indicated in patients with biallelic *MUTYH* mutations.

What is the risk of gastrointestinal lesions in patients with a PTEN mutation?

PTEN hamartoma tumor syndrome (PHTS) is characterized by a high risk of developing benign hamartomatous lesions and a high risk of developing malignant tumors, particularly of the breast, thyroid, and endometrium. Screening programs are designed to detect these tumors at an early stage. In **Chapter 13**, we evaluated the frequency of benign and malignant colorectal tumors in a cohort of 156 patients with a germline *PTEN* mutation, retrieved from nine countries. We calculated a cumulative lifetime risk to develop benign colorectal lesions of 69% at age 60 years. The most frequent findings were hamartomatous polyps. Nearly half of the patients with colorectal tumors had also upper gastrointestinal lesions. Four patients were reported to have colorectal cancer (ages 53, 57, 59, 62 years). The cumulative risk of CRC at age 60 was 18%, which is about three- to fourfold increased compared with the general population. We were not informed whether the cancers developed from hamartomas or other colonic lesions. However, based on our results and similar findings in recent studies (19,20), we propose colonosopic surveillance every five years starting at the age of 40 years, or five years before the first CRC diagnosis in the family.

Concluding remarks

This thesis shows the complexity of establishing guidelines for management of hereditary tumor syndromes. As most of these syndromes are rare, most recommendations are based on small patient numbers and retrospective analyses, whereas performing prospective randomized studies in large study cohorts would be preferred. Large international research collaborations may overcome this problem. Furthermore, clustering of patients with rare and complex diseases in specialized hospitals will optimize treatment. Clinical guidelines for treatment of these patients should not be considered as rigid instructions, but should be used as a support in decision making. Eventually, multidisciplinary decision making with the clinical expert, the patient, and the family, supported by evidence based guidelines, will optimize treatment.

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Nederlandse samenvatting

Dankwoord

Curriculum Vitae

List of publications

Nederlandse samenvatting

In dit proefschrift worden klinische aspecten van de erfelijke polyposissyndromen familiaire adenomateuze polyposis (FAP), *MUTYH*-geassocieerde polyposis (MAP) en *PTEN* hamartoma tumor syndroom (PHTS) beschreven. Het doel hiervan is optimalisatie van diagnostiek, periodieke controle en behandeling van patiënten met deze syndromen. In de Introductie (Hoofdstuk 1) werden diverse onderzoeksvragen geformuleerd, die hieronder behandeld worden.

Deel I Familiaire adenomateuze polyposis (FAP)

Kan genetische informatie worden toegepast bij beslissingen over de behandeling van FAP?

Hoofdstuk 2 is een overzichtsartikel waarin genotype-fenotypecorrelaties worden beschreven. Sinds de ontdekking van het *APC*-gen in 1991 toonden veel studies een associatie aan tussen de plaats van de mutatie op het *APC*-gen en het aantal colorectale poliepen. Op basis van deze studies stellen wij voor om het *APC*-gen te verdelen in drie regio's (genotypes) met bijbehorend aantal poliepen (fenotypes): het eerste genotype betreft mutaties voor codon 157, na codon 1595 en in de alternatieve *splice site* regio van codon 9 (codon 312-412); deze veroorzaken over het algemeen een mild fenotype met minder dan 100 colorectale poliepen. Het tweede genotype betreft mutaties tussen codon 1250 en 1464, waarbij een zeer ernstig fenotype wordt verwacht met duizenden colorectale poliepen. Het derde genotype, met mutaties in de codons 158-311, 413-1249 en 1465-1594 is geassocieerd met een intermediair fenotype, gekenmerkt door honderd tot duizend colorectale poliepen. Voor tumoren buiten de darm, die frequent voorkomen bij FAP, werden geen duidelijke genotype-fenotypecorrelaties gevonden.

