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Colorectal cancer surveillance by colonoscopy in a prospective, population-based long-term Swiss screening study – outcomes, adherence, and costs

Langzeitüberwachung nach dem kolorektalen Karzinomscreening mittels Koloskopie in einer prospektiven Bevölkerungsstudie in der Schweiz: Resultate, Adhärenz und Kosten

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ABSTRACT

Background The success of colorectal cancer (CRC) screening depends mainly on screening quality, patient adherence to surveillance, and costs. Consequently, it is essential to assess the performance over time.

Methods In 2000, a closed cohort study on CRC screening in individuals aged 50 to 80 was initiated in Uri, Switzerland. Participants who chose to undergo colonoscopy were followed over 18 years. We investigated the adherence to recommended surveillance and collected baseline characteristics and colonoscopy data. Risk factors at screening for the development of advanced adenomas were analyzed. Costs for screening and follow-up were evaluated retrospectively.

Results 1278 subjects with a screening colonoscopy were included, of which 272 (21.3 %; 69.5 % men) had adenomas, and 83 (6.5 %) had advanced adenomas. Only 59.8 % participated in a follow-up colonoscopy, half of them within the recommended time interval. Individuals with advanced adenomas at screening had nearly five times the risk of developing advanced adenomas compared to individuals without adenomas (24.3 % vs. 5.0 %, OR 4.79 CI 2.30–9.95). Individuals without adenomas developed advanced adenomas in 4.9 %, including four cases of CRC; three of them without control colonoscopy. The villous component in adenomas smaller than 10 mm was not an independent risk factor. Costs for screening and follow-up added up to CHF 1 934 521 per 1 000 persons screened, almost half of them for follow-up examinations; 60 % of these costs accounted for low-risk individuals.

Conclusion Our findings suggest that follow-up of screening colonoscopy should be reconsidered in Switzerland; in particular, long-term adherence is critical. Costs for follow-up could be substantially reduced by adopting less expensive long-term screening methods for low-risk individuals.

ZUSAMMENFASSUNG

Hintergrund Hauptfaktoren einer erfolgreichen Darmkrebs-Früherkennung sind Qualität der Früherkennung, Bereitschaft der Patienten zur Teilnahme an der Überwachung und die Kosten. Eine regelmässige Evaluation des Screening-Programms ist zentral.

Methoden Im Jahr 2000 wurde in Uri, Schweiz, eine geschlossene Kohortenstudie zur Darmkrebsvorsorge bei Personen im Alter von 50 bis 80 Jahren initiiert. Teilnehmer, die sich für eine Koloskopie entschieden, wurden über 18 Jahre beobachtet. Wir untersuchten die Einhaltung der empfohlenen Vorsorgeuntersuchungen und erfassten die Ausgangscharakteristika und Koloskopiedaten. Risikofaktoren beim Screening für die Entwicklung fortgeschrittener Adenome wurden analysiert. Die Kosten für das Screening und die Nachsorge wurden retrospektiv ausgewertet.

Ergebnisse 1278 Personen mit einer Screening-Koloskopie wurden eingeschlossen, von denen 272 (21,3 %; 69,5 % Männer) Adenome und 83 (6,5 %) fortgeschrittene Adenome aufwiesen. Nur 59,8 % nahmen an einer Folgekoloskopie teil und hiervon die Hälfte innerhalb des empfohlenen Zeitraums. Personen mit fortgeschrittenen Adenomen beim Screening hatten ein fast fünfmal höheres Risiko, erneut fortgeschrittene Adenome zu entwickeln, als Personen mit unauffälliger Screeningkoloskopie (24,3 % vs. 5,0 %, OR 4,79 CI 2,30–9,95). 4.9 % aller Personen ohne Adenome in der Screening-Kolonoskopie entwickelten im Verlauf fortgeschrittene Adenome, darunter vier CRC Fälle. 3 von diesen 4 CRC Fälle kamen nicht zur Kontrollkoloskopie. Die Kosten für das Screening und die Nachuntersuchung beliefen sich auf CHF 1 934 521 pro 1000 untersuchte Personen, fast die Hälfte davon entfiel auf die Nachuntersuchung. 60 % dieser Kosten entfielen auf Personen mit niedrigem Risiko.

Schlussfolgerung Unsere Ergebnisse deuten darauf hin, dass die Nachsorge der Screening-Koloskopie in der Schweiz neu überdacht werden sollte, da die Adhärenz über längeren Zeitraum schlecht ist. Die Kosten für die Nachuntersuchungen könnten erheblich gesenkt werden, wenn bei Personen mit geringem Risiko weniger teure Langzeit-Screening-Methoden angewandt würden.

Introduction

Colorectal cancer (CRC) remains a public health burden in many industrialized countries [1]. It can be partially prevented by screening. CRC incidence is declining in the US mainly due to widely implemented screening [2]. However, in Switzerland, CRC is still among the top three causes of cancer-related death [3]. In central and Eastern Europe, colorectal cancer has the highest mortality [4].

Case-control and cohort studies have shown that colonoscopy screening reduces CRC-related incidence and mortality [5, 6, 7, 8]. Colonoscopy can detect cancer at an earlier stage and prevent CRC by removing antecedent adenomas. Screening colonoscopy should be followed by adapted surveillance in a colonoscopy program, depending on the initial screening findings and risk factors [9, 10].

However, surveillance and screening are controversial [11, 12]. The cost and cost-effectiveness of screening and surveillance have been analyzed with different models to weigh the benefits, harms, and costs of colonoscopy. Only a few studies have been performed on surveillance and adherence to guidelines after colorectal cancer screening by colonoscopy. In Europe particularly, evidence on surveillance is scarce [13, 14, 15]. Reasons for the low interest in Europe might include the lack of endoscopic capacity, the missing evidence from randomized trials, and, most importantly, the reluctance of many Europeans to undergo colonoscopy [16].

The overall conclusion of the models supports the decision to provide population screening [4, 17, 18, 19]. Outcomes highly depend on different assumptions that vary between areas and countries and change over time. Apart from differences in cancer incidence and mortality, essential variables include the scheduling and adherence to endoscopic screening and surveillance, procedure costs, complication rates, and quality of examinations. Therefore, it is necessary to understand how screening and surveillance by colonoscopy are performed in reality, and whether model assumptions are correct for a given area. This is crucial to improve the screening strategy and the surveillance process.

We report findings from a population-based closed cohort screening study for CRC in Switzerland. We analyzed real-life clinical outcomes, adherence, and cost of surveillance by colonoscopy in the canton Uri over 18 years and examined screening findings as potential endoscopic predictors of future cancer risk. Our results will help improve future population-based screening programs.

Methods

Study design and study population

In 2000, a closed cohort study on CRC screening began in the canton Uri, a well-defined rural area of Switzerland with 32 526 inhabitants, which is surrounded by mountains [20]. For geographic reasons, the region has a low population migration of persons aged over 50 years [21]. Medical and endoscopic care in the study area is provided by only one hospital with a gastroenterology center, which allowed for comprehensive observation over many years.

From 1 June 2000 to 31 May 2001, individuals aged 50 to 80 (equivalent to 9727 persons) could choose between colonoscopy, sigmoidoscopy, or fecal occult blood test (Haemoccult/FOBT) free of charge. People were invited by a personal letter and further informed by articles in the newspaper, television, and local public lectures. The profession of participating individuals was assessed and compared with the distribution of the profession of the area

(Swiss federal census 2000). Written informed consent was required. Colonoscopies were performed by four experienced board-certified endoscopists and four gastroenterology trainees of the Gastroenterology Unit of the University of Basel, who had previously conducted at least 200 colonoscopies. Individuals were asked if they would like to have sedation; on request, midazolam or propofol was given initially, or during the examination. After 30 days, participants received an anonymous questionnaire asking about procedure and sedation satisfaction. Individuals with a personal history of CRC or polyps, inflammatory bowel disease, intestinal surgery, and those who had undergone colonic examination by endoscopy or radiology within the previous five years were excluded, as described in previous publications [5, 20]. Patients with symptoms suspect of colorectal disease were evaluated according to clinical need but not included in the study.

