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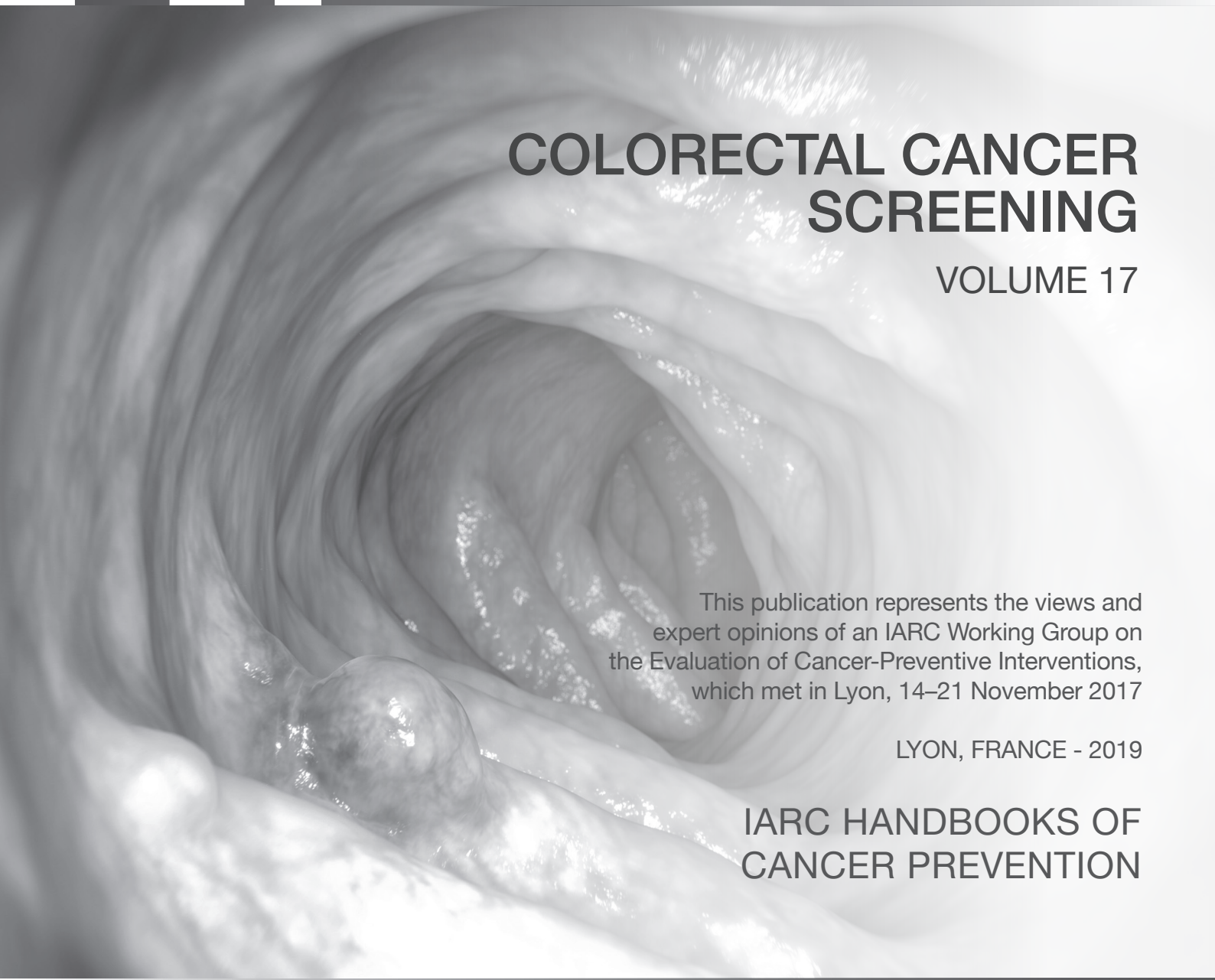

COLORECTAL CANCER SCREENING

VOLUME 17

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3.8 Populations at high risk of colorectal cancer

Populations at high risk for the development of CRC include the following categories of individuals: those with (i) a specific genetic predisposition; (ii) a family history of colorectal neoplasia; (iii) a personal history of colorectal neoplasia (cancer or premalignant lesions); and (iv) pre-existing medical conditions including inflammatory bowel disease, acromegaly, previous ureterosigmoidostomy, and cystic fibrosis (Table 3.8.1). Because individuals at high risk require more intensive testing, the term "surveillance" is generally used, and the term "screening" is reserved for asymptomatic populations at average risk.

3.8.1 Genetic predisposition

This category includes all individuals with specific genetic characteristics that confer a higher-than-average risk of developing CRC and other cancer types (Table 3.8.2). These genetic abnormalities induce syndromes that can be divided into three broad categories: (i) non-polyposis syndromes, (ii) adenomatous polyposis syndromes, and (iii) non-adenomatous polyposis syndromes. It should be noted that although current strategies for identifying individuals at high risk of CRC consist of syndrome-specific genetic testing, stimulated by the recognition of the phenotype associated with that syndrome and followed by surveillance of affected individuals, there is increasing interest in multigene panel testing for individuals with CRC when a hereditary component is suspected. This is now possible with the advent of massively parallel or next-generation sequencing, and it has been suggested that using a panel of high-penetrance genes associated with CRC in patients referred to cancer genetics services could be an efficient and cost-effective means of identifying genetic predisposition to CRC (Gallego et al., 2015).

(a) Non-polyposis syndromes

(i) Lynch syndrome

Definitions

Lynch syndrome is caused by germline mutations in mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), which result in a deficiency in MMR functions and confer an increased risk of developing hypermutated tumours that display high microsatellite instability (MSI-H tumours) (Stoffel & Yurgelun, 2016).

Lynch syndrome is the underlying cause of about 3% of all CRCs and is also associated with ovarian cancer, endometrial cancer, stomach cancer, and other cancer types (Hampel et al., 2008). Lynch syndrome was initially called hereditary non-polyposis CRC (HNPCC), to distinguish it from CRC genetic syndromes with a polyposis phenotype, but this term was later dropped in recognition of the wide range of cancer types to which Lynch syndrome predisposes (Umar et al., 2004). CRCs that arise in patients with Lynch syndrome also suffer loss of one or two of the MMR proteins that are coded for by the MMR genes (Umar et al., 2004). The estimated population prevalence of mutations in MMR genes is about 1 in 3000 (Dunlop et al., 2000). Recent evidence from a large prospective Lynch syndrome database estimated the lifetime risk of any cancer by age 70 years to be about 80%; the cumulative excess risk at age 60 years varies from 46% for *MLH1* mutations to 0% for *PMS2* mutations (Møller et al., 2017). [These estimates may be attenuated as a result of surveillance.]

