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## Effects and costs of colorectal cancer screening and follow-up after polypectomy

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# 6

## **Colorectal cancer risk after colonoscopic polypectomy**

## **Abstract**

### *Background*

Adenoma patients are generally advised to have surveillance after polypectomy. The surveillance schedule should depend on the colorectal cancer risk after initial polypectomy.

### *Aims*

To estimate the relative colorectal cancer risk in the first years after colonoscopic polypectomy compared with the age- and sex-matched general population.

### *Patients*

553 consecutive adenoma patients whose initially detected adenomas were colonoscopically removed in the endoscopy department of the Slotervaart Hospital, a general hospital in Amsterdam, the Netherlands. Colonoscopic surveillance was offered to the patients.

### *Methods*

Colorectal cancer incidence was studied in these 553 adenoma patients. A literature search was performed to identify all studies on relative colorectal cancer risk after polypectomy.

### *Results*

The colorectal cancer relative risk in the patients from the Slotervaart Hospital was 0.9 (0.3-2.0). Five other studies on colorectal cancer relative risk after colonoscopic polypectomy were identified by the literature search. Two studies that excluded patients with large sessile polyps published relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). Relative risk estimates in the three studies that included patients with large sessile polyps were 0.7 (0.2-1.4), 0.8 (0.2-2.3) and 1.3 (0.6-2.3). In all studies patients were offered regular colonoscopic surveillance.

### *Conclusions*

The present review shows that the colorectal cancer risk in the first years after colonoscopic polypectomy in adenoma patients does not exceed the colorectal cancer risk in the general population. The results support the lengthening of the surveillance interval to 5 years for most adenoma patients.

## Introduction

Colorectal cancer is a major cause of morbidity and mortality in developed countries. The estimated number of new colorectal cancer cases for the United States in 2002 is 148,300 and 56,600 deaths from colorectal cancer are expected [American Cancer Society 2002]. It is generally believed that the majority of cancers originate from adenomas. It is therefore recommended that adenoma patients undergo initial complete colonoscopy in order to detect and remove all adenomas. However, some adenomas are missed at the initial colonoscopy, and new adenomas may develop at significant rates. Therefore, patients in whom adenomas are removed are recommended to be surveilled regularly by colonoscopy with an interval of 3 or 6 years, while less intensive screening strategies is recommended for the general population. Surveillance should not be performed too frequently, because colonoscopies are expensive and involve complication risks. The optimal surveillance interval depends amongst others on the colorectal cancer risk in adenoma patients after initial polypectomy. There is a wide variation in published relative colorectal cancer risk estimates. In the National Polyp Study, the colorectal cancer risk in the first six years after adenoma removal was only 0.2 of the risk in the general population [Winawer 1993a]. Contrarily, the colorectal cancer risk in the Funen adenoma surveillance trial was 1.3 of the risk in the Danish normal population [Jørgensen 1993]. The aim of the present study is to estimate the relative colorectal cancer risk in the first years after colonoscopic polypectomy compared with the age- and sex-matched general population. It is explored whether differences in estimated relative colorectal cancer risk are explained by differences in inclusion criteria and in which way surveillance guidelines deal with these criteria. This is estimated from primary data provided by the endoscopy department of the Slotervaart hospital, Amsterdam, the Netherlands, and from a literature search to identify all other studies concerning relative colorectal cancer risk in the first years after colonoscopic polypectomy. Surveillance was performed in all studies and the effect of surveillance on colorectal cancer risk is explored.