Study conduct and interventions

Participants who chose to undergo colonoscopy for screening were followed over 18 years. Based on the endoscopically obtained findings, the participants were advised when a follow-up colonoscopy should be done. After five years, people received a personal reminder letter about the necessary endoscopic control. All colonoscopies (screening and follow-up) from 2000 to 2018 were prospectively recorded with detailed endoscopic and histologic findings. Adenomas were removed and examined histologically. This included biopsies, simple polypectomies, complex polypectomies including endoscopic mucosal resection, and surgical resection of large polyps. In addition, we evaluated the management of complications. Experienced pathologists later reviewed histology of polyps in the proximal colon initially diagnosed as hyperplastic at screening for differentiation from serrated adenomas.

Individuals with adenomas at screening were followed in a post-polypectomy surveillance program. Based on screening findings, individuals were recommended to repeat colonoscopy according to the Swiss Society of Gastroenterology Guidelines on surveillance and were followed through until 2018. The guidelines, revised three times within the last 18 years [22, 23, 24, 25], divide patients into risk groups based on normal coloscopy, including the finding of hyperplastic polyps, and adenomas with low and high risk. Low-risk adenomas (risk category 1) are defined as 1–2 adenomas smaller than 10 mm with no high-grade dysplasia and no positive 1° family history for colorectal cancer. High-risk adenomas (risk category 2) were defined as more than two adenomas, (tubulo-)villous or serrated adenomas, adenomas > 10 mm or with high-grade dysplasia or positive 1° family history for CRC. Risk categories 3 and 4 refer to cancer in adenoma [24] (**Appendix 1**).

For individuals without adenoma at screening, repeat screening colonoscopy after ten years followed by surveillance colonoscopy was recommended. Individuals who did not attend their follow-up colonoscopies were followed by checking medical records and inquiring with primary care physicians for the development of CRC.

Adherence to the surveillance program

Adherence to the surveillance program/repeat screening after ten years was assessed. We measured adherence to the surveillance program with the help of two categorical variables: “attendance of first follow-up colonoscopy (yes/no)” and “on-time attendance of first follow-up colonoscopy (yes/no)” in the 18 years following the first screening colonoscopy. Individuals who had moved away from the canton of Uri or died within two years of the scheduled follow-up data were excluded from the adherence analysis. We further evaluated whether individuals responded to a follow-up reminder within one year of the recommended follow-up interval. In case of a change of the guideline, the old and new recommendations for timing of follow-up were accepted.

Clinical and endoscopic endpoints

The database contained the following variables for each study participant at the initial screening colonoscopy: age, smoking status (yes/no), family history (a = 1°, b = 2°, n = negative), and objective body mass index (BMI) measurements (height in m^2/weight in kg). BMI was categorized into normal weight (BMI< 25 mg/kg^2), overweight (BMI 25–29.9 mg/kg^2), class I obesity (BMI 30–34.9 mg/kg^2), class II obesity (BMI> 35 mg/kg^2) [26]. The family history covered both 1° and 2° relatives with any cancer and family history of CRC only.

Next to baseline characteristics, the available database contained screening and follow-up colonoscopy dates and colonoscopy results. Findings were categorized per patient and visit as follows:

- No adenoma
- At least one adenoma < 5 mm but no adenoma ≥ 5 mm
- At least one adenoma ≥ 5 mm and < 10 mm, but no adenoma ≥ 10 mm
- At least one adenoma ≥ 10 mm
- High-grade dysplasia
- Carcinoma

In addition, the number and location of adenomas, as well as histologic findings (tubular, villous, or serrated), were recorded.

Advanced adenomas were further defined as adenomas of > 10 mm, high-grade dysplasia, or cancer. Villous and tubulovillous adenomas were not included in the definition of advanced adenomas since newer data suggest that the villous component might not be an independent risk factor for adenoma progression [27, 28]. As well, the new ESGE guidelines are no longer dependent on histology in terms of villous vs. tubular components [29].

Resource use and costs

We performed a retrospective efficacy and cost analysis. Resource use for screening and surveillance included a possible but not mandatory consultation with the general practitioner, preparation for colonoscopy, colonoscopy including sedation and surveillance, histology, surgical resection of adenomas, and treatment of complications. The direct cost was derived from claims data utilization at the Uri Cantonal Hospital and combined with the correspond-

ing TARMED tariff [30] or with Swiss specific sources as specified in the following:

Costs for colonoscopies were based on a flat-rate agreement between the insurance companies and the hospital's endoscopy unit for screening colonoscopies, with or without biopsies or simple polypectomies of polyps up to 10 mm (**Appendix 2**). This flat rate equals the prize for colonoscopies calculated according to the TARMED tariff used in Switzerland and does not represent a reduced prize for screening. Costs for the initial screening colonoscopy, which has been offered free of charge, have been calculated according to the payments which would have been asked by the insurance companies outside the study. For complex polypectomies and histological workup, costs were calculated individually according to the TARMED tariff [30] and were sourced from the hospital invoice for outpatient colonoscopies. Costs for surgical resection of larger polyps and costs for complications were sourced from the hospital invoice, separately for obligatory general insurance and additional cost for private insurance, if applicable. Hospital invoices for obligatory general insurance were generated by the base rate and the cost weight of diagnosis-related groups according to diagnosis, treatment, patient age, and comorbidities. The costs for the workup and treatment of detected cancer were not included.

Statistical analysis

Descriptive statistics were used to assess the sociodemographic characteristics of the study participants and their endoscopic findings at baseline and subsequent colonoscopies.

Multivariable logistic regressions were used to assess whether adherence to the surveillance program varied by covariates, including gender, age, BMI, smoking status, family history, and endoscopic findings at screening.

We also performed a time-to-event analysis for the first appearance of an advanced lesion during the follow-up colonoscopies, separately for each of the four screening result categories: “no adenomas at screening,” “< 5 mm”, “5–9 mm”, and “advanced adenoma.” We presented the cumulative incidence of advanced adenomas in the follow-up colonoscopies for the four subgroups in a Kaplan-Meier plot.

Statistical analyses were conducted with Stata/SE version 16.1 (StataCorp LP, College Station, TX) and R version 4.0.0.

Screening costs were compared with carcinomas prevented and the reduced mortality using approximated incidence and mortality reductions found in three different studies: after six-year follow up in a prospective cohort study of Switzerland [5], after up to 22 years in the Nurse's Health Study combined with the Health Professionals Follow-up Study [31] and over 12 years in a retrospective study by Lee in the United States [32]. These data were compared with estimated costs of treating CRC in Switzerland [33].

Results

A total of 9 727 persons in Uri were eligible for screening. 1736 persons accepted one of several screening options. 73.2.% (1271 of 1736) individuals chose colonoscopy as their preferred screening method, corresponding to 13.1 % of those eligible for screening (1271 of 9727). In addition, 59 persons switched from FOBT or sigmoidoscopy to screening by colonoscopy until 2008. Fifty-two persons had to be excluded for various reasons such as cancer symptoms, endoscopy during the last five years, and incomplete colonoscopy (19 probands). A total of 1278 individuals with screening colonoscopy were included in this follow-up study and represented our baseline population; 12.6 % of participants had a 1° family history of CRC. Nineteen persons were lost to follow-up because they moved out of the area, and 165 persons died during the 18-year follow-up period (▶ **Fig. 1**).

Endoscopic findings at initial screening colonoscopy

Baseline characteristics and initial findings at screening are shown in ▶ **Table 1** and ▶ **Table 2**. Slightly more men (54.5 %) than women attended the screening coloscopy; 7.4 % of participants were older than 75 years. Professions of participating individuals were comparable to the professions of all inhabitants of the area, with the exception that farmers did attend colorectal cancer screening less often.