CRCs with MMR deficiency account for about 15% of all CRCs, but not all of these are Lynch syndrome cancers; most (12% of all CRCs) are sporadic cancers that arise through the serrated pathway (and are more likely to be located in the proximal colon), in which the *MHL1* gene is silenced not by a mutation but by hypermethylation of the promoter region of the gene (Stoffel

Table 3.8.1 High-risk groups for the development of colorectal cancer

High-risk group	Lifetime risk of colorectal cancer
Hereditary colorectal cancer	> 50%
Familial colorectal cancer	20–90%
Individuals with a personal history of colorectal cancer or colorectal adenoma	15–20%
Individuals with other diseases (e.g. ulcerative colitis)	10–20%

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Table 3.8.2 Genetically determined conditions associated with increased risk of colorectal cancer

Category	Condition	Mutations
Non-polyposis syndromes	Lynch syndrome	Mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*)
	Familial colorectal cancer	Mutations in *FAN1*, *RPS19*, *RPS20*, and *NTHL1*, but unifying genetic cause not identified
Adenomatous polyposis syndromes	Familial adenomatous polyposis	Mutation in *APC*
	MUTYH-associated polyposis	Mutation in *MUTYH*
	Polymerase proofreading-associated polyposis	Mutations in *POLE* and *POLD1*
	Constitutional mismatch repair deficiency	Biallelic germline mutations in MMR genes
Non-adenomatous polyposis syndromes	Peutz–Jeghers syndrome	Mutation in *STK11*
	Cowden syndrome	Mutation in *PTEN*
	Juvenile polyposis syndrome	Mutations in *BMPR1A* and *SMAD4*
	Serrated polyposis syndrome	Mutations in *GREM1* and *MUTYH*, but unifying genetic cause not identified
Genetic variants	Increased risk of colorectal cancer	Multiple single-nucleotide polymorphisms

& Yurgelun, 2016). Therefore, isolated MSI-H tumours that show *MLH1* loss of function are unlikely to be caused by Lynch syndrome. Nevertheless, the presence of a MSI-H tumour heightens the probability of Lynch syndrome, and therefore has important implications for screening and surveillance. In addition, there is evidence that MSI-H tumours do not benefit from adjuvant 5-fluorouracil chemotherapy (Carethers et al., 2004), although, stage for stage, they have a better prognosis compared with non-MSI-H tumours (Gryfe et al., 2000); more recently, evidence has emerged that metastatic MSI-H tumours respond well to immune checkpoint inhibitors (Le et al., 2015).

The Amsterdam family history criteria are a set of diagnostic criteria developed to help identify families with an autosomal dominant pattern of inherited risk of CRC; the criteria are the following: three or more family members with CRC or another Lynch syndrome cancer, in two or more consecutive generations with one case diagnosed at age < 50 years, and one of the affected relatives being a first-degree relative of the other two, with familial adenomatous polyposis excluded (Vasen et al., 1991). However, fewer than 50% of people with identified mutations in MMR genes come from families that fulfil these criteria (Stoffel & Yurgelun, 2016). In addition, about 50% of families that do fulfil the criteria do not have mutations in MMR genes. Such families

are described using the term "familial CRC" (see below).

Effectiveness of surveillance

If a carrier of a MMR mutation has been identified, or if a family fulfils the Amsterdam criteria, even in the absence of an identifiable mutation, then endoscopic surveillance is universally recommended. In a case–control study of Lynch syndrome family members, regular colonoscopy at intervals of 3 years was shown to reduce the risk of CRC by 50%, to prevent death from CRC, and to produce a relative reduction in all-cause mortality of 65% (Järvinen et al., 2000). [The Working Group noted that these results were derived from fairly small numbers (133 in the study group and 119 in the control group).]

A longitudinal cohort study conducted in the Netherlands reported a 70% reduction in the standardized mortality ratio for CRC after the introduction of colonoscopy every 1–2 years starting at age 20–25 years for Lynch syndrome family members with at least one family member identified with a germline mutation in one of the MMR genes (de Jong et al., 2006).

Surveillance strategies

There is debate about the optimal surveillance interval. Three prospective studies (Engel et al., 2010; Vasen et al., 2010; Stuckless et al., 2012) and one retrospective study (Mecklin et al., 2007) have examined the performance of colonoscopy surveillance in Lynch syndrome family members (Table 3.8.3). Most cancers diagnosed between surveillance episodes were diagnosed at an early stage (stage I or II), and most were located in the proximal colon, emphasizing the need for careful proximal colonoscopy. On the basis of these studies, recent European guidelines suggest that the surveillance interval should be 1–2 years (Vasen et al., 2013).

A cost–effectiveness analysis concluded that, on average, regular endoscopic examination confers an increase in life expectancy of 7 years for Lynch syndrome family members, and total colonoscopy is the preferred surveillance modality, given the high risk of adenomas and cancer and the high incidence of lesions in the proximal colon (Vasen et al., 1998). The evidence relating to the age at which surveillance should start indicates that age 25 years is appropriate, because it is from this age that the risk increases substantially, both in those defined by family history (Lynch et al., 1993) and in those with proven mutations (Vasen et al., 1996).

(ii) Familial colorectal cancer

Definition

The term "familial colorectal cancer", previously known as familial colorectal cancer type X (FCCTX), is used to describe the 40–50% of families with CRC that fulfil the Amsterdam criteria but are not found to have germline mutations in the MMR genes (Stoffel & Yurgelun, 2016). There is some debate about whether patients with MSI-H tumours with no mutations in MMR genes should be included in this group. Either way, current evidence suggests that this is a genetically heterogeneous group, and although several candidate genes have been identified, no unifying genetic pattern has emerged yet (Muzny et al., 2012).

Surveillance strategies

CRC risk is slightly lower in patients with familial CRC than in those with Lynch syndrome (see Section 3.8.1(a)). However, it is generally agreed that even when genetic screening has excluded genetically defined Lynch syndrome, the surveillance strategy in families that fulfil the Amsterdam criteria should be the same as that for patients with Lynch syndrome (Cairns et al., 2010).

Table 3.8.3 Outcomes from surveillance of patients with Lynch syndrome

Reference	Number of participants	Mean duration of follow-up (years)	Surveillance interval recommended (years)	Number (%) of interval cancers	Location in proximal colon (%)	Local stage (stage I or II) (%)	Deaths from colorectal cancer
Mecklin et al. (2007)	420	6.7	2	26 (62%)	57	80	5
Engel et al. (2010)	1126	3.7	1	25 (2.2%)	NR	95	NR
Vasen et al. (2010)	745	7.2	1–2	33 (4.4%)	62	83	0
Stuckless et al. (2012)	109	~10	1–2	21 (19.2%)	62	78	1

NR, not reported.
Adapted from Vasen et al. (2013).