In de hoofdstukken 3 en 4 stellen wij voor om informatie over genotype-fenotypecorrelaties te gebruiken bij klinische besluitvorming. Een cohort FAP-patiënten werd op basis van de plaats van de mutatie ingedeeld in de bovenbeschreven groepen. Vervolgens werd het risico op rectumexcisie en rectumcarcinoom na colectomie met ileorectale anastomose (IRA)

berekend. Zoals verwacht hadden de groepen met een genotype dat een ernstiger fenotype voorspelt een hoger risico op rectumexcisie en rectumcarcinoom (61-74% versus 10% cumulatief risico op rectumexcisie 20 jaar na primaire IRA voor ernstig versus mild genotype, $p<0.05$). Genetische informatie mag nooit de enige richtlijn zijn voor besluitvorming rond een behandeling, omdat het fenotype binnen een familie met FAP sterk kan variëren. Echter, op basis van een combinatie van endoscopische en genetische gegevens kan het ziektebeloop voorspeld worden. Een recente studie bevestigde genotype-fenotypecorrelaties en toonde in een patiëntengroep met een ernstig genotype een kortere overlevingsduur dan in een groep met mildere genotypes.

Kunnen risicofactoren worden geïdentificeerd voor het optreden van postoperatieve fertiliteitsproblemen?

De meeste FAP-patiënten ondergaan een profylactische colectomie tijdens de jaren waarin zij vruchtbaar zijn. Informatie over de gevolgen van een ileorectale anastomose (IRA) of ileo-pouch-anale anastomose (IPAA) op de fertiliteit van vrouwen is beperkt. Wij evalueerden in een cohort van 138 vrouwen met FAP door hen gerapporteerde postoperatieve fertiliteitsproblemen. Zeventien procent meldde fertiliteitsproblemen als gevolg van de colectomie. Dit percentage is iets hoger dan de geschatte subfertiliteit in de algemene Nederlandse populatie (ongeveer 10%). In onze studie werd geen significant verband aangetoond tussen postoperatieve fertiliteitsproblemen en operatie- of ziektegebonden factoren zoals type operatie, indicatie, aantal operaties, complicaties, desmoidtumor, kanker of overige comorbiditeit. Vrouwen die fertiliteitsproblemen rapporteerden waren significant jonger ten tijde van de eerste operatie dan vrouwen zonder problemen (22 versus 28 jaar, $p= 0.01$), wat suggereert dat een uitgebreide buikoperatie op jonge leeftijd kan leiden tot verminderde fertiliteit. Dit wordt meest waarschijnlijk veroorzaakt door anatomische veranderingen en vorming van littekenweefsel als gevolg van de operatie, hoewel ook andere, bijvoorbeeld psychologische factoren een rol kunnen spelen. Een eerdere studie beschreef dat het bij vrouwen met FAP die een IPAA hadden ondergaan langer duurde tot ze zwanger

waren dan voor vrouwen die een IRA hadden ondergaan. In onze studie wordt geen verschil gezien tussen type operatie en postoperatieve fertiliteitsproblemen. Dit kan verklaard worden doordat wij een andere onderzoeksmethode gebruikten. In een recente meta-analyse werd het risico op fertiliteitsproblemen na IPAA bevestigd en werden opties voor preventie en behandeling voorgesteld, zoals uitstellen van de operatie, rectumsparende operatie, embyocryopreservatie en gebruik van anti-adhesieve producten. Het merendeel van de studies die in deze meta-analyse werden geïncludeerd onderzocht echter patiënten met colitis ulcerosa. Toekomstige studies zouden bij voorkeur gericht moeten zijn op FAP-patiënten. Bovendien kan bij een meta-analyse publicatiebias niet worden uitgesloten; toekomstige studies zouden daarom prospectief opgezet moeten worden.

Wat is de uitkomst van patiënten met gevorderde adenoomvorming in het duodenum of duodenumcarcinoom?

Veel patiënten met FAP hebben ook adenomen in het duodenum. Een deel van hen ontwikkelt duodenumcarcinoom. Om het klinische beloop van FAP-patiënten met een ernstig aangedaan duodenum te onderzoeken werden uit de polyposisregistratie van de Stichting Opsporing Erfelijke Tumoren alle patiënten met gevorderde adenoomvorming (36/1066, 3,4%) of kanker (18/1066, 1,7%) van het duodenum geselecteerd (Hoofdstuk 6). Patiënten met duodenumcarcinoom hadden een slechte prognose; de mediane overleving was elf maanden. Ontwikkeling van kanker kan worden voorkomen door profylactische duodenectomie, hoewel er bij deze operatie een aanzienlijke kans is op postoperatieve morbiditeit en zelfs mortaliteit. Bovendien ontwikkelde 50% van de patiënten na de operatie nieuwe adenomen in het neoduodenum. Desondanks rechtvaardigt de extreem slechte prognose van duodenumkanker agressieve chirurgische interventie in patiënten met gevorderde duodenumadenomen. Om adenoomvorming van het duodenum te controleren en het optimale moment voor chirurgie te bepalen is intensieve periodieke controle van het duodenum vereist.