According to the anonymous questionnaire (with a response rate of 89.1 %), 30 % of the participants received sedation at initial endoscopy. Also, 91.3 % affirmed that they would definitively choose colonoscopy as the preferred screening method again, and 95.3 % of the responders reported recommending screening colonoscopy to a friend [20]. 68 % reported no or negligible pain and only 8.6 % significant pain at endoscopy.

The bowel preparation was mainly acceptable. Preparation was inadequate in 11 participants, of whom 6 were excluded, and in 5, colonoscopy was repeated. In 19 participants, bowel preparation was only moderate but could be adequately cleaned endoscopically.

The numbers of colonoscopies performed by board-certified endoscopists varied between 53 to 424, and the ones by trainees between 98 and 345. Cecal intubation rate was 95.4 %. Adenomas were found in 272 participants (adenoma detection rate 21.3 %, 27.1 % in men, and 14.3 % in women), 83 of whom were classified as advanced adenomas. 69.5 % of those with adenomas were men. Six men, but no women, presented with CRC. Adenoma detection rate and cecal intubation rate were not inferior in gastroenterology trainees. The performance of individual endoscopists varied. One board-certified endoscopist with 81 colonoscopies in the study did not reach the currently asked quality parameters.

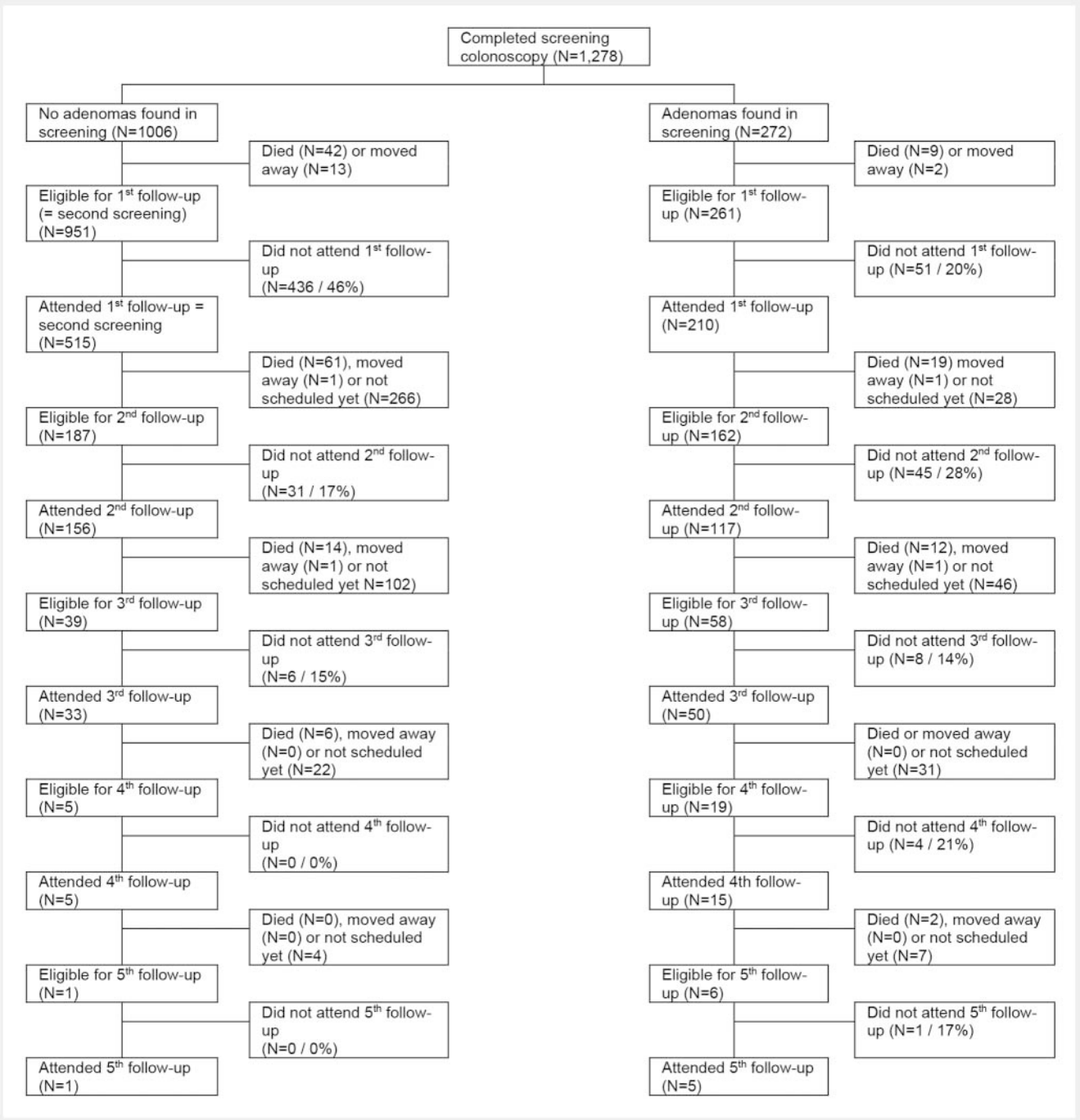
Adherence to the surveillance program

▶ **Table 3** and ▶ **Fig. 1** show that 59.8 % ever participated in the first follow-up colonoscopy, and only 47.6 % of them did so in time. The unadjusted and adjusted regressions models show that CRC family history and having adenomas found in the primary screening were positively associated with general attendance. Approximately 77.4 % of those with at least one adenoma < 5 mm at screening attended the follow-up colonoscopy compared to the 54.0 % without adenoma (adjusted Odds Ratio (aOR) 3.37, 95 % CI 1.95–5.81, p < 0.01). Similarly, those with adenomas

smaller than 9 mm or those with advanced adenomas were more likely to participate in the follow-up (78.4 % vs. 54.0 %,

aOR 3.88, 95 % CI 2.23–6.76, p < 0.01 and 87.5 % vs. 54.0 %, aOR 8.33, 95 % CI 4.15–16.74, p < 0.01). Individuals with a 1° family history of CRC were more likely to participate than those without (68.0 % vs. 58.6 %, aOR 1.72, 95 % CI 1.13–2.61). In contrast, advanced age was negatively associated with attending the follow-up colonoscopy. Individuals older than 60 were less likely to adhere to the surveillance program than those aged 50–54. Gender, smoking status, and family history of any cancer were not associated with ever participation.

▶ **Table 3** further illustrates a similar pattern for timely attendance. Individuals with adenomas found in the primary screening or who had a 1° family history of CRC were also positively associated with on-time attendance at follow-up in the unadjusted and



▶ **Fig. 1** Flow chart describing attendance of patients in follow-ups after colorectal cancer screening with colonoscopy. Persons with adenomas found in screening were transferred to the surveillance program, persons without adenomas invited to a second screening with surveillance if needed thereafter.

adjusted regression models. In contract to the analysis of general attendance, age was not associated with attendance on time.

80 % (210 of 261) of those with adenomas at screening (post-polypectomy surveillance group) attended the first follow-up colonoscopy, but approximately 20 % were lost to follow-up at each subsequent Colonoscopy (▶ **Fig. 1**). In contrast, only 515 of 951 (54 %) persons without adenoma ever attended a second screening examination, and several did not attend follow-up visits. In the surveillance group, 42 of 272 died during the 18-year follow-up, and four moved away; in the group without adenomas at screening colonoscopy (from now on called "adenoma-free screening group"), 123 of 1006 died during the follow-up, and 15 moved away. Overall, only 1.5 % over 18 years could not be followed up because they moved out of the area.