(b) Adenomatous polyposis syndromes

(i) Familial adenomatous polyposis

Definition

Familial adenomatous polyposis (FAP) is caused by germline mutations in the adenomatous polyposis coli (*APC*) gene, a tumour suppressor gene that has a role in Wnt signalling and is mutated in most cases of sporadic CRC that do not display MSI (Muzny et al., 2012). FAP is easily recognized in most patients because of its phenotypic characteristics, consisting of hundreds to thousands of adenomatous polyps throughout the large bowel. The population prevalence is about 1 in 14 000, and FAP accounts for fewer than 1% of all CRCs (Bülow et al., 1995) [this percentage is now about 0.07%, as a result of effective recognition and surgical prophylaxis].

Although FAP displays an autosomal dominant pattern of inheritance, about 25% of cases are not associated with a family history and are caused by new mutations. It is in this de novo subgroup that most of the cancers now arise, because there is no opportunity to identify gene mutation carriers from a family history (Cairns et al., 2010). There is significant phenotypic heterogeneity in FAP mutations, and some mutations are associated with an attenuated form of FAP (attenuated FAP) that leads to fewer polyps and a later age of onset of both polyps and cancer (Sieber et al., 2006). In most cases of FAP, polyposis will develop in the second or third decade of life, and the risk of developing CRC is 90% by age 70 years (Vasen et al., 2008).

FAP is also associated with adenocarcinoma of the duodenum and the ampulla of Vater (lifetime risk, ~7%), diffuse fundic gland polyposis of the stomach, gastric adenomas, and papillary thyroid cancer (Stoffel & Yurgelun, 2016).

Effectiveness of surveillance

During the period from the 1970s to the 1990s, polyposis registries were set up in several countries (including Denmark, Finland, Sweden, and the USA) to improve the management of this condition. In studies based on these registries, the incidence of CRC in symptomatic patients with FAP was much higher than that in asymptomatic individuals with FAP who were under surveillance (47–70% vs 3–10%) (Alm, 1975; Bussey, 1975; Järvinen et al., 1984; Bülow, 1986; Vasen et al., 1990). In addition, the registration of FAP cases followed by regular surveillance consistently reduced CRC-specific mortality (Bertario et al., 1994; Bülow et al., 1995; Belchetz et al., 1996; Heiskanen et al., 2000).

Surveillance strategies

For classic FAP, it is usual to offer sigmoidoscopy surveillance, because the rectum appears to be affected in all cases. In the case of attenuated FAP, in which the polyp load is smaller and polyps are more likely to be located in the proximal colon, colonoscopy is recommended (Vasen et al., 2008).

In terms of the interval between examinations, because studies on the natural history of FAP indicate that, on average, 10–15 years elapse between the diagnosis of the first adenoma and the development of invasive malignancy, endoscopy (colonoscopy or sigmoidoscopy as recommended) every 2 years is recommended (Bussey, 1975; Vasen et al., 2008).

The age at which endoscopic screening should start is dependent on the risk of developing invasive malignancy. Early studies carried out in the 1970s and 1980s found that the risk of developing CRC before age 20 years is very low, and data from the European FAP registries indicate that no cases have been recorded before age 10 years (Vasen et al., 2008). Therefore, for classic FAP, sigmoidoscopy surveillance is recommended from about age 11 years (Vasen et al., 2008). In attenuated FAP, because the onset of CRC is much later, with no case having been reported before age 24 years (Burt et al., 2004; Nielsen et al., 2007), it is recommended that colonoscopy at intervals of 2 years should start at about age 20 years. The duration of surveillance after the appearance of the first adenomas should be decided jointly by the patient and the surgeon; there may be good reasons for deferring colectomy, but because the risk of CRC increases rapidly after age 25 years (Cairns et al., 2010), it should be carried out before then, unless the polyp load is very small and there is no high-grade dysplasia.

In the unusual situation where no mutation can be identified in an individual with a FAP phenotype, for their first-degree relatives, in whom the risk of having FAP is 50%, annual endoscopic surveillance from the early teenage years until age 30 years, and thereafter every 3–5 years until age 60 years, is recommended by consensus (Cairns et al., 2010).

If colectomy and ileorectal anastomosis have been carried out, lifelong annual endoscopic surveillance is recommended, because the risk of cancer in the remaining large bowel is about 25% (Nugent & Phillips, 1992).

(ii) Rare adenomatous polyposis syndromes

MUTYH-associated polyposis is an autosomal recessive condition caused by biallelic mutations in *MUTYH*, a base excision repair gene (Stoffel & Yurgelun, 2016). The phenotype is highly variable, ranging from multiple polyps, both adenomatous and hyperplastic, to CRC in the absence of coexisting polyps. *MUTYH*-associated polyposis is a rare cause of CRC, but two mutations (*Y165C* and *G382D*) have been identified that have a carrier rate of about 1% in populations of European origin (Balaguer et al., 2007).

Polymerase proofreading-associated polyposis (Palles et al., 2013) and constitutional mismatch repair deficiency (Bakry et al., 2014) are caused by germline mutations that increase the risk of CRC; because they are so rare, they are not considered in further detail here.

Strategies for surveillance

There is no evidence specifically relating to surveillance strategies for these very rare conditions, but a similar approach to that taken with FAP is recommended.

(c) Non-adenomatous polyposis syndromes

(i) Hamartomatous polyposis syndromes

Peutz–Jeghers syndrome (PJS) results from germline mutations in the *STK11* gene, although in about 50% of cases that meet the clinical criteria, genetic testing is negative (Hemminki et al., 1998). Affected individuals develop

multiple hamartomas throughout the gastrointestinal tract and mucocutaneous pigmentation, and have an increased risk of cancer of the colorectum, stomach, and other extraintestinal sites. The lifetime risk of these cancers has been estimated to be between 45% and 90%. The population prevalence is probably about 1 in 50 000, and these cancers account for fewer than 0.01% of all CRCs (Cairns et al., 2010). The cumulative risk by age 70 years is on the order of 40% (Hearle et al., 2006). When a *STK11* gene mutation has been identified, complete colonoscopy is recommended at intervals of 2 years from age 25 years (Cairns et al., 2010). Because PJS is rare, the effectiveness of this approach has not been clearly established.

Cowden syndrome, also called *PTEN* hamartoma tumour syndrome (PHTS), is defined by germline mutations in the *PTEN* tumour suppressor gene, which is involved in the Akt/PKB signalling pathway, and is associated with an increased risk of a variety of cancer types. The phenotype is highly variable, and in the gastrointestinal tract consists of hamartomas, adenomas, serrated polyps, lipomas, and ganglioneuromas (Heald et al., 2010). When a *PTEN* gene mutation has been identified, the risk of CRC does appear to be increased, but the increase in risk has not been precisely defined, and definitive guidance for surveillance is not available (Cairns et al., 2010).

Juvenile polyposis syndrome (JPS) is another hamartomatous polyposis syndrome and is associated with mutations in the *BMPR1A* and *SMAD4* genes (Roth et al., 1999; Woodford-Richens et al., 2000). The risk of developing CRC is significant, amounting to 40% (Brosens et al., 2007). The prevalence of JPS is estimated to be 1 in 120 000, and it accounts for fewer than 0.01% of CRCs (Cairns et al., 2010). When a *BMPR1A* or *SMAD4* gene mutation has been identified, colonoscopy is recommended at intervals of 2 years from age 15 years (Cairns et al., 2010). Because JPS is rare, the effectiveness of this approach has not been clearly established.