Wat zijn de implicaties van recente bevindingen van betrokkenheid van de Wnt-pathway bij type II diabetes?

In de afgelopen jaren zijn diverse technieken ontwikkeld die snelle analyse van grote hoeveelheden genetische informatie mogelijk maken. Genoomwijde analyses (GWAS) worden gebruikt om varianten in het DNA (single nucleotide polymorphisms, SNPs) te vergelijken tussen aangedane en niet-aangedane personen. SNPs die vaker voorkomen in aangedane personen zijn mogelijk geassocieerd met de betreffende ziekte. De recente ontdekking van een associatie tussen type II diabetes en TCF7L2 (of TCF4) polymorfismen riep bij ons de vraag op of type II diabetes vaker voorkomt bij FAP-patiënten, omdat TCF7L2 als transcriptiefactor functioneert in de Wnt-pathway die geactiveerd is in patiënten met een *APC* mutatie in de kiembaan. In onze studie vonden we een hogere prevalentie van type II diabetes in patiënten met FAP ten opzichte van de algemene populatie (Hoofdstuk 7). Deze klinische studie bevestigt de eerder beschreven laboratoriumbevindingen en ondersteunt de hypothese dat de Wnt-pathway betrokken is bij type II diabetes.

Deel II Desmoidtumoren

Wat zijn de kenmerken van FAP-patiënten met desmoidtumoren? Kunnen verschillen tussen FAP-gerelateerde- en sporadische desmoiden gebruikt worden om FAP te voorspellen? Wat zijn risicofactoren voor de ontwikkeling van desmoidtumoren? Wat is de uitkomst van verschillende behandelstrategieën voor desmoidtumoren?

In de hoofdstukken 8, 9, 10 en 11 worden epidemiologie, etiologie, diagnose en behandeling van desmoidtumoren besproken. Desmoidtumoren zijn een aanzienlijk probleem bij FAP. FAP-patiënten hebben gedurende hun leven 14% kans een desmoidtumor te ontwikkelen en onze studie toonde dat het risico om te overlijden aan (complicaties van) de desmoidtumor substantieel is (14%) (Hoofdstuk 8). Bovendien was een secundaire proctectomie in een aantal gevallen problematisch of zelfs onmogelijk door een desmoidtumor.

Klinische kenmerken van FAP-gerelateerde- en sporadische desmoidtumoren werden vergeleken in Hoofdstuk 9. Deze studie toonde dat minimaal 7.5% van alle desmoidtumoren is geassocieerd met FAP, vooral bij lokalisatie van de tumor in het abdomen of in de buikwand. Als het risico op een desmoidtumor voorspeld kan worden zou het beleid hierop afgestemd kunnen worden. Onze studie (Hoofdstuk 10) in 2260 Europese FAP-patiënten, waarvan 220 met een desmoidtumor, toonde dat een *APC*-mutatie 3' van codon 1444 en abdominale chirurgie in het verleden significante risicofactoren zijn voor het ontwikkelen van een desmoidtumor, ongeacht de lokalisatie. Bij subanalyse van het risico op intra-abdominale desmoiden bleek alleen abdominale chirurgie in het verleden een significante risicofactor te zijn. Ook was het voorkomen van desmoidtumoren bij familieleden een significante risicofactor voor het ontwikkelen van desmoiden. Dit is eerder ook beschreven. Andere onderzochte factoren zoals leeftijd van diagnose van de desmoidtumor, geslacht en colorectaal carcinoom waren geen onafhankelijke risicofactoren voor de ontwikkeling van desmoidtumoren.

In Hoofdstuk 11 evalueerden we de diverse behandelmodaliteiten voor desmoidtumoren zoals medicamenten (non-steroidal anti-inflammatory drugs (NSAIDs), anti-oestrogeentherapie, andere medicatie), chirurgie en chemotherapie. Bij intra-abdominale desmoidtumoren was de progressievrije overleving vergelijkbaar na een chirurgische of een niet-chirurgische benadering (medicijnen of afwachtend beleid). In beide groepen bereikte ongeveer tweederde een stabiele situatie of regressie van de desmoidtumor, en ongeveer eenvijfde van de patiënten overleed ten gevolge van de desmoidtumor. Extra-abdominale- en buikwanddesmoiden werden in de meeste gevallen chirurgisch verwijderd met globaal goede uitkomsten; driekwart bleef stabiel of ging in regressie en in deze groepen overleden geen patiënten aan de desmoidtumor. Evaluatie van medicamenteuze therapieën toonde een vergelijkbare progressievrije overlevingsduur in patiënten die NSAIDs of hormonale medicatie gebruikten. Effecten van chemotherapie waren moeilijk te interpreteren vanwege het kleine aantal personen dat op deze manier behandeld werd. Chemotherapie met doxorubicine leek het meest effectief te zijn.