Endoscopic findings in the follow-up colonoscopy

The findings during follow-up are summarized in ▶ **Table 4**. The adenoma detection rate at the first follow-up colonoscopy (27 %) was strongly influenced by the initial findings of adenomas. Among participants with adenomas at baseline, the adenoma detection rate rose to 59.5 %, whereas it decreased to 13.8 % among participants without adenoma at screening. Overall, 8 % developed advanced adenomas, 15.7 % in the post-polypectomy surveillance group, and 4.9 % in the adenoma-free screening group. CRC was even found in 4 individuals, all of them in the

▶ **Table 1** Descriptive statistics of the study population (N = 1278).

	Individuals without adenomas in screening colonoscopy (N = 1006)		Individuals with adenomas in screening colonoscopy (N = 272)		Total (N = 1278)	
	N	(%)	N	(%)	N	(%)
Gender						
Female	498	(49.5)	83	(30.5)	581	(45.5)
Male	508	(50.5)	189	(69.5)	697	(54.5)
BMI						
Normal weight (< 25)	424	(42.2)	90	(33.1)	514	(40.2)
Overweight (25–29.9)	422	(42.0)	134	(49.3)	556	(43.5)
Class I obesity (30–34.9)	132	(13.1)	40	(14.7)	172	(13.5)
Class II obesity (> 35)	21	(2.1)	8	(2.9)	29	(2.3)
Missing	7	(0.7)	0	(0.0)	7	(0.5)
Age at first screening						
50–54 years	171	(17.0)	32	(11.8)	203	(15.9)
55–59 years	259	(25.7)	51	(18.8)	310	(24.2)
60–64 years	230	(22.8)	55	(20.2)	285	(22.3)
65–69 years	166	(16.5)	63	(23.2)	229	(17.9)
70–74 years	112	(11.3)	45	(16.5)	157	(12.3)
75 + years	68	(7.7)	26	(10.6)	94	(7.4)
Family history for CRC						
None	856	(85.1)	239	(87.9)	1095	(85.7)
1°	134	(13.3)	27	(9.9)	161	(12.6)
2°	16	(1.6)	6	(2.2)	22	(1.7)
Family history of any cancer						
None	495	(49.2)	140	(51.5)	635	(49.7)
1°	457	(45.4)	119	(43.7)	576	(45.1)
2°	54	(5.4)	13	(4.8)	67	(5.2)
Current smoking status						
Non-smoker	868	(86.3)	207	(76.1)	1075	(84.1)
Smoker	111	(11.0)	56	(20.6)	167	(13.1)
Missing	27	(2.7)	9	(3.3)	36	(2.8)

▶ **Table 2** Endoscopic findings* at the first colonoscopy (N = 1278).

	N	(%)
Any adenoma		
None	1006	(78.7)
One or more	272	(21.3)
Advanced adenoma*		
None	1195	(93.5)
One or more	83	(6.5)
Carcinoma found		
None	1272	(99.5)
One	6	(0.5)
High graded dysplasia		
None	1274	(99.7)
One	4	(0.3)
Villous or tubulo-villous adenoma ≥ 10 mm		
None	1235	(96.6)
One or more	43	(3.4)
Villous or tubulo-villous adenoma 5–9 mm		
None	1256	(98.3)
One or more	22	(1.7)
Villous or tubulo-villous adenoma < 5 mm		
None	1266	(99.1)
One or more	12	(0.9)
Tubular adenoma ≥ 10 mm		
None	1242	(97.2)
One	23	(1.8)
Two or more	13	(1.0)
Tubular adenoma 5–9 mm		
None	1184	(92.6)
One	68	(5.3)
Two or more	26	(2.0)
Tubular adenoma < 5 mm		
None	1177	(92.1)
One	68	(5.3)
Two or more	33	(2.6)
Serrated adenoma ≥ 10 mm		
None	1273	(99.6)
One or more	5	(0.4)
Serrated adenoma 5–9 mm		
None	1270	(99.4)
One or more	8	(0.6)
Serrated adenoma < 5 mm		
None	1263	(98.8)
One or more	15	(1.2)

* Multiple findings per person are possible. **An advanced adenoma is defined as either a carcinoma, high-grade dysplasia, or an adenoma ≥ 10 mm.

adenoma-free screening group. Three of them were investigated due to symptoms, one 12 and two 13 years after the initial screening coloscopy. Two were in the rectum, and one in the coecum. None of these CRC cases received a follow-up colonoscopy between screening and diagnosis. The cancer stages at diagnosis were T4NxM1, T3NoMo, and T3N2Mo. One (T3N1Mo) was diagnosed as an interval cancer in the rectum seven years after a negative follow-up coloscopy without adenoma. We saw no additional cancers in the group that did not attend the follow-up colonoscopies.

Advanced adenomas at follow-up depended significantly on initial screening results (▶ **Table 5**, ▶ **Fig. 2**). Individuals with advanced adenomas at the screening had nearly five times the risk of developing advanced adenomas again (24.3 % vs. 5.0 %, aOR 4.787, 95 % CI 2.304–9.947) compared with low-risk individuals in whom no adenomas were found at screening. Adenomas ≥ 10 mm had an increased risk of developing new advanced adenomas during follow-up, regardless of histology. Villous histology of adenomas < 10 mm did not affect the risk for later advanced adenomas significantly (17.4 % vs. 7.8 %, aOR 2.002, 95 % CI 0.561–7.138), as did tubular adenomas < 10 mm (16.4 % vs. 6.2 %, aOR 1.899, 95 % CI 0.987 – 3.63). However, even individuals with adenomas < 5 mm had a slightly increased risk (13.9 % vs. 5.0 %, aOR 2.564, 95 % CI 1.098–5.989). Those without adenomas at screening developed advanced adenomas later (▶ **Fig. 2**). A history of 1°relatives with CRC did not influence the occurrence of advanced adenomas during follow-up. Smoking increased the risk, as did increasing age, but failed to reach statistical significance.

Costs of Screening with Colonoscopy

The direct costs for screening and follow-up are shown in ▶ **Table 6**, ▶ **Table 7** and ▶ **Table 8**. They included the costs of the 1278 screening and 1110 follow-up colonoscopies, including bowel preparation, histology, and consultation with the general practitioner for advice as needed. Adenomas were surgically resected in 3 patients at screening and in 4 patients at follow-up (2 × trans-anal adenoma resection, 4 × right hemicolectomy, and 1 × sigmoid resection). Severe complications occurred in 5 cases, two at screening and three at follow-up (4 × severe bleeding and one perforation of the sigma at a stenosis due to recurrent diverticulitis at follow-up). Hospitalization was required in 4, and the patient with perforation required surgery (resection of the

▶ **Table 3** Participation in the first follow-up colonoscopy by sample characteristics (univariate and multivariate logistic regression outcomes).