(ii) Serrated polyposis syndrome

Serrated polyposis syndrome (SPS) is defined as more than 5 serrated colonic polyps proximal to the sigmoid, with at least 2 polyps larger than 10 mm, any serrated polyps in the proximal colon when there is a first-degree relative with SPS, or more than 20 serrated polyps (WHO Classification of Tumours Editorial Board, 2019; Rex et al., 2012). Although germline mutations in the *GREM1* and *MUTYH* genes have been associated with SPS (Jaeger et al., 2012), this is not universal. Individuals with SPS have an increased risk of CRC with MMR deficiency (IJspeert et al., 2017).

When the World Health Organization (WHO) criteria for SPS have been met, or when a *GREM1* or *MUTYH* mutation has been identified, colonoscopy at intervals of 1–2 years is recommended (East et al., 2017) [this is a weak recommendation, based on low-quality evidence]. Recent work indicates that several clinical risk factors could be used to stratify patients with SPS for different surveillance intervals (IJspeert et al., 2017).

3.8.2 Family history of colorectal neoplasia

(a) Definitions

It is well established that individuals with a family history of CRC have a higher risk of developing CRC. A close familial relationship, an early age at diagnosis, and the number of affected relatives are each indicators of elevated risk (Cairns et al., 2010). There is a large body of evidence from observational studies, most of which have been summarized in meta-analyses, which consistently found an approximately 2-fold increased risk of CRC in people with a first-degree relative with CRC compared with people with no such family history (Johns & Houlston, 2001; Baglietto et al., 2006; Butterworth et al., 2006; Johnson et al., 2013; Table 3.8.4).

Table 3.8.4 Meta-analyses of studies on the incidence of colorectal cancer in individuals with a family history of colorectal neoplasia

Reference	Number of studies Study design	Years of publication	Study design analysed	Family history	Number of studies in analysis	Summary estimate (95% CI)
Johns & Houlston (2001)	26 Cohort Case–control	1958–1999	Mixed	≥ 1 FDR	26	2.25 (2.00–2.53)
				≥ 2 FDR	6	4.25 (3.01–6.08)
				FDR at age < 45 yr	5	3.87 (2.40–6.22)
				FDR at age 45–59 yr	5	2.25 (1.85–2.72)
				FDR at age > 59 yr	3	1.82 (1.47–2.25)
Baglietto et al. (2006)	20 Cohort Case–control	1982–2003	Mixed	≥ 1 FDR	20	2.26 (1.86–2.73)
Butterworth et al. (2006)	47 Cohort Nested case–control Case–control Cross-sectional	1979–2004	Mixed	≥ 1 FDR	47	2.24 (2.06–2.43)
				≥ 2 FDR	10	3.97 (2.60–6.06)
				FDR at age < 50 yr	4	3.55 (1.84–6.83)
				FDR at age ≥ 50 yr	4	2.18 (1.56–3.04)
				≥ 1 SDR	5	1.73 (1.02–2.94)
			Cohort	≥ 1 FDR	13	2.29 (1.93–2.71)
			Case–control	≥ 1 FDR	34	2.21 (2.02–2.42)
Johnson et al. (2013)	16 Cohort Case–control Nested case–control Cross-sectional	1989–2009	Mixed	≥ 1 FDR	16	1.80 (1.61–2.02)

CI, confidence interval; FDR, first-degree relative or relatives; SDR, second-degree relative or relatives; yr, year or years.

The risk of CRC can be increased 2–4-fold if two or more first-degree relatives are affected with CRC (Fuchs et al., 1994; Taylor et al., 2010; Schoen et al., 2015; Weigl et al., 2016). The strength of the association decreases with increasing age. In people with a first-degree family history of CRC, the risk of CRC was found to be highest before or at age 40 years and to decrease with age afterwards (Samadder et al., 2015).

If a first-degree relative was diagnosed with CRC before age 50 years, then the risk of CRC was found to be more than 3-fold that of people with no family history of CRC (Butterworth et al., 2006; Taylor et al., 2010), more than 2-fold if the diagnosis was before age 60 years (Johns & Houlston, 2001; Samadder et al., 2014, 2015), and mostly less than 2-fold if the diagnosis was after age 60 years (Taylor et al., 2010; Samadder et al., 2014, 2015).

The risk of CRC in people with a family history of adenomatous polyps has not been as well investigated, and only a few well-designed studies exist (Lowery et al., 2016). Winawer et al. (1996) reported an almost 2-fold increased risk if adenomas were detected in a first-degree relative, and an even higher risk if the adenoma was detected before age 60 years; these findings were later confirmed by other studies (Ahsan et al., 1998; Cottet et al., 2007). A recent study in Hong Kong Special Administrative Region, China, investigated the risk of advanced adenomas in people with a family history of adenomatous polyps and found a much higher risk if the affected first-degree relative had an advanced adenoma compared with any adenoma (Ng et al., 2016). People with one affected second-degree relative were found to have a 20–50% higher risk of CRC, and the risk was somewhat higher with a greater number of affected second-degree relatives or if second-degree relatives were younger than 50 years or younger than 60 years at diagnosis (Taylor et al., 2010; Samadder et al., 2014, 2015; Weigl et al., 2016).

The association of a family history of adenomatous polyps with an increased risk of colorectal neoplasia is presumably due to a combination of heritable factors and shared environmental factors. It is recognized that up to 30% of CRCs are attributable to hereditary factors, but only 5% are attributable to the highly penetrant mutations that account for the syndromes described above (Broderick et al., 2017). It follows that the remainder (25%) are probably caused, at least in part, by the accumulation of low-penetrance genetic variants. Genome-wide association studies (GWAS) have so far identified up to 37 single-nucleotide polymorphisms (SNPs) with a positive association with CRC, although recent meta-analyses did not confirm the association with CRC for 22 of the SNPs (Montazeri et al., 2016). The presence or absence of these SNPs can be used to construct a polygenic risk score, and it has been shown that people with a polygenic risk score in the top 1% have an almost 3-fold increased risk of CRC compared with the population median (Frampton et al., 2016). However, it should be emphasized that the effect of family history cannot be explained entirely by genetic variation, because it has been shown that family history by itself is a risk factor that operates independently from the SNPs that are currently known to be associated with CRC (Weigl et al., 2018).

(b) Surveillance strategies

People with a family history of CRC are generally advised to start CRC screening earlier than the population at average risk. Colonoscopy is the preferred and recommended examination for screening and surveillance in this high-risk group, because a large proportion of cancers are also located in the proximal colon (Slattery & Kerber, 1994; Cairns et al., 2010; Rex et al., 2017).