## Material and Methods

### *Cohort study in the Slotervaart hospital*

Data of all 553 patients diagnosed with adenomas between 1988 and 1998 in the Slotervaart hospital, a general hospital in Amsterdam, the Netherlands, were collected. The date of birth, gender, and reason for the first visit (incomplete) were recorded. Data collected for each colon examination were date of the examination, examination method (colonoscopy, sigmoidoscopy, and barium enema), reach of the scope, and the result of the examination. The number of adenomas and the site of the adenomas were not systematically recorded. Date and results of the examinations recorded in the endoscopy department were matched with the pathology reports of these patients in the Pathological Anatomical Nation-wide Automated Archive (Palga). The histology of the adenomas was

not always recorded in these pathology reports. Patients were included in the present study if an adenoma was registered in the Palga registry at the time of the first colon examination at the endoscopy department. Several colon examinations within a week, for example a barium enema and a sigmoidoscopy examination, were considered to be one examination in this study. Patients were excluded if they had a diagnosed colorectal carcinoma before or within 7 days after the initial examination, and if they had a diagnosis of inflammatory bowel disease. Patients were followed until 1 October 1998 for the occurrence of colorectal cancer. The patient record was examined for all patients in whom colorectal cancer was diagnosed more than 7 days after the initial examination according to the pathology reports to decide whether or not it was a metachronous cancer.

Follow-up time was calculated as the time between the initial examination registered at the endoscopy department and 1 October 1998. Calculation of expected number of colorectal cancers is based on site-, sex- and age-specific colorectal cancer incidence rates in general population of the Netherlands in 1995 multiplied by the observed number of person years at risk [Visser 1998]. The ratio of observed to expected cases is reported as a rate ratio. 95% Confidence intervals are based on the exact Poisson distribution and are calculated using STATA 7.0.

#### *Literature search*

A literature search was performed to find all publications in which colorectal cancer incidence after colonoscopic polypectomy in adenoma patients is compared with colorectal cancer incidence in the general population. A literature search was performed in PubMed database of the National Library of Medicine in October 2002 to find all publications with the following Medline headings: “colorectal neoplasms” and “colonoscopy” and either “adenoma” or “adenomatous polyps” or “colonic polyps”. Moreover, the Medline subheading “surgery” was added to the search to identify articles concerning polypectomy. The search resulted in 115 selected articles. The titles and abstracts of the publications were scanned and publications containing primary data on colorectal cancer incidence in adenoma patients after colonoscopic polypectomy were considered for inclusion. Publications that did not compare the cancer incidence in adenoma patients with the background incidence in the age- and sex-matched general population were excluded. 95% Confidence intervals are based on the exact Poisson distribution and are calculated using STATA 7.0.

## **Results**

#### *Retrospective cohort study in the Slotervaart hospital*

Table 6.1 shows the characteristics of the 553 adenoma patients from the Slotervaart Hospital at the initial colon examination with polypectomy. The patients were regular referrals from the Amsterdam West sector with approximately 375,000 inhabitants. Mean age at the initial examination was 62.1 years. In most patients (77%) the reason for colonoscopy was unknown. These were usually patients with symptoms who had a sigmoidoscopy and who were referred to colonoscopy due to the detection of adenomas.

**Table 6.1** Patients and adenoma characteristics in present study at initial examination (n=553).

Characteristic	Number (%) of patients	
<i>Age at initial polypectomy</i>		
<50	91	(16)
50-59	120	(22)
60-69	191	(35)
70-79	136	(25)
80+	15	(3)
<i>Sex</i>		
Male	292	(53)
Female	261	(47)
<i>Reason for referral</i>		
Family history	62	(11)
Symptoms	8	(1)
Polyp at sigmoidoscopy	23	(4)
Earlier adenoma	33	(6)
Unknown	427	(77)
<i>Histology of adenoma with highest grade of abnormality</i>		
Tubular	195	(35)
Tubulovillous	199	(36)
Villous	20	(4)
Carcinoma in situ	10	(2)
Unknown	129	(23)

Screening in average-risk asymptomatic individuals was not performed at the time in the Netherlands. Mean follow-up time of the adenoma patients was 5.3 years and the mean number of colonic examinations, including the initial examination was 2.2. 66% of the patients had at least one surveillance examination, 35% had at least two surveillance examinations, and 15% had three or more surveillance examinations. Surveillance was stopped before the end date of the study in 86 patients (16%), mostly due to their age. 93% of the initial and 84% of the surveillance examinations were performed with colonoscopy. Otherwise, a combination of barium enema and sigmoidoscopy was generally performed. The cecum was reached in 94% of the initial colonoscopies and in 91% of the surveillance colonoscopies. 22% of the surveillance examinations occurred within a year since the previous examination, 40% occurred in the second year, and 12% in the third year since the previous examination. Adenomas were found in 24% of the surveillance examinations.