	Attendance of first follow-up colonoscopy (0,1)					On time attendance of first follow-up colonoscopy (0,1)				
		Unadjusted model		Adjusted model			Unadjusted model		Adjusted model	
	(%)	OR	95 % CI	OR	95 % CI	(%)	OR	95 % CI	OR	95 % CI
Overall	(59.8)					(47.6)				
Gender										
Female	(56.9)	Ref.		Ref.		(44.1)	Ref.		Ref.	
Male	(62.3)	1.255	0.993–1.587	1.028	0.794–1.330	(50.3)	1.280	0.948–1.727	1.120	0.793–1.583
BMI										
Normal weight (< 25)	(60.5)	Ref.		Ref.		(48.6)	Ref.		Ref.	
Overweight (25–29.9)	(60.0)	0.982	0.761–1.269	0.972	0.738–1.281	(49.2)	1.023	0.741–1.413	0.874	0.609–1.253
Class I obesity (30–34.9)	(58.0)	0.904	0.629–1.299	0.882	0.600–1.297	(40.4)	0.718	0.447–1.151	0.604	0.360–1.013
Class II obesity (> 35)	(55.6)	0.817	0.374–1.785	0.853	0.362–2.013	(40.0)	0.705	0.245–2.032	0.467	0.145–1.502
Age at first screening										
50–54 years	(69.1)	Ref.		Ref.		(52.3)	Ref.		Ref.	
55–59 years	(65.7)	0.854	0.578–1.262	0.859	0.574–1.284	(44.0)	0.719	0.461–1.121	0.759	0.469–1.227
60–64 years	(61.7)	0.721	0.486–1.070	0.703	0.467–1.057	(48.5)	0.859	0.542–1.359	0.886	0.538–1.459
65–69 years	(52.1)	0.485	0.323–0.728**	0.393	0.256–0.604**	(50.0)	0.913	0.553–1.508	0.818	0.471–1.420
70–74 years	(53.4)	0.512	0.324–0.810**	0.406	0.250–0.659**	(45.1)	0.749	0.420–1.337	0.586	0.308–1.115
75 + years	(39.1)	0.287	0.162–0.509**	0.195	0.104–0.363**	(40.7)	0.628	0.271–1.454	0.487	0.192–1.234
Family history of CRC										
None	(58.6)	Ref.		Ref.		(43.7)	Ref.		Ref.	
1°	(68.0)	1.497	1.042–2.151*	1.717	1.131–2.608*	(71.2)	3.182	2.020–5.014**	3.861	2.276–6.550**
2°	(57.1)	0.941	0.393–2.253	0.772	0.302–1.974	(33.3)	0.645	0.192–2.166	0.529	0.141–1.985
Family history of any cancer										
None	(58.6)	Ref.		Ref.		(43.7)	Ref.		Ref.	
1°	(60.6)	1.042	0.819–1.325	0.933	0.704–1.235	(52.6)	1.485	1.094–2.015*	1.006	0.696–1.454
2°	(55.7)	0.854	0.502–1.455	0.766	0.435–1.349	(47.1)	1.189	0.586–2.412	1.426	0.668–3.043
Current smoking status										
Non-smoker	(58.8)	Ref.		Ref.		(47.2)	Ref.		Ref.	
Smoker	(66.5)	1.390	0.979–1.973	1.108	0.758–1.620	(49.5)	1.097	0.727–1.656	0.818	0.514–1.299

▲ **Table 3** (Continuation)

	Attendance of first follow-up colonoscopy (0,1)					On time attendance of first follow-up colonoscopy (0,1)				
		Unadjusted model		Adjusted model			Unadjusted model		Adjusted model	
	(%)	OR	95 % CI	OR	95 % CI	(%)	OR	95 % CI	OR	95 % CI
Endoscopic findings in main screening										
No adenoma	(54.0)	Ref.		Ref.		(39.3)	Ref.		Ref.	
Only adenoma(s) <5mmm	(77.4)	2.911	1.718–4.932**	3.365	1.947–5.814**	(75.4)	4.727	2.614–8.548**	6.224	3.329–11.639**
Only adenoma(s) 5–9 mm	(78.4)	3.090	1.829–5.219**	3.879	2.226–6.759**	(71.0))	3.782	2.181–6.557**	4.378	2.441–7.854**
Adenoma(s) >10 mm, high grade dysplasia or carcinoma	(87.5)	5.956	3.032–11.699**	8.331	4.146–16.741**	(57.1)	2.058	1.240–3.415**	2.589	1.493–4.492**
N				1,170					700	

* $p < 0.05$; ** $p < 0.01$; BMI: body mass index; CI: confidence interval; CRC: colorectal cancer OR: odds ratio.

sigma). Five patients requiring surgical resection of the adenomas and four patients with complications had private insurance, which generated additional costs (**Appendix 2**). Other minor complications in 6 patients required no specific treatment and did not result in additional costs. There was no case of mortality during either screening or surveillance. The calculated costs for screening and follow-up of 1000 people were CHF 1 934 521. The screening cost of 1000 persons, excluding administrative costs, was CHF 774 694, and follow-up costs amounted to CHF 675 574. The costs for cases with adenomas at screening per 1000 were CHF 1 169 897, much higher than for follow-up of persons without adenomas at Screening (CHF 541 920).

Discussion

The success of surveillance after coloscopy screening depends mainly on efficiency, adherence, and costs. In this surveillance study, we followed almost all colonoscopy screening participants over 18 years because of the closed area with low migration of only 1.5 % per year and only one hospital with a gastroenterological endoscopy center. In our study, only 59.8 % of screened individuals attended at least one follow-up coloscopy, and only half of them were controlled in time. 80.4 % of persons with adenomas at screening started with surveillance by colonoscopies, but at the end of the 18-year follow-up, only 58.6 % were still attending surveillance. Many persons in this population-based study stopped coming to the controls, which is a significant problem in real life over time. This problem becomes even more significant when screening starts at an earlier age (i. e., 45 years). Many participants will not continue surveillance after 20 years, although their cancer risk increases with age. Attendance was meager when no adenoma was found at screening. 46 % of those did not attend the second screening after ten years. This low participation rate in surveillance does not seem to be a Swiss-specific problem. Djinbachian et al. [34] also observed a low overall adherence of less than 50 %, 73.6 % after detecting high-risk lesions, and only 24.4 % after detecting low-risk lesions. Individual opportunistic screening without systematic quality control is performed in many European countries, which seems to be no longer appropriate. The variation in performance even of experienced board-certified endoscopists further emphasizes the need for well-controlled screening programs with quality control and re-invitation in order to improve adherence and quality of surveillance [35].

Thirty days after colonoscopy screening, participants were asked, via an anonymous questionnaire, whether they would choose colonoscopy again. 91.3 % of participants (out of 89 % responding to this questionnaire) affirmed that they would choose colonoscopy again [20], but 40 % never attended a follow-up examination. Barriers and promotors for surveillance should be evaluated for screening [36]. Awareness of the risk of later CRC in individuals without adenoma at screening may be low, or fear of the findings might discourage people from attending follow-up. The presence of specific risk factors such as obesity, smoking, family history of cancer, or increasing age did not significantly improve participation rates. Even a 1° family history of CRC

▶ **Table 4** Endoscopic findings* at the follow-ups for patients attending at least one follow-up (N = 725).

Variable		Individuals without adenoma (N = 515)		Individuals with adenoma (N = 210)		Total (N = 725)	
		N	(%)	N	(%)	N	(%)
Any adenoma							
	None	357	(69.3)	58	(27.6)	415	(57.2)
	One or more	158	(30.7)	152	(72.4)	310	(42.8)
Advanced adenoma							
	None	490	(95.1)	177	(84.3)	667	(92.0)
	One or more	25	(4.9)	33	(15.7)	58	(8.0)
Carcinoma found							
	None	511	(99.2)	210	(100.0)	721	(99.5)
	One or more	4	(0.8)	0	(0.0)	4	(0.5)
High graded dysplasia							
	None	515	(100.0)	208	(99.0)	723	(99.7)
	One or more	0	(0.0)	2	(1.0)	2	(0.3)
Villous or tubulo-villous adenoma ≥ 10 mm							
	None	510	(99.0)	200	(95.2)	710	(97.9)
	One or more	5	(1.0)	10	(4.8)	15	(2.1)
Villous or tubulo-villous adenoma 5–9 mm							
	None	510	(99.0)	199	(94.8)	709	(97.8)
	One or more	5	(1.0)	11	(5.2)	16	(2.2)
Villous or tubulo-villous adenoma < 5 mm							
	None	512	(99.4)	196	(93.3)	708	(97.7)
	One or more	3	(0.6)	14	(6.7)	17	(2.3)
Tubular adenoma ≥ 10 mm							
	None	501	(97.3)	189	(90.0)	690	(95.2)
	One or more	14	(2.7)	21	(10.0)	35	(4.8)
Tubular adenoma 5–9 mm							
	None	441	(85.6)	113	(53.8)	554	(76.4)
	One or more	74	(14.4)	97	(46.2)	171	(23.6)
Tubular adenoma < 5 mm							
	None	441	(85.6)	124	(59.0)	565	(77.9)
	One or more	74	(14.4)	86	(41.0)	160	(22.1)
Serrated adenoma ≥ 10 mm							
	None	511	(99.2)	208	(99.0)	719	(99.2)
	One or more	4	(0.8)	2	(1.0)	6	(0.8)
Serrated adenoma 5–9 mm							
	None	503	(97.7)	206	(98.1)	709	(97.8)
	One or more	12	(2.3)	4	(1.9)	16	(2.2)
Serrated adenoma < 5 mm							
	None	510	(99.0)	205	(97.6)	715	(98.)
	One or more	5	(1.0)	5	(2.4)	10	(1.4)

▶ **Table 4** (Continuation)

Variable		Individuals without adenoma (N = 515)		Individuals with adenoma (N = 210)		Total (N = 725)	
		N	(%)	N	(%)	N	(%)
Total polyps lost							
	None	507	(98.5)	207	(98.6)	714	(98.5)
	One or more	8	(1.5)	3	(1.4)	11	(1.5)

* Multiple findings per person are possible. **An advanced adenoma is defined as either a carcinoma, high graded dysplasia or an adenoma ≥ 10 mm.