Expert organizations tend to recommend earlier screening with colonoscopy in first-degree relatives of patients with CRC (Table 3.8.5). For example, screening colonoscopy should begin at

Table 3.8.5 Screening recommendations for individuals with a family history of colorectal neoplasia

Recommending association Reference	Family history	Recommended starting age of surveillance	Recommended surveillance interval
United States Multi-Society Task Force on Colorectal Cancer Rex et al. (2017)	CRC or advanced adenoma in 2 FDR diagnosed at any age CRC or advanced adenoma in 1 FDR diagnosed at age < 60 yr	Colonoscopy beginning 10 yr before the age at diagnosis of the youngest affected FDR or at age 40 yr, whichever is earlier	Colonoscopy every 5 yr
	CRC or advanced adenoma in 1 FDR diagnosed at age ≥ 60 yr	Begin screening at age 40 yr; tests are as per the average-risk screening recommendations Annual FIT if colonoscopy is refused	Intervals are as per the average-risk screening recommendations
German Guideline Program in Oncology GGPO (2019)	CRC in FDR	Colonoscopy beginning 10 yr before the age at diagnosis of the youngest affected FDR or at age 40–45 yr, at the latest	Colonoscopy after no more than 10 yr
	Adenoma in FDR detected at age < 50 yr	Colonoscopy 10 yr before the age at which the adenoma was detected in the affected FDR	Colonoscopy after no more than 10 yr
British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland Cairns et al. (2010)	CRC in 3 FDR, none aged < 50 yr CRC in 2 FDR, mean age < 60 yr	Colonoscopy at age 50 yr	Colonoscopy every 5 years to age 75 yr
	CRC in 2 FDR diagnosed at age ≥ 60 yr CRC in 1 FDR diagnosed at age < 50 yr	Once-only colonoscopy at age 55 yr	If normal, no follow-up
Asia Pacific Working Group on Colorectal Cancer Sung et al. (2015)	Not specified	Early screening is warranted for FDR of patients with CRC	No recommendation yet
Pan American Health Organization PAHO (2016)	Not specified	Screening should begin before age 50 yr	No recommendation yet
Cancer Council Australia Cancer Council Australia Colorectal Cancer Guidelines Working Party (2017)	CRC in 1 FDR diagnosed at age < 55 yr CRC in 2 FDR diagnosed at any age CRC in 1 FDR and ≥ 2 SDR diagnosed at any age	FIT every 2 yr from age 40 yr to age 49 yr Colonoscopy every 5 yr from age 50 yr to age 74 yr	
	CRC in ≥ 3 FDR or SDR, with ≥ 1 diagnosed at age < 55 yr CRC in ≥ 3 FDR diagnosed at any age	FIT every 2 yr from age 35 yr to age 44 yr Colonoscopy every 5 yr from age 45 yr to age 74 yr	

CRC, colorectal cancer; FDR, first-degree relative or relatives; FIT, faecal immunochemical test; SDR, second-degree relative or relatives; yr, year or years.

age 40 years in the USA and at age 40–45 years in Germany, or at least 10 years before the age at which CRC was diagnosed in the youngest affected first-degree relative (Brenner et al., 2008; GGPO, 2019; Rex et al., 2017). Expert organizations in the United Kingdom recommend screening colonoscopy for people with a family history of CRC starting at age 50–55 years (Cairns et al., 2010). A recent exception to the strong emphasis on colonoscopy is the recommendation of Cancer Council Australia, which recommends screening with FIT biennially in the first 10 years from age 35 years or 40 years, depending on the family history risk category, followed by colonoscopy every 5 years (Cancer Council Australia Colorectal Cancer Guidelines Working Party, 2017). In other countries and regions, development of guidelines is currently under way (PAHO, 2016; Sung et al., 2015).

The most up-to-date guidelines from the United States Multi-Society Task Force on Colorectal Cancer no longer differentiate between a history of CRC and a history of advanced adenomas in first-degree relatives with respect to the timing of the first screening colonoscopy (Rex et al., 2017). Also, the Task Force recommends a shorter surveillance interval of 5 years for those with two first-degree relatives or one first-degree relative younger than 60 years diagnosed with either CRC or advanced adenoma (Rex et al., 2017).

The United Kingdom guidelines recommend colonoscopy intervals every 5 years if CRC was detected in three first-degree relatives (none younger than 50 years) or in two first-degree relatives at a mean age at diagnosis of younger than 60 years (Cairns et al., 2010). European and German guidelines do not support special surveillance intervals for risk groups defined by family history (Dove-Edwin et al., 2005; Malila et al., 2012; GGPO, 2019).

The surveillance interval of 5 years for individuals with affected first-degree relatives was first mentioned in the guidelines for screening and surveillance from the USA in 2003 (Winawer et al., 2003), but evidence for the effectiveness of specific surveillance intervals is lacking. A recent RCT compared the detection rates of advanced adenomas in people with first-degree relatives diagnosed with CRC before age 50 years or with two first-degree relatives diagnosed with CRC at any age, and found no statistically significant difference at colonoscopy after 3 years (3.5%) and after 6 years (6.9%) (Hennink et al., 2015).

Most guidelines incorporate the age of the affected first- or second-degree relatives (< 60 years or ≥ 60 years), to account for the higher risk of CRC if the affected relative was diagnosed at a comparably younger age, which is supported by many studies (e.g. Winawer et al., 1996; Cottet et al., 2007). Still, the population frequency of having first-degree relatives diagnosed with CRC after age 60 years is 3.4%, so it is much more likely than having first-degree relatives diagnosed before age 60 years (0.8%) or before age 50 years (0.3%) (Taylor et al., 2010).

(c) Effectiveness of surveillance

The recommendation for individuals with a family history of CRC and with a negative colonoscopy to undergo another colonoscopy after 5 years instead of after 10 years, as is recommended for people at average risk, is based largely on the assumption that polyps grow more rapidly or transform more rapidly into cancer in this risk group, derived from clinical experience in the absence of empirical evidence. Only recently have a few observational studies actually analysed the effectiveness of colonoscopy in relation to family history of CRC (Brenner et al., 2011; Nishihara et al., 2013; Samadder et al., 2017). All three studies used CRC incidence as the outcome (Table 3.8.6).