Five colorectal cancers were diagnosed during the follow-up period. Table 6.2 shows characteristics of these patients. The number of adenomas removed at the initial examination was not known for all patients, but was retrieved for the cancer cases. Patient 1 had asked for screening at the age of 57 years because of a family history of colorectal cancer. The initial colonoscopy did not reach the ascending colon and cecum. A radiological examination was performed shortly afterwards at which no lesions were detected. A metastasized tumor was diagnosed in the cecum two years later. In Patient 2,

adenomas were diagnosed at the age of 56 years. The patient had a surveillance colonoscopy one year later at which only hyperplastic polyps were diagnosed. Two years later a Dukes' C carcinoma was diagnosed in this patient at another hospital. Patient 3 had an initial colonoscopic examination at the age of 77 years. One year later, a sigmoidoscopy was performed at which no additional adenomas were detected. The next surveillance colonoscopy one year later was incomplete and did not reach the ascending colon and the cecum. One tubulovillous adenoma was removed at this surveillance colonoscopy. Surveillance was stopped at the age of 79 years due to the patient's age. At the age of 83 a tubulovillous adenoma containing a Dukes' A adenocarcinoma in the ascending colon was diagnosed at another hospital. Patient 4 had an initial colonoscopic examination at the age of 77 years at which tubular adenomas were removed and at the surveillance colonoscopy one year later two tubular adenomas were removed. Thereafter, surveillance was stopped due to the age of the patient. At the age of 85, a Dukes' A adenocarcinoma in the rectum was detected at another hospital. Patient 5 had two tubulovillous adenomas removed at the age of 70 years. A sigmoidoscopy was performed one year later at which no additional adenomas were detected. Two years after this examination, a polyp containing a Dukes' A adenocarcinoma was detected in the sigmoid. None of the cancers were detected at surveillance. One carcinoma was registered in the period between the initial examination and the first surveillance examination.

**Table 6.2** Characteristics of colorectal cancer cases in present study. TV=tubulovillous adenoma; T=tubular adenoma.

Patient no.	1	2	3	4	5
Sex	Male	Male	Female	Male	Male
Age at cancer diagnosis (yr.)	59	60	83	85	73
Histology of adenomas at initial examination	Unknown	TV	Unknown	T	TV
Number of adenomas removed at initial examination	4	2	3	7	2
Number of examinations after initial examination	0	1	2	1	1
Time between initial examination and cancer diagnosis (yr.)	2.0	3.4	6.0	8.3	2.9
Time between last examination and cancer diagnosis (yr.)	2.0	1.9	4.1	6.9	2.0
Anatomical site of cancer	Cecum	Cecum	Ascending colon	Rectum	Sigmoid
Dukes' stage	D	C	A	A	A

Colorectal cancer incidence in adenoma patients during the complete follow-up period was 0.86 (0.3-2.0) of the expected incidence in the general population (n=5). Colorectal cancer incidence in adenoma patients between the initial examination and first surveillance examination was 0.43 (0.0-2.4) of the expected incidence in the general population with the same age and sex distribution (n=1). The relative risk compared to the general population in 70 patients who had an incomplete examination was 1.2(0.0-6.5) (n=1). The relative risk compared to the general population in 483 patients with complete initial colonoscopies was 0.8 (0.2-2.1) (n=4). The relative risk compared to the general population in the 62 patients with a family history of colorectal cancer was 4.4 (0.1-24.6) (n=1).