▶ **Table 5** Finding of advanced adenomas in follow-up colonoscopy by sample characteristics at screening (univariate and multivariate logistic regression outcomes).

		Unadjusted models		Adjusted model 1 with endoscopic findings according to size		Adjusted model 2 with endoscopic findings according to type	
	(%)	OR	95 % CI	OR	95 % CI	OR	95 % CI
Overall	(8.1)						
Gender							
Female	(6.9)	Ref.		Ref.		Ref.	
Male	(9.1)	1.365	0.779–2.390	1.034	0.549–1.946	1.144	0.605–2.165
BMI							
Normal weight (< 25)	(7.7)	Ref.		Ref.		Ref.	
Overweight (25–29.9)	(8.2)	1.071	0.590–1.947	0.898	0.470–1.713	0.890	0.462–1.714
Class I obesity (30–34.9)	(9.6)	1.271	0.563–2.865	1.054	0.448–2.477	0.984	0.411–2.358
Class II obesity (> 35)	(6.7)	0.857	0.108–6.826	0.867	0.103–7.261	0.735	0.086–6.265
Age at first screening							
50–54 years	(5.3)	Ref.		Ref.		Ref.	
55–59 years	(6.2)	1.184	0.453–3.091	1.062	0.396–2.851	1.058	0.395–2.832
60–64 years	(7.3)	1.419	0.542–3.713	1.286	0.477–3.465	1.288	0.479–3.465
65–69 years	(7.9)	1.531	0.551–4.250	1.148	0.391–3.372	0.960	0.314–2.934
70–74 years	(16.9)	3.632	1.360–9.699*	2.678	0.936–7.667	2.917	1.027–8.286*
75 + years	(18.5)	4.058	1.182–13.939*	2.894	0.786–10.664	2.928	0.772–11.105
Family history of CRC							
None	(8.2)	Ref.		Ref.		Ref.	
1°	(7.7)	0.931	0.427–2.029	1.050	0.425–2.589	0.914	0.360–2.322
2°	(8.3)	1.015	0.128–8.031	1.182	0.131–10.684	1.250	0.143–10.947
Family history of any cancer							
None	(8.3)	Ref.		Ref.		Ref.	
1°	(8.6)	1.040	0.602–1.798	0.977	0.513–1.860	1.022	0.536–1.950
2°	(2.9)	0.337	0.044–2.554	0.437	0.055–3.503	0.486	0.061–3.855
Current smoking status							
Non-smoker	(7.4)	Ref.		Ref.		Ref.	
Smoker	(12.2)	1.726	0.895–3.326	1.657	0.813–3.376	1.645	0.802–3.374

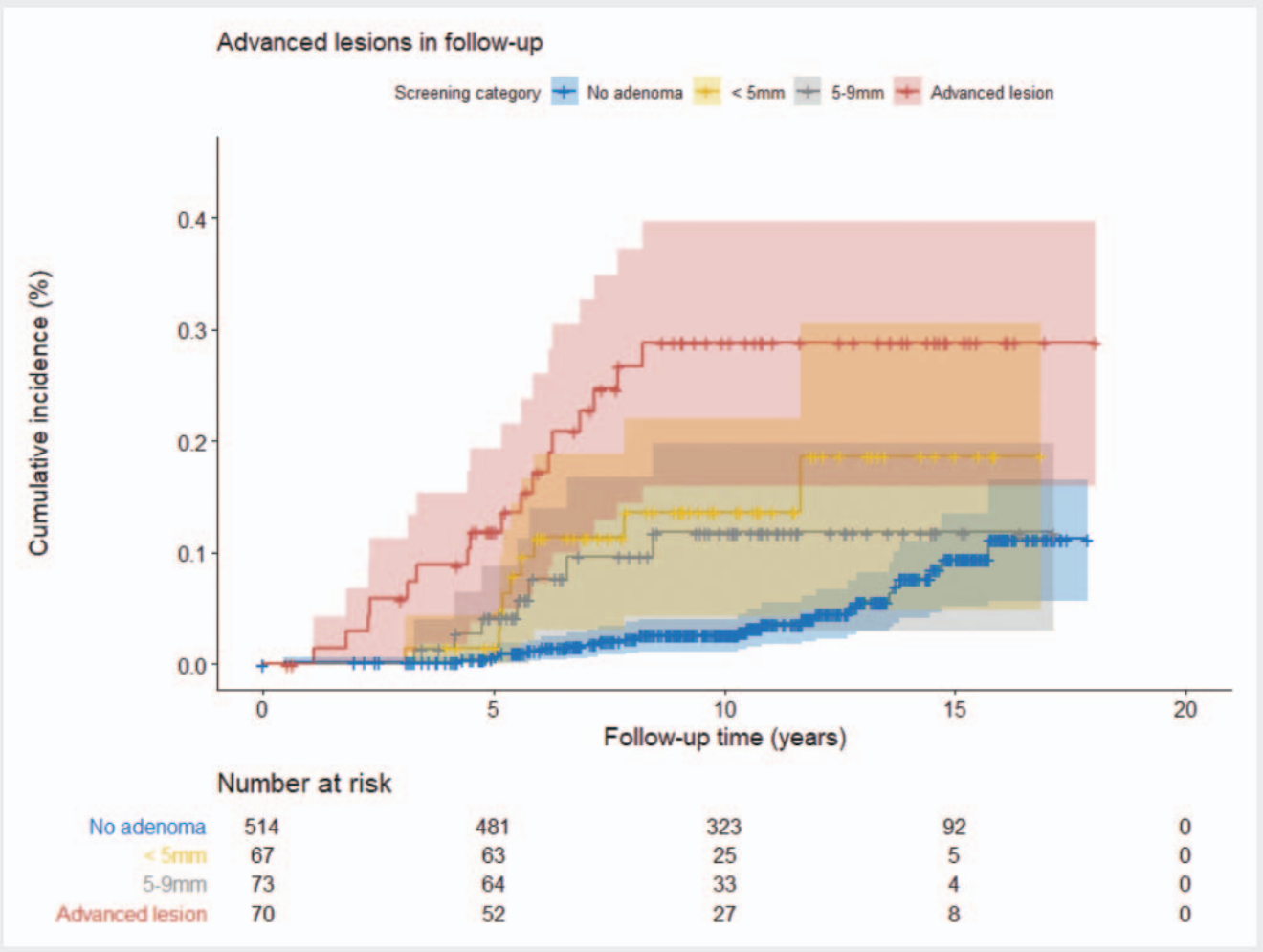
▶ **Table 5** (Continuation)