In the study by Brenner et al. (2011), a very similar and strong reduction in the risk of CRC was observed if a colonoscopy was performed in the previous 1–10 years, regardless of whether first-degree relatives were affected. Nishihara

Table 3.8.6 Studies of the effectiveness of colonoscopy in individuals with a family history of colorectal cancer on colorectal cancer incidence

Reference Country	Study design Sample size	Study period Age group	Family history category Colonoscopy group	Relative risk (95% CI)	Adjustments
Brenner et al. (2011) Germany	Population-based case–control study 1688 cases 1932 controls	2003–2007 ≥ 50 yr	FDR with CRC: No colonoscopy Any colonoscopy 1–10 yr previously No FDR with CRC: No colonoscopy Any colonoscopy 1–10 yr previously	Odds ratio: 1 0.20 (0.13–0.32) 1 0.23 (0.19–0.28)	Age, sex, age, education level, general health screening, smoking status, BMI, use of NSAIDs, and use of HRT
Nishihara et al. (2013) USA	Prospective cohort study 88 902 participants	1988–2008 30–55 yr at baseline	FDR with CRC: No colonoscopy Any colonoscopy ≤ 5 yr previously Any colonoscopy > 5 yr previously No FDR with CRC: No colonoscopy Any colonoscopy ≤ 5 yr previously Any colonoscopy > 5 yr previously	Hazard ratio: 1 0.44 (0.30–0.66) 0.91 (0.55–1.52) 1 0.42 (0.35–0.51) 0.43 (0.32–0.58)	Age, sex, BMI, smoking status, aspirin use, physical activity level, red meat intake, total energy intake, alcohol consumption, folate intake, calcium intake, use of multivitamins, use of NSAIDs, and use of cholesterol-lowering drugs
Samadder et al. (2017) USA	Prospective cohort study 131 349 individuals with negative first colonoscopy at average risk, 7515 with first negative colonoscopy and FDR with CRC	2001–2011 50–80 yr at baseline	FDR with CRC: Negative colonoscopy 0–2 yr previously Negative colonoscopy 2.1–5 yr previously Negative colonoscopy 5.1–7 yr previously Negative colonoscopy 7.1–10 yr previously No FDR with CRC: Negative colonoscopy 0–2 yr previously Negative colonoscopy 2.1–5 yr previously Negative colonoscopy 5.1–7 yr previously Negative colonoscopy 7.1–10 yr previously	SIR: 0.15 (0.00–0.43) 0.47 (0.14–0.79) 0.77 (0.20–1.34) 0.65 (0.08–1.22) 0.15 (0.08–0.23) 0.26 (0.19–0.32) 0.33 (0.22–0.43) 0.60 (0.44–0.76)	Age and sex

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FDR, first-degree relative; HRT, hormone replacement therapy; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; yr, year or years.

et al. (2013) analysed the reduction in CRC risk by time since colonoscopy and found no reduction in risk in people with a first-degree family history of CRC whose most recent colonoscopy was performed more than 5 years earlier, whereas a significant reduction in risk was observed in people with no first-degree family history of CRC. [The Working Group noted that these results should be interpreted with caution with respect to considerations of surveillance intervals, because the studies did not differentiate between positive and negative index colonoscopies and because the absolute risk of CRC in people with a first-degree family history of CRC is generally higher than that in people with no such family history.]

Samadder et al. (2017) investigated the differences in CRC risk by time since a first negative colonoscopy in relation to a first-degree family history of CRC. In that study, which linked the Utah Population Database with cancer registry data and health-care data, the risk of CRC after a negative colonoscopy was generally reduced in individuals with no first-degree family history of CRC (measured up to 10 years after the negative colonoscopy). In individuals with a first-degree family history of CRC, the risk was similarly reduced up to 5 years after a negative colonoscopy; there was also a suggestion of a reduced risk 5–10 years after a negative colonoscopy in this group, but the standardized incidence ratios were not statistically significant for this interval. [The Working Group considered that the authors' interpretation that the results support a surveillance interval of 5 years in people with a first-degree family should be interpreted with caution, because of the limited power of the analyses in this risk group.]

3.8.3 Personal history of colorectal neoplasia

(a) Definitions

For a detailed description of the histopathology of colorectal neoplasia, see Section 1.2. Advanced adenomas are characterized by size (≥ 10 mm) and/or high-grade dysplasia and/or villous histology, and are considered high-risk adenomas, although the most common and strongest risk factor among the advanced characteristics is the size of the tumour. Any of these characteristics distinguishes them from non-advanced adenomas.

Sessile serrated lesions and polyps are common, are located mainly in the proximal colon, and are difficult to detect because of their sessile or flat morphology. Sessile serrated lesions smaller than 10 mm with no cytological dysplasia are classified among the low-risk lesions (Lieberman et al., 2012). Sessile serrated lesions 10 mm or larger and sessile serrated lesions with cytological dysplasia are considered to be high-risk lesions, with significant malignant potential (Erichsen et al., 2016). Traditional serrated adenomas are much less common, have a sessile or pedunculated shape, and are located mainly in the distal colon. Because of their malignant potential, they are considered high-risk adenomas (Erichsen et al., 2016).

Patients with a previous history of CRC have an increased risk of developing a subsequent cancer in the remaining colorectum (Bouvier et al., 2008), and in patients with a previous diagnosis of advanced adenoma, the risk of CRC is also increased (Atkin & Saunders, 2002).

(b) Increase in risk of cancer

Studies on the subsequent risk of colorectal neoplasia and CRC mortality in patients with low-risk adenomas and with high-risk adenomas at baseline examination are presented in Table 3.8.7 and Table 3.8.8, respectively.

In an earlier meta-analysis of observational studies, the risk of advanced adenomas

Table 3.8.7 Studies on subsequent risk of colorectal neoplasia and colorectal cancer mortality in patients with low-risk adenomas at baseline examination (selected recent studies)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Lieberman et al. (2007) USA	Prospective cohort study 1994–1997 1171 with neoplasia, 501 neoplasia-free controls	5.5 yr	Advanced neoplasia	No adenoma 1–2 tubular adenomas < 10 mm	1.00 1.92 (0.83–4.42)	Age and family history of CRC
Martínez et al. (2009) USA	Pooled prospective cohort studies 9167 with adenomas	3.9 yr (median)	Advanced neoplasia	2 adenomas vs 1 adenoma Adenoma size: 5–9 mm vs < 5 mm	1.39 (1.17–1.66) 1.17 (0.95–1.42)	Age, sex, race, family history of CRC, previous polyp, smoking status, BMI, baseline number of adenomas, adenoma size, location, histology, high-grade dysplasia, and study
Miller et al. (2010) USA	Retrospective cohort study 391 with and without adenomas	5–10 yr	Advanced neoplasia	No adenoma Adenoma < 5 mm Adenoma 5–9 mm Tubular adenoma 1 adenoma 2 adenomas	1.0 1.5 (0.6–3.9) 1.1 (0.4–3.3) 0.9 (0.4–2.3) 0.9 (0.3–3.2) 1.5 (0.5–4.5)	Unadjusted
Brenner et al. (2012) Germany	Case–control study 2582 cases, 1798 controls	10 yr	CRC	No previous endoscopy LRA < 3 yr ago LRA 3–5 yr ago LRA 6–10 yr ago	1.0 0.2 (0.1–0.2) 0.4 (0.2–0.6) 0.8 (0.4–1.5)	Age, sex, residence, education level, general health screening, family history of CRC, smoking status, use of NSAIDs, and use of HRT
Cottet et al. (2012) France	Prospective cohort study 5779 with adenomas	7.7 yr	CRC	LRA	SIR: 0.68 (0.44–0.99)	Age and sex
Løberg et al. (2014) Norway	Retrospective cohort study 1993–2011 40 826 with adenomas	7.7 yr (median)	CRC mortality	Low-risk adenoma	SMR: 0.75 (0.63–0.88)	Age Low risk: 1 adenoma, no villous growth pattern, no high-grade dysplasia
Atkin et al. (2017) United Kingdom	Retrospective cohort study 1990–2010 11 944 with intermediate-risk adenomas	7.9 yr (median)	CRC	Lower-risk group	0.51 (0.29–0.84)	Age and sex Lower risk, any of these: 1–2 adenomas 10–19 mm, 3–4 adenomas < 10 mm