#### Literature search

The literature search identified five other studies that published estimates of the relative colorectal cancer risk after initial colonoscopic polypectomy compared with the rate in the general population, see Table 6.3. The studies are described below. The aim of the National Polyp Study was to evaluate the effect of surveillance in adenoma patients [Winawer 1993a, Winawer 1993b]. Patients were excluded if they had a family or personal history of familial polyposis, inflammatory bowel disease, or a personal history of polypectomy or colorectal cancer. A total of 9112 subjects referred for colonoscopy were candidates for the study. Patients were excluded if colonoscopy detected no polyps, non-adenomatous polyps only, colorectal cancer or a sessile adenoma with a base larger

**Table 6.3** Reported colorectal cancer incidence in patients in whom adenomas were removed and relative colorectal cancer risk compared with the age- and sex-matched general population.

Study	No. patients	Patients with sessile polyps included	Mean follow-up time (yr.)	Person years	No. cases	Relative risk (95% CI)
National Polyp Study [Winawer 1993a, Winawer 1993b]	1418	No	5.9	8401	5	0.2 (0.1-0.6)*
Citarda <i>et al.</i> [Citarda 2001]	1693	No	10.5	14211**	6**	0.3 (0.1-0.7)**
Lund <i>et al.</i> [Lund 2001]	776	Yes	6.6	5138	6	0.7 (0.2-1.4)***
Meagher <i>et al.</i> [Meagher 1994]	645	Yes	4.4	2847	3	0.8 (0.2-2.3)
Funen Adenoma Surveillance Study [Jørgensen 1993]	1056	Yes	4.3	not published	10	1.3 (0.6-2.3)
Cohort study in Slotervaart hospital	553	Yes	5.3	2924	5	0.9 (0.3-2.0)

\* relative risk is 0.3 (0.1-0.8) if the first 2 years of follow-up are excluded

\*\* excluding the first 2 years of follow-up

\*\*\* relative risk is 0.4 (0.1-1.1) if two malignant polyps are excluded



than 3cm. The 1418 adenoma patients who entered the study had had a complete initial colonoscopy at which all detected polyps were removed. A surveillance colonoscopy was offered in Arm A at 1, 3, and 6 years after initial colonoscopy, and in Arm B at 3, and 6 years after initial colonoscopy. Mean follow-up time was 5.9 years. Five colorectal cancers were found during the trial (2 in arm A and 3 in arm B), the relative colorectal cancer risk compared to the general population being 0.2 (0.1-0.6).

Citarda *et al.* [Citarda 2001] studied 1693 patients enrolled between 1980 and 1987 who had had at least one adenoma larger than 5mm in diameter removed at the initial examination that consisted of complete colonoscopy or (incomplete) colonoscopy and double contrast enema. Data were collected from seven reference centers for gastrointestinal disease and neoplasms in Italy. Patients with genetic syndromes, previous adenomas or colorectal cancer, previous colonic resection, inflammatory bowel disease or sessile adenomas more than 3cm in diameter were excluded. Follow up ended by a total colon examination or telephone interview. The mean number of follow-up years was 10.5 years. The surveillance strategy in these patients was not reported, but 74% of the patients had a colonoscopy in the last four years of the study. The relative colorectal cancer risk compared to the general population excluding the first two years after initial examination was 0.3 (0.1-0.7). Three colorectal cancers diagnosed within 2 years after the initial examination were excluded.

Lund *et al.* [Lund 2001] studied colorectal cancer incidence in 776 patients who underwent colonoscopy for the following reasons: colorectal symptoms, possible polyp or other findings on barium enema, or positive fecal occult blood test detected in the Nottingham screening trial. The initial examination consisted of complete colonoscopy or (incomplete) colonoscopy and a barium enema. Six months after the initial examination a further sigmoidoscopy was performed. Patients were randomized to surveillance by flexible sigmoidoscopy or colonoscopy at varying intervals. Follow-up was until March 1998 for patients in the Nottingham fecal occult blood screening study and for patients not in this study total follow-up was until the last visit within the surveillance study. They found a relative colorectal cancer risk compared to the general population of 0.4 (0.1-1.1). However, two malignant Dukes' A polyps were not considered invasive cancer in that study that would have been defined as colorectal cancer in all other studies. This increases the relative risk compared to the general population to 0.7 (0.2-1.4).