		Unadjusted models		Adjusted model 1 with endoscopic findings according to size		Adjusted model 2 with endoscopic findings according to type	
	(%)	OR	95 % CI	OR	95 % CI	OR	95 % CI
Endoscopic findings in main screening							
No adenoma	(5.0)	Ref.		Ref.			
Only adenoma(s) < 5mmm	(13.9)	3.028	1.346–6.811**	2.564	1.098–5.989*		
Only adenoma(s) 5–9 mm	(8.7)	1.794	0.709–4.543	1.621	0.620–4.235		
Adenoma(s) > 10 mm, high grade dysplasia or carcinoma	(24.3)	6.043	3.066–11.909**	4.787	2.304–9.947**		
Villous or tubulo-villous adenoma ≥ 10 mm							
None	(7.3)	Ref.				Ref.	
One or more	(23.1)	3.831	1.720–8.533**			2.455	0.990–6.087
Villous or tubulo-villous adenoma ≤ 9 mm							
None	(7.8)	Ref.				Ref.	
One or more	(17.4)	2.479	0.814–7.552			2.002	0.561–7.138
Tubular adenoma ≥ 10 mm							
None	(7.0)	Ref.				Ref.	
One or more	(34.5)	6.988	3.074–15.883**			4.343	1.691–11.155**
Tubular adenoma ≤ 9 mm							
None	(6.2)	Ref.				Ref.	
One or more	(16.4)	2.980	1.684–5.274**			1.899	0.987–3.653
Serrated adenoma ≥ 10 mm							
None	(8.2)	Ref.				Ref.	
One or more	(0.0)	Not estimated				Not estimated	
Serrated adenoma ≤ 9 mm							
None	(8.0)	Ref.				Ref.	
One or more	(13.3)	1.762	0.388–8.009			2.950	0.616–14.127
N				700		700	

* $p < 0.05$; ** $p < 0.01$; Note: An advanced adenoma is defined as either a carcinoma, high-grade dysplasia, or an adenoma ≥ 10 mm. The study sample excludes 68 individuals who moved away or died before the first follow-up. BMI: body mass index; CI: confidence interval; CRC: colorectal cancer OR: odds rati

improved participation only slightly. Costs were also unlikely to be a relevant factor in our study, as initial screening uptake was low despite being offered free of charge [20]. Additionally, endoscopic surveillance is reimbursed by Swiss health insurance. Income and level of education did not appear to influence the participation in screening since the participant's occupations correlated with the population's, except for farmers, who were less likely to participate. Attendance might be improved by performing more colonoscopies under sedation, but less than 10 % of participants reported anonymously having experienced relevant pain during endoscopy.

The extended follow-up allowed us to look for risk factors for the development of CRC. Because of the small sample size, advanced adenomas needed to be used as a surrogate parameter for CRC development. Individuals with advanced adenomas at screening had a significantly increased risk of developing advanced adenomas during follow-up (OR 4.79; 95 % CI 2.30–9.48). This increased recurrence of adenomas is in line with the findings of Liebermann [37] and He [38]. In the Polish retrospective follow-up of a nationwide colonoscopy screening program, large adenomas > 20 mm were independently associated with an increased risk of CRC [27]. However, in our study, even adenomas of < 5 mm were associated with an increased risk of later appearance of advanced lesions, and individuals without adenomas initially developed advanced adenomas in 4.9 %, including CRC in four persons. Three of them did not attend follow-up colonoscopy,



▶ **Fig. 2** Cumulative incidence of advanced adenomas during follow-up colonoscopies separated for screening results categories. The colored areas represent the 95 % confidence intervals.

and in all of them, CRC occurred later than 12 years after non-suspicious screening. In contrast to previous findings [28, 39, 40] and the recommendations of the Swiss and US guidelines for surveillance [22, 23, 24, 39, 41], we found no more advanced adenomas at follow-up in individuals with initial (tubulo-) villous adenomas < 10 mm in size. Only (tubulo-)villous adenomas > 10 mm showed an increased risk. These findings agree with earlier studies [27, 28] and the new European guidelines [29], suggesting that the villous component is not a relevant independent risk factor. Since (tubulo-) villous adenomas are often considered advanced adenoma in trials, and the villous component is poorly defined, it is difficult to decide whether they truly represent an independent risk. We hope for more data through the ongoing randomized European surveillance study [42].

Cost is a significant factor in any screening program. Our calculated direct costs of CHF 1 934 521 (USD 2 203 419) per 1000 persons screened are close to Sonnenberg's findings of a lifetime cost of 1,9 million USD per 1000 persons screened by colonoscopy every ten years [18]. These costs need to be compared with CRC prevented and related deaths. Based on the findings in the Nurses' Health Study and the Health Professionals Follow-up Study [31], the large community-based study by Lee et al. [32], the prospective follow-up study by Manser and colleagues [32], and the duration of our follow-up period of 18 years, we estimate roughly that 12 CRC cases and three deaths in 1000 individuals were prevented.

A substantial part of the cost is due to the surgical removal of adenomas and treatment of complications. In the future, adenomas may be more frequently removed endoscopically by endoscopic mucosal resection or endoscopic submucosal dissection, which may reduce cost but could provoke more complications, especially in the cecum. The rate of severe complications in this cohort study, with major bleeding in four patients and one perforation in 2388 colonoscopies, was within the range reported by others [43]. A meta-analysis of population-based studies found a perforation rate of 0.5/1000 and a bleeding rate of 2.6/1000 [44].

The high costs for screening and surveillance need to be compared to the lifetime costs for CRC treatment. The actual costs are not known in Switzerland. In 1997, the costs for rectal cancer were $ 40 230 and for colon cancer $ 33 079 during the first three years after detection [33]. Costs today are expected to be substantially higher due to new, more efficient, and more expensive

▶ **Table 6** Direct costs of screening (N = 1278).

	People without adenoma at screening (N = 1006)	People with adenoma found at screening (N = 272)	Overall sample (N = 1278)
Measured costs at screening			
Consultation with the primary physician*	CHF 54 835	CHF 14 797	CHF 69 632
Preparation of the colon***	CHF 26 460	CHF 7 140	CHF 33 600
Endoscopy	CHF 517 495	CHF 219 357	CHF 736 852
Histology	CHF 9 879	CHF 42 188	CHF 52 067
Surgical resection of adenomas*	CHF 0	CHF 55 203	CHF 55 203
Cost due to complications	CHF 0	CHF 10 400	CHF 10 400
Total measured costs	CHF 608 669	CHF 349 085	CHF 957 754
Additional cost for private insurances			
for surgical resection of adenomas		CHF 27 614	CHF 27 614
for treatment of complications		CHF 6 240	CHF 6 240
Total including additional costs			CHF 991 608
Calculated cost per 1,000 screenees	CHF 603 838	CHF 1 283 401	CHF 774 694

* 80 % of the patients had a HA consultation for CHF 68; **Cleaning solution CHF 26.25 per colonoscopy

▶ **Table 7** Costs of the follow-up colonoscopies (N = 1110).

	People without adenoma at screening (N = 1006)**	People with adenoma at screening (N = 272)***	Overall sample N = 1278 ****
Measured costs			
Preparation of the colon*	CHF 18 664	CHF 10 474	CHF 29 138
Endoscopy	CHF 405 694	CHF 221 098	CHF 626 792
Histology	CHF 25 686	CHF 32 695	CHF 58 381
Surgical resection of adenomas	CHF 28 934	CHF 31 544	CHF 60 478
Cost due to complications	CHF 29 547	CHF 3224	CHF 32 771
Total measured costs	CHF 508 525	CHF 299 035	CHF 807 560
Additional cost for special insurances			
for surgical resection of adenomas	CHF 5475	CHF 15 839	CHF 21 314
for treatment of complications	CHF 31 172	CHF 3338	CHF 34 510
Total including additional costs	CHF 545 172	CHF 318 212	CHF 863 384
Calculated cost per 1,000 screenees	CHF 541 920	CHF 1 169 897	CHF 675 574

* Cleaning solution CHF 26.25 per colonoscopy **711 colonoscopies ***399colonoscopies ****1110 colonoscopies

treatments and may approach the costs of screening and surveillance.