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; LRA, low-risk adenoma; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

Table 3.8.8 Studies on subsequent risk of colorectal neoplasia and colorectal cancer mortality in patients with high-risk adenomas at baseline examination (selected studies)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Lieberman et al. (2007) USA	Prospective cohort study 1994–1997 1171 with neoplasia, 501 neoplasia-free controls	5.5 yr	Advanced neoplasia	No adenoma > 3 tubular adenomas < 10 mm 1 tubular adenoma ≥ 10 mm Villous adenoma HGD adenoma	1.00 5.01 (2.10–11.96) 6.40 (2.74–14.94) 6.05 (2.48–14.71) 6.87 (2.61–18.07)	Age and family history of CRC
Martínez et al. (2009) USA	Pooled prospective cohort studies 9167 with adenomas	3.9 yr (median)	Advanced neoplasia	3 adenomas vs 1 adenoma 4 adenomas vs 1 adenoma ≥ 5 adenomas vs 1 adenoma Proximal adenoma vs distal adenoma vs adenoma < 5 mm 10–19 mm ≥ 20 mm Tubulovillous/villous vs tubular High-grade dysplasia, yes vs no	1.85 (1.46–2.34) 2.41 (1.71–3.40) 3.87 (2.76–5.42) 1.68 (1.43–1.98) 2.27 (1.84–2.78) 2.99 (2.24–4.00) 1.28 (1.07–1.52) 1.05 (0.81–1.35)	Age, sex, race, family history of CRC, previous polyp, smoking status, BMI, baseline number of adenomas, adenoma size, location, histology, high-grade dysplasia, and study
Miller et al (2010) USA	Retrospective cohort study 1997–2006 391 with and without adenomas	5–10 yr	Advanced neoplasia	No neoplasia Adenoma ≥ 10 mm ≥ 3 adenomas Villous/tubulovillous adenoma	1.0 2.2 (0.7–6.6) 1.9 (0.8–4.6) 4.2 (1.5–11.5)	Unadjusted
Brenner et al. (2012) Germany	Case–control study 2003–2010 2582 cases, 1798 controls	10 yr	CRC	No previous endoscopy HRA < 3 yr ago HRA 3–5 yr ago HRA 6–10 yr ago	1.0 0.4 (0.3–0.7) 0.5 (0.3–0.8) 1.1 (0.5–2.6)	Age, sex, residence, education level, general health screening, family history of CRC, smoking status, use of NSAIDs, and use of HRT
Cottet et al. (2012) France	Prospective cohort study 1990–1999 5779 with adenomas	7.7 yr	CRC	High-risk adenoma	SIR: 2.23 (1.67–2.92)	Age and sex
Løberg et al. (2014) Norway	Retrospective cohort study 1993–2011 40 826 with adenomas	7.7 yr (median)	CRC mortality	High-risk adenoma	SMR: 1.16 (1.02–1.31)	Age Higher risk, any of these: ≥ 2 adenomas, adenoma with villous histology, high-grade dysplasia

Table 3.8.8 (continued)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Holme et al. (2015) Norway	Trial follow-up study 1999–2001 91 175 screening trial participants	10.9 yr (median)	CRC	Polyp-free Serrated polyp ≥ 10 mm Adenoma ≥ 10 mm Villous histology High-grade dysplasia ≥ 3 adenomas	1.0 3.3 (1.3–8.6) 2.8 (1.5–5.2) 1.1 (0.5–2.5) 2.7 (1.3–5.8) 2.3 (1.2–4.5)	Age and sex
Atkin et al. (2017) United Kingdom	Retrospective cohort study 1990–2010 11 944 with intermediate-risk adenomas	7.9 yr (median)	CRC	Higher-risk group	SIR: 1.30 (1.06–1.57)	Age and sex Higher risk, any of these: suboptimal examination quality, proximal polyps, high-grade dysplasia, adenoma ≥ 20 mm

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; HRA, high-risk adenoma; HRT, hormone replacement therapy; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

after 5 years in adults with one or two low-risk adenomas was similar to that in the population at average risk (Saini et al., 2006). More recent studies with up to 10 years of follow-up have confirmed no increased risk of CRC over the longer interval (Lieberman et al., 2007; Miller et al., 2010; Brenner et al., 2012; Cottet et al., 2012).

In the National Cancer Institute Pooling Project in the USA, the risk of advanced neoplasia was increased more than 2-fold in people with a history of adenomas of 10–19 mm compared with adenomas smaller than 5 mm, after 3–5 years of follow-up, and was increased 3-fold in people with a history of adenomas 20 mm or larger (Martínez et al., 2009). In the same study, the risk of advanced neoplasia was increased by about 30% if the adenoma showed villous or tubulovillous histology. However, in that study there was no association of high-grade dysplasia with subsequent occurrence of advanced neoplasia, although such associations were observed in other studies (Winawer et al., 2006; Atkin et al., 2017).

In another study, compared with the reference group with no neoplasia at baseline examination, the risk of advanced neoplasia increased strongly (RR, 6.05–6.87) in patients with adenomas 10 mm or larger, with villous histology and with high-grade dysplasia, after 5.5 years of follow-up (Lieberman et al., 2007). [The Working Group noted the large confidence intervals in these associations.]

(c) Surveillance strategies

The surveillance strategy for individuals with a personal history of colorectal neoplasia depends on the findings at baseline examination (Table 3.8.9). The section below summarizes the currently available surveillance strategies in such populations.

RCTs (European Polyp Surveillance I–III) are currently under way to assess the intervals for follow-up of patients with low-risk adenomas (5 years vs 10 years) and compared with those with high-risk adenomas (3 years vs 5 years) (Jover et al., 2016).

(i) One or two tubular adenomas smaller than 10 mm at baseline examination

As a result of improvements in colonoscopy, the detection rates of polyps, particularly those of small polyps, have increased (Brenner et al., 2015). Findings of one or two tubular adenomas with no villous components or high-grade dysplasia are considered to be low-risk adenomas.

Recent expert guidelines from countries with long-standing screening practices, such as the USA and countries in Europe, generally recommend having surveillance colonoscopy 5–10 years after the removal of low-risk adenomas (Lieberman et al., 2012; Hassan et al., 2013), or following recommendations for the next screening as if there had been no relevant findings at colonoscopy (Atkin et al., 2012). The United Kingdom guidelines recommend surveillance after 5 years, or no surveillance (Cairns et al., 2010) (see Table 3.8.9).