Meagher *et al.* [Meagher 1994] reviewed records of all patients who underwent colonoscopic polypectomy by a single surgeon between 1974 and 1991 in Australia. Patients with colorectal cancer, inflammatory bowel disease, familial adenomatous polyposis were excluded. There were 645 patients who underwent removal of at least one adenoma and had at least one surveillance colonoscopic examination. Patients were followed until their most recent colonoscopic examination for a mean of 4.4 years. During the follow-up period, 3 patients developed cancer, while 3.75 were expected in the general population, the relative risk being 0.8 (0.2-2.3).

The Funen adenoma surveillance study followed 1056 patients for the occurrence of adenomas [Jørgensen 1993]. The initial colonoscopy consisted of complete colonoscopy in 1027 patients, 19 patients had incomplete colonoscopy and barium enema

and 10 patients had an incomplete colonoscopy only. Patients were randomized to surveillance intervals varying from 6 to 48 months. Most surveillance examinations were performed by colonoscopy. The rate ratio in the Funen adenoma surveillance study was 1.3 (0.6-2.3).

The percentage of colorectal cancers detected at surveillance varies widely among the studies, from 100% in the National Polyp Study and the study of Meagher *et al.*, approximately 50% in the studies in Funen, of Citarda *et al.*, and Lund *et al.*, to 0% in the study in the Slotervaart hospital.

The results of the studies presented above are not combined into one estimate for the relative colorectal cancer risk after colonoscopic polypectomy, because the studies differ in design and protocol. The National Polyp Study and the study of Citarda *et al.* excluded patients with large ( $\geq 3$ cm) sessile adenomas and found low colorectal cancer relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). The relative risk estimates compared to the general population in studies that included patients with large sessile polyps was 0.7 (0.2-1.4) in the study of Lund *et al.*, 0.8 (0.2-2.3) in the study of Meagher *et al.* and 1.3 (0.6-2.3) in the Funen adenoma surveillance study. The total number of colorectal cancers observed in the studies that included large sessile adenomas, including the study in the Slotervaart hospital, was 24 where 27 cancers were expected in the general population, a relative risk of 0.9. The overlap in confidence interval of the studies that included large sessile adenomas is 0.6-1.4.

## Discussion

Adenoma patients are considered to be at high risk for colorectal cancer, because adenomas are precursors of colorectal cancer. Therefore, once detected, an adenoma is removed, colonoscopy is performed and patients are regularly surveilled by colonoscopy. Meanwhile, the colorectal cancer risk in adenoma patients after removal of adenomas is not well known. The follow-up study in the Slotervaart hospital shows a relative colorectal cancer risk after colonoscopic polypectomy of 0.9 (0.3-2.0) compared to the general population. A literature search identified five other studies concerning the relative colorectal cancer risk in adenoma patients. The relative risk ranged from 0.2 (0.1-0.6) in the National Polyp Study to 1.3 (0.6-2.3) in the Funen adenoma surveillance study.

The National Polyp Study and the study of Citarda *et al.*, which excluded patients with large sessile polyps at initial examination, found low colorectal cancer relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). The relative risk estimates in studies that included patients with large sessile polyps ranged from 0.7 (0.2-1.4) in the study of Lund *et al.* to 1.3 (0.6-2.3) in the Funen adenoma surveillance study. This comparison suggests that large-sessile-polyp patients are at high risk for colorectal cancer, even after polypectomy. This stresses the importance of studying the colorectal cancer incidence in these patients in all reviewed studies. None of the studies reported the cancer incidence in large-sessile-polyp patients. In the Slotervaart study, none of the cancers were diagnosed in these patients. Studying incidence in large-sessile-polyp patients may explain differences between studies and may result in detailed surveillance guidelines for these

patients. The present updated guidelines of the American Gastroenterological Association state that patients with a large sessile adenoma should have a shorter surveillance interval than other adenoma patients based on clinical judgement [Winawer 2003].