Nearly half of the costs were attributable to the follow-up of the individuals studied. The relative contribution of colonoscopy surveillance to the effect of CRC screening has not been established, but in a recent US study [45], surveillance accounted for only 1.3 % of CRC deaths. The need for follow-up colonoscopies is primarily based on incomplete evidence and expert consensus [11]. However, the findings consistently show that CRC risk is substantially increased when advanced adenomas are found at screening. European and US guidelines for surveillance do agree on surveillance in these high-risk subjects [29, 39] (▶ **Table 9**).

The need for surveillance of smaller adenomas remains uncertain; however, these account for 60 % of follow-up costs. There is

▶ **Table 8** Total cost of screening and follow-ups.

	Individuals without adenoma (N = 1006)	Individuals with adenoma (N = 272)	Total (N = 1278)
Measured costs			
Consultation with the primary physician	CHF 54 835	CHF 14 797	CHF 69 632
Preparation of the colon	CHF 45 124	CHF 17 614	CHF 62 738
Endoscopy	CHF 923 189	CHF 440 455	CHF 1 363 644
Histology	CHF 35 565	CHF 74,883	CHF 110 448
Surgical resection of adenomas	CHF 28 934	CHF 86 747	CHF 115 681
Cost due to complications	CHF 29 547	CHF 13 624	43 171
Total cost for private insurance	CHF 36 647	CHF 53 031	CHF 89 678
Total costs without administration	**CHF 1 153 841**	**CHF 701 151**	**CHF 1 854 992**
Calculated cost per 1000 screenees	CHF 1 146 959	CHF 2 577 761	CHF 1 451 480
Administration	CHF 486 144	CHF 131 182	CHF 617 326
Total costs with administration	**CHF 1 639 985**	**CHF 832 333**	**CHF 2 472 318**
Calculated cost per 1000 screenees	CHF 1 630 204	CHF 3 060 048	CHF 1 934 521

▶ **Table 9** Comparison of the actual guidelines for post-polypectomy follow-up from the European Society of Gastrointestinal Endoscopy (ESGE), the US Multi-Society Task Force on CRC and the Swiss Society of Gastroenterology (SGG).

	ESGE[1]	USMSTF[2]	SGG[3]
No adenoma found at baseline colonoscopy	10 years screening colonoscopy if no programe		
1–2 tubular adenoma < 10 mm	Colonoscopy 10 years (screening)	7–10 years	5 years
3–4 tubular adenoma < 10 mm		3–5 years	3 years
5–10 tubular adenoma < 10 mm		3 years	3 years
1–2 serrated adenoma < 10 mm		5–10 years	5 years
3–4 serrated adenoma < 1 0 mm		3–5 years	5 years
Villous or tubulovillous adenoma < 10 mm		3 years	3 years
Tubular adenoma ≥ 10 mm	3 years	3 years	3 years
High grade dysplasia			
5–10 tubular adenoma < 10 mm			
≥10 tubular adenoma < 10 mm		1 year	
tubular adenoma ≥ 20 mm		6 months	

[1] Hassan et al. Endoscopy 2020 [29]; [2] Gupta et al. Gastroenterology 2020 [39]; [3]www.sggssg.ch[25]

also no consensus in the new US and ESGE guidelines on the management of these small adenomas [29, 39]. Whereas the USMSTF proposes that individuals with 3–4 adenomas smaller than 10 mm should be re-examined after 3–5 years, the ESGE recommends that these individuals undergo re-colonoscopy only after ten years; and Helsingen et al. [12] question the need for screening at all in low-risk persons. In our study, the risk of developing new advanced adenomas was slightly but significantly increased in people with small adenomas. The need for some form of follow-up is further emphasized by the occurrence of 4 CRC cases in 951 low-risk participants and 4.9 % (25 of 515) who developed advanced adenomas even though they did not have an adenoma at screening. In a retrospective study of 17 UK hospitals with 33,011 persons, CRC incidence was 40–50 % lower in low-risk individuals with a single surveillance visit showing the benefit of follow-up [10]. However, CRC incidence is not higher or even lower in these individuals than in the general population, even without further screening [10, 46, 47]. Advanced adenomas occurred later in the low-risk group in our study than in high-risk individuals with advanced adenomas at screening, but the carcinomas detected after 12 and 13 years were already advanced. The later and less frequent recurrence of advanced adenomas in low-risk individuals indicates that follow-up may not necessarily be done with colonoscopy but should be done after ten years at the latest.

Adherence to follow-up colonoscopies is a relevant problem, especially in individuals without adenomas at screening. Colonoscopy is an inconvenient, psychologically distressing, invasive, and expensive examination. It requires increasingly more resources for follow-up as the adenoma detection rate grows. Surveillance with a second colonoscopy screening in low-risk individuals could be replaced by surveillance with the more affordable screening method using a quantitative fecal immunochemical blood test (FIT) every one to two years. Evidence indicates that the use of FIT at screening has better acceptance and detects many cancers early [16, 20, 48, 49, 50, 51]. The stool test should at least be offered to low-risk individuals as an additional choice for colonoscopy. Very few carcinomas will be missed by a quantitative FIT using a low cutoff to detect occult blood in the stool [51,

52]. To keep a high adherence to a stool-based screening program, a regular invitation with sending the test for every screening round would be necessary, however [20, 53]. Otherwise, adherence will also decrease rapidly. In addition, general measures such as giving up smoking and reducing weight should not be forgotten.

This study has several limitations. One limitation is the relatively small sample size of this screening study and the representativeness of a white population with only a few migrants of the general Swiss population. Due to the small sample size, we had to use advanced adenomas as a surrogate parameter for CRC development, although the exact transition rate to cancer and time to progression is still unknown. We could hence not evaluate whether variations in the endoscopic quality at the initial screening influenced the later appearance of advanced adenomas. During follow-up, the guidelines for the recommended timing of follow-up colonoscopy changed thrice. We considered both guidelines as appropriate, which may have led to better adequacy of the surveillance. In any case, adherence remained low. Another limitation is the varying time interval of surveillance for the different risk groups, making it difficult to compare them. However, this represents the guidelines of surveillance in a real-life setting. In addition, colonoscopy quality has improved over time, and the adenoma detection rate would be higher today than at the time of screening while assuming that serrated adenomas, in particular, could be missed.

Nevertheless, our study's adenoma detection rate can be considered appropriate for the year 2001. The high cecal intubation rate and the relatively low complication rate underline the good quality of the initial screening under real-life conditions. We found no CRC in the early interval indicating that the quality of screening was acceptable. In addition, the costs of colonoscopy slightly decreased over time, whereas costs for cancer treatment increased.

In conclusion, post-polypectomy surveillance is essential to reduce the incidence of CRC and associated deaths. Even in individuals without adenomas at screening, there remains a risk of developing CRC. Our long-term study in a well-defined area with tight controls highlights the problem of low adherence to follow-up examinations and the inadequately high cost for follow-up colonoscopies, particularly in low-risk individuals. The barriers to surveillance need to be improved, but the method of surveillance in the low-risk population should be reconsidered.

Statement of Ethics:

The authors declare that the data were collected after obtaining written informed consent from each participant in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the ethical committee of Lucerne, Switzerland (Antrag Nr 200).

Conflict of Interest Statement:

The authors declare no conflict of interest. The initial screening study was supported by grants to Urs Marbet from the Swiss Cancer League and Regional Cancer Leagues of Central Switzerland, the Gastroenterological Society GastroMed Swiss, and the Basel Foundation for Cancer Research. No other financial relationships relevant to this publication were disclosed. Unrelated to the submitted work Michaela Barbier has received personal fees from Vifor.

Data availability statement:

The data that support the findings will be available on request from the corresponding author

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Conflict of Interest

The authors declare that they have no conflict of interest.

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