A recent meta-analysis and two individual studies that have not yet been considered in the existing guidelines observed a lower risk of CRC incidence and mortality after the removal of low-risk adenomas compared with that in the general population at average risk. These results, in addition to the results of earlier studies, challenge current recommendations and suggest that an extended interval of surveillance or no surveillance may apply after the removal of low-risk adenomas (Atkin et al., 2017; Dubé et al., 2017; Løberg et al., 2017). [The Working Group noted that in the studies of Atkin et al. (2017) and Løberg et al. (2017) the definitions of low-risk adenomas were more inclusive than only one or two adenomas smaller than 10 mm.]

Table 3.8.9 Expert guidelines for colonoscopy surveillance after adenoma removal

Findings at baseline examination	Guideline recommendations for time until surveillance colonoscopy				
	United States Multi-Society Task Force on Colorectal Cancer (Lieberman et al., 2012)	European Union (Atkin et al., 2012)	European Society of Gastrointestinal Endoscopy (Hassan et al., 2013)	British Society of Gastroenterology (Cairns et al., 2010; East et al., 2017)	Cancer Council Australia (Barclay et al., 2013)
1–2 tubular adenomas < 10 mm	5–10 yr	Routine screening	Screening after 10 yr	5 yr or screening	5 yr
3–4 tubular adenomas < 10 mm	3 yr	3 yr	3 yr	3 yr	3 yr
5–10 tubular adenomas < 10 mm	3 yr	1 yr	3 yr	1 yr	1 yr
≥ 1 advanced adenomas	3 yr	3 yr	3 yr	–	–
1–2 adenomas ≥ 10 mm	3 yr	3 yr	3 yr	3 yr	3 yr
≥ 3 adenomas ≥ 10 mm	3 yr	3 yr	3 yr	1 yr	< 5 adenomas ≥ 10 mm: 3 yr 5–9 adenomas ≥ 10 mm: 1 yr > 9 adenomas ≥ 10 mm: < 1 yr
≥ 1 adenoma ≥ 20 mm	–	1 yr	–	–	–
Sessile serrated lesion ≥ 10 mm or with dysplasia	3 yr	–	3 yr	3 yr	3 yr
Sessile serrated lesion < 10 mm and no dysplasia	5 yr	–	5 yr	Routine screening	5 yr
Traditional serrated adenoma	3 yr	–	3 yr	3 yr	–

yr, year or years.

(ii) Three or more adenomas at baseline examination

Patients with three or more adenomas at baseline examination have an increased risk of colorectal neoplasia soon after the baseline examination. It is assumed that with the prevalence of multiple adenomas, single adenomas may be missed; this may explain, at least in part, the higher adenoma detection rates at follow-up examinations (Lieberman et al., 2012). In an analysis of the National Cancer Institute Pooling Project, the risk of advanced adenomas during a follow-up of 3–5 years increased in a linear manner with each additional adenoma detected at baseline (Martínez et al., 2009).

According to guidelines from the USA and the European Society of Gastroenterology, patients with 3–10 adenomas smaller than 10 mm are considered to have a high risk of colorectal neoplasia and are advised to have surveillance colonoscopy 3 years after the baseline examination. According to guidelines from Australia, the European Union, and the United Kingdom, patients with three or four small adenomas are considered to be an intermediate-risk group, and surveillance after 3 years is recommended, whereas patients with five or more small adenomas are classified as a high-risk group, and a surveillance interval of 1 year is recommended (Cairns et al., 2010; Atkin et al., 2012; Barclay et al., 2013). For the small group of patients with more than 10 adenomas at baseline examination, the recommendation is to have genetic counselling or surveillance colonoscopy within less than 3 years (Lieberman et al., 2012; Hassan et al., 2013).

(iii) One or more advanced adenomas at baseline examination

Patients with one or more advanced adenomas belong to the high-risk group. Guidelines from Europe and the USA recommend that such patients undergo surveillance colonoscopy after 3 years (Atkin et al., 2012; Lieberman et al., 2012; Hassan et al., 2013); the European Union guidelines also suggest surveillance after 1 year if an adenoma is 20 mm or larger (Atkin et al., 2012). The United Kingdom guidelines recommend a surveillance interval of 3 years if one or two adenomas are 10 mm or larger (intermediate risk) and a surveillance interval of 1 year if at least three adenomas are 10 mm or larger (high risk) (Cairns et al., 2010). The guidelines from Australia recommend a surveillance interval of 3 years after the detection of one to four adenomas 10 mm or larger, and a surveillance interval of 1 year after the detection of five to nine adenomas 10 mm or larger (Barclay et al., 2013).

(iv) Serrated lesions and polyps at baseline examination

The quality of evidence with respect to surveillance after the removal of serrated lesions and polyps is still low and limited (Hiraoka et al., 2010; Schreiner et al., 2010; Lieberman et al., 2012; Holme et al., 2015; Szylberg et al., 2015; East et al., 2017; Dekker & IJspeert, 2018). Expert guidelines from Europe and the USA recommend surveillance colonoscopy after 3 years for patients with high-risk serrated polyps and lesions, and after 5 years for those with low-risk serrated polyps and lesions (Lieberman et al., 2012; Hassan et al., 2013). The United Kingdom guidelines also recommend a surveillance interval of 3 years for patients with high-risk serrated adenomas, but no special surveillance is recommended for those with low-risk serrated polyps and lesions (Cairns et al., 2010).

3.8.4 Medical conditions

Several medical conditions have been associated with the risk of developing CRC: inflammatory bowel disease, acromegaly, ureterosigmoidostomy, and cystic fibrosis.

Patients with inflammatory bowel disease, both ulcerative colitis and Crohn disease, have

an increased risk of CRC. Patients with a long history of extensive colitis (> 10 years with > 50% involvement of the colon) have 7 times the risk of patients with inflammatory bowel disease of lesser severity (Beaugerie et al., 2013). In addition, patients with ulcerative colitis with primary sclerosing cholangitis have a 4-fold increased risk of CRC compared with those without ulcerative colitis, and have an increased risk from the time of diagnosis (Soetikno et al., 2002).

Acromegaly is caused by increased levels of circulating growth hormone and its tissue mediator, insulin-like growth factor 1 (IGF-1). Although acromegaly is rare, this condition has been recognized as a risk factor for CRC and adenomas; prospective studies have found an odds ratio of 1.9 for adenoma and of 6.0 for CRC (Jenkins, 2006).

Adenomas and adenocarcinomas can form at the anastomosis site after ureterosigmoidostomy, although it is unclear whether they arise from the colonic or ureteric epithelium. It has been estimated that this occurs in 2.6% of patients, with a median latency of 26 years (Kälble et al., 2011).

Cystic fibrosis is also known to be associated with an increased risk of CRC, and the risk of CRC is higher in individuals who have had an organ transplant (Gini et al., 2018).

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