Besides the in- or exclusion of patients with large sessile polyps, other factors may contribute to differences in reported colorectal cancer risk. Firstly, the completeness of the initial and follow-up examinations may have influenced the reported colorectal cancer risk. As an example, in the Slotervaart study, the initial colonoscopy had not visualized the cecum in Patient 1. Although the initial colonoscopy was followed by barium enema, a carcinoma was diagnosed in the cecum two years later. Patient 3 had had initial complete colonoscopy, followed by a follow-up sigmoidoscopy and incomplete follow-up colonoscopy. Four years later, cancer was diagnosed in the ascending colon. It is possible that the cancer incidence in this study would have been lower if incomplete colonoscopies had systematically been followed by repeat colonoscopy. For example, in the National Polyp Study, an initial or follow-up colonoscopy was repeated if the gastroenterologist was not confident that all polyps had been cleared.

Secondly, the follow-up strategy in older adenoma patients may have affected cancer incidence. In the Slotervaart study, two cancers were diagnosed in patients (Patient 3 and Patient 4) who had stopped follow-up several years before diagnosis due to their high age (>75 yr.). These two Dukes' A cancers may have been prevented if these patients had continued follow-up. In the reviewed studies, follow-up was not stopped in older patients. If the two cancers in the Slotervaart study would have been prevented, the relative colorectal cancer risk would decrease to 0.52 (0.1-1.5).

In all reviewed studies, the study population was subjected to surveillance. Surveillance decreases colorectal cancer incidence after a certain time period. On the other hand, colorectal cancer incidence increases at the moment of surveillance by detection of asymptomatic cancers. A modeling study showed that it takes approximately 6 years before the cumulative incidence is reduced [Zauber 2000]. Therefore, given the short follow-up time of the studies, surveillance may have raised rather than decreased the cancer incidence.

The wide variation in the percentage of colorectal cancers detected at surveillance (asymptomatic cancers) and not by symptoms among the studies can be explained by the small number of cancer cases per study. Furthermore, the percentage asymptomatic cancers is correlated with the average number of surveillance examinations per patient. In the Slotervaart hospital 0% (n=5) of the cancers were detected at surveillance and the average number of surveillance examinations was 1.2. The Lund study had 1.5 surveillance examinations (mainly sigmoidoscopy) and 33% (n=6) of the cancers were detected at surveillance. The Funen study had 3.1 surveillance examinations per patient and 60% (n=10) of the cancers were detected at surveillance. In the National Polyp Study, 100% (n=5) of the cancers were surveillance-detected. The National Polyp Study patients had on average 1.2 surveillance examinations, but some of them consisted of several colonoscopies, because colonoscopy was repeated if the first colonoscopy was incomplete. The Citarda study and the Meagher study did not publish the number of surveillance examinations performed during the study.

In the updated guidelines of the American Gastroenterological Association, the surveillance interval for patients with 1 or 2 small (<1cm) adenomas was lengthened from 3 to 5 years [Winawer 2003]. Lengthening is supported by the present result that adenoma patients with no large sessile polyps are at lower colorectal cancer risk than the general population in the first years after polypectomy. The results of the review do not rule out that the surveillance interval can also be extended for other patients, such as patients with large adenomas, or patients with 3 or more adenomas. This could be confirmed by a trial. Any conclusions about surveillance intervals longer than 5-6 years cannot be drawn from the reviewed studies, because the studies only report the colorectal cancer risk in the first years after polypectomy.

The present review shows that the colorectal cancer risk in the first years after colonoscopic polypectomy in adenoma patients (including those with large sessile polyps) does not exceed the colorectal cancer risk in the general population. It is suggested that the risk for patients with non-sessile adenomas is lower than in the general population. The results support lengthening of the surveillance interval to 5 years in recent guidelines for adenoma patients with 1 or 2 small adenomas.

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