De uitkomst van deze vier studies naar desmoidtumoren benadrukken de ernst van met name intra-abdominale desmoidtumoren. Op basis van onze resultaten stellen wij de volgende benadering voor. Ten eerste moet in het geval dat een patiënt zich presenteert met een desmoidtumor de mogelijkheid van FAP in gedachten worden gehouden. Wij adviseren colonoscopie in alle patiënten die zich op de leeftijd van 60 jaar of jonger met een desmoidtumor presenteren en alle patiënten met een intra-abdominale- of buikwanddesmoidtumor ongeacht de leeftijd. Ten tweede, bij patiënten met FAP moet rekening worden gehouden met de risicofactoren voor desmoidontwikkeling. Omdat een voorgeschiedenis van abdominale chirurgie een duidelijke risicofactor is moet in overweging worden genomen of colorectale chirurgie kan worden uitgesteld. Het feit dat een positieve familieanamnese een risicofactor is veronderstelt dat genetische *modifiers* een rol spelen bij het ontstaan van desmoidtumoren. Dit is een interessant onderwerp voor toekomstig onderzoek. Ten derde adviseren wij als behandeling voor intra-abdominale desmoidtumoren een afwachtend beleid of medicamenteuze therapie. Recente onderzoeken tonen een trend richting een afwachtend beleid in patiënten met een stabiele desmoidtumor. Chemotherapie en chirurgie moeten gereserveerd worden voor progressief groeiende tumoren, of desmoiden die obstructie veroorzaken. In geval van extra-abdominale- of buikwanddesmoiden lijkt chirurgie een veilige optie te zijn, tenzij grote postoperatieve defecten verwacht worden.

Deel III Andere polyposissyndromen

Wat is het natuurlijk beloop van MUTYH-geassocieerde polyposis?

Ongeveer tien jaar geleden werd een nieuw polyposisgen ontdekt: *MUTYH*. Sindsdien zijn vele studies verschenen die de kenmerken van patiënten met *MUTYH*-geassocieerde polyposis (MAP) beschrijven. Meestal ontwikkelen MAP-patiënten tussen de tien en enkele honderden colorectale adenomen vanaf ongeveer 46-jarige leeftijd, en velen presenteren zich met colorectaal carcinoom (crc). Er was echter weinig bekend over het natuurlijk beloop van MAP. Wij onderzochten dit onderwerp in een studie waarbij samengewerkt werd met diverse

andere instituten. Er werden 254 MAP-patiënten uit drie verschillende landen geïncludeerd. Patiënten met een biallelische *MUTYH*-mutatie hebben op 60-jarige leeftijd een cumulatief risico op crc van 63%. Een opmerkelijke bevinding was dat van de patiënten die zich presenteerden met crc ongeveer de helft minder dan 50 adenomen had, en de helft meer dan 50 adenomen. Dit veronderstelt dat het aantal adenomen niet een belangrijke rol speelt bij het risico op het ontstaan van crc. Een andere opmerkelijke bevinding was dat patiënten die zich met crc presenteerden een aanzienlijk risico hadden op een tweede crc (11% na 5 jaar). Ook patiënten die bij eerste diagnose alleen adenomen hadden bleken een cumulatief risico op crc te hebben van 10% na 5 jaar follow-up. Deze bevindingen suggereren dat er een versnelde adenoom-tot-carcinoom-ontwikkeling is in patiënten met MAP. Mogelijk spelen DNA-herstelgenen hierbij een rol, die ook zijn betrokken bij Lynch syndroom. In recente studies werd een link verondersteld tussen *base excision repair* en laag-frequente *MSI-pathways*. Ook werd gesuggereerd dat het *MLH1*-gen mogelijk een doel is van *MUTYH*-transversies. Hoewel de meeste MAP-patiënten een mild polyposis fenotye hebben toont onze studie dat er een snelle ontwikkeling van adenoom naar crc kan zijn. Daarom zijn intensieve periodieke controles van het colorectum geïndiceerd in deze patiënten.

Wat is risico op gastrointestinale afwijkingen bij patiënten met een mutatie in het PTEN-gen?

Het *PTEN* hamartoma tumor syndroom (PHTS) wordt gekenmerkt door een hoog risico op ontwikkeling van maligne tumoren, met name in borst, schildklier en endometrium. Om deze tumoren in een zo vroeg mogelijk stadium te ontdekken zijn screeningsprogramma's ontwikkeld. In hoofdstuk 13 evalueren we de frequentie van goedaardige en kwaadaardige colorectale tumoren in een cohort van 156 patiënten met een *PTEN*-mutatie in de kiembaan. Patiëntgegevens uit negen landen werden verzameld. Het cumulatief risico op het ontwikkelen van goedaardige afwijkingen in de darm was 69% op de leeftijd van 60 jaar. Meest voorkomend waren hamartomateuze poliepen. Bijna de helft van de patiënten had ook afwijkingen in de bovenste tractus digestivus. Vier patiënten ontwikkelden crc op de leeftijd van 53, 57, 59 en 62 jaar, respectievelijk. Het cumulatief risico op crc was 18% op 60-jarige

leeftijd, wat ongeveer drie- tot vier keer verhoogd is ten opzichte van de algemene populatie. We hadden geen informatie of deze crc's ontstaan waren uit hamartomen of uit andere afwijkingen. Op basis van ons onderzoek en vergelijkbare bevindingen in eerdere studies stellen wij voor om bij patiënten met PHTS iedere vijf jaar een colonoscopie te verrichten, of vaker, afhankelijk van de bevindingen. Dit zou gestart kunnen worden vanaf 40-jarige leeftijd of vijf jaar vóór de eerste diagnose van crc in de familie.

Afsluitende opmerkingen

Dit proefschrift toont dat het maken van richtlijnen voor erfelijke polyposissyndromen een complexe zaak is. De meeste van deze syndromen zijn zeldzaam, waardoor veel aanbevelingen gebaseerd zijn op kleine patiëntgroepen en retrospectieve analyses, terwijl studies bij voorkeur worden uitgevoerd als prospectief gerandomiseerd onderzoek in grote patiëntcohorten. Dit probleem kan worden opgelost door internationale samenwerking. De behandeling van patiënten met zeldzame en complexe aandoeningen zal optimaal zijn als deze wordt geconcentreerd in gespecialiseerde centra. Klinische richtlijnen moeten niet gezien worden als starre voorschriften, maar moeten gebruikt worden als ondersteuning bij klinische besluitvorming. De meest optimale behandeling zal uiteindelijk gekozen kunnen worden door middel van multidisciplinaire besluitvorming, waarbij klinische experts, de patiënt en de familie betrokken zijn, ondersteund door wetenschappelijk onderbouwde richtlijnen.

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Curriculum Vitae

Marry (Maria Hendrika) Nieuwenhuis werd op 12 november 1982 geboren te Lisse. In 2001 behaalde zij het VWO-diploma aan het Driestar College te Gouda en begon zij met de studie Geneeskunde aan de Universiteit Leiden. Tijdens de studie verrichte ze bij de Stichting Opsporing Erfelijke Tumoren (STOET) een wetenschapsstage met het onderwerp “The role of genetics in the choice of surgery in familial adenomatous polyposis”. Hiermee won zij de Gastro-enterologische Student Award 2006 van de Nederlandse Vereniging voor Gastro-enterologie (NVGE) en de LUMC Student Research Award 2006. Na het artsexamen in 2007 werkte zij een jaar als anios op de afdeling Klinische Geriatrie van het Kennemer Gasthuis in Haarlem. In 2009 vervolgde zij als arts-onderzoeker het onderzoek bij de STOET, wat leidde tot dit proefschrift. Van 2010 tot 2012 was zij coördinator van de Polyposis Contactgroep, waarvoor zij o.a. patiëntcontactdagen organiseerde en twee informatiefolders over polyposis samenstelde. Sinds 2011 werkt zij als arts-onderzoeker bij het GAMBA-project, waarbij genetisch onderzoek wordt verricht in een cohort van polyposispatiënten zonder bekend gendefect.

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