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Colorectal cancer risk after colonoscopic polypectomy: a population-based study and literature search

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Abstract

Adenoma patients are considered to be at an elevated risk for colorectal cancer, even after their adenomas have been removed. The aim of this study was to estimate the colorectal cancer risk after colonoscopic polypectomy compared with age- and gender-matched general population controls. Colorectal cancer incidence was studied in 553 consecutive patients without cancer whose adenomas were colonoscopically removed in the endoscopy department of a general hospital. The colorectal cancer relative risk in these patients was 0.9 (0.3–2.0). A literature search was performed to identify all published studies on relative colorectal cancer risk after polypectomy. The relative risk estimates in seven other studies ranged from 0.2 (0.1–0.6) to 1.3 (0.6–2.3). The difference can, be explained partially by the inclusion or exclusion of patients with large sessile polyps and other factors. Our review shows that colorectal cancer risk after colonoscopic polypectomy does not exceed the risk in the general population.
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Keywords: Colorectal neoplasms; Colonoscopy; Surveillance; Adenoma; Colorectal cancer

1. Introduction

Colorectal cancer is a major cause of morbidity and mortality in developed countries. Approximately 334 000 new colorectal cancer cases were estimated in 1995 in Europe and the 5-year relative survival rate was approximately 45% [1]. It is generally believed that most cancers originate from adenomas. It is therefore recommended that patients with adenomas undergo a complete colonoscopy in order to remove all of these adenomas. However, adenomas may have been missed and new adenomas may develop rapidly. Therefore, colonoscopic surveillance is recommended in these patients. Surveillance should not be performed too frequently as colonoscopies are both risky and expensive. The surveillance interval is related to the average colorectal cancer risk after initial polypectomy. However, there is a wide variation in published relative colorectal cancer risk estimates compared with estimates for the general population. The aim of the present study was to estimate the risk in the initial years after the colonoscopic polypectomy compared with the age- and gender-matched general population. Data from a Dutch community hospital, and from a literature search were used. Surveillance was performed in most studies and the effect of surveillance on colorectal cancer risk is explored. We also studied whether differences in estimated risk are explained by differences in inclusion criteria.

2. Patients and methods

2.1. Amsterdam study

Data for all 553 consecutive patients diagnosed with adenomas between 1988 and 1998 in the Slotervaart

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hospital, a general hospital in Amsterdam, the Netherlands, were collected. The patient's date of birth, gender, and reason for the first visit were recorded. The date of the examination, examination method (colonoscopy, sigmoidoscopy, and barium enema), reach of the scope, and the result of the examination were noted at each colon examination. The 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). Patients were included in the present study if an adenoma was registered in the Palga registry at the time of the first examination at the endoscopy department. Patients were excluded if they had a history of colorectal carcinoma or a colorectal carcinoma diagnosed within seven days after the initial examination, if they had no adenomas or non-adenomatous polyps only and if they had a diagnosis of inflammatory bowel disease. 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 followed until 1 October 1998. The patient's records were examined for all patients in whom colorectal cancer was diagnosed after the initial examination to decide whether or not it was a metachronous cancer. Patients were invited for surveillance colonoscopies according to the 1988 Dutch recommendations [2]: the first surveillance colonoscopy was scheduled within a year after the initial examination. The interval between repeat surveillance colonoscopies was 3 or 5 years, depending on the number of adenomas detected.

The follow-up time was calculated as the time between the initial examination registered at the endoscopy department and 1 October 1998. The calculation of the expected number of colorectal cancers is based on site-, gender- and age-specific colorectal cancer incidence rates in the Netherlands in 1995 multiplied by the number of person-years at risk [3]. The ratio of observed to expected cases is reported as a relative risk.

2.2. Literature search

A literature search was performed to find all publications in which colorectal cancer incidence in patients who underwent colonoscopic polypectomy of adenomas is compared with colorectal cancer incidence in the general population. We refer to, patients without (a history of) colorectal cancer who underwent colonoscopic polypectomy of adenomas as adenoma patient in the remainder of this paper. This is consistent with the definition used in the Amsterdam study. The literature search was performed using the PubMed database of the National Library of Medicine in May 2004 and paper were selected using the following Medline headings: ''colorectal neoplasms'' and ''colonoscopy'' and either ''adenoma'' or ''adenomatous polyps'' or ''colonic polyps''. The search resulted in 496 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. Twenty-two publications concerned follow-up studies in adenoma patients. Fifteen of these publications were excluded because they did not compare the cancer incidence in adenoma patients with the incidence in the age- and gender-matched general population. The seven remaining publications were included in our review. 95% Confidence intervals (CIs) are based on the exact Poisson distribution were calculated using STATA 7.0 software (StataCorp, College Station, Texas, USA).

3. Results

3.1. Amsterdam study

Table 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 not recorded. In the Netherlands, these are usually patients with symptoms who had a sigmoidoscopy and who were referred to colonoscopy due to the detection of adenomas.

Table 1
Characteristics of the patients and their adenomas at the initial examination in the Amsterdam study ($n = 553$)

	Number (%) of patients
Age at initial polypectomy (years)	
<50	91(16)
50–59	120(22)
60–69	191(35)
70–79	136(25)
80+	15 (3)
Gender	
Male	292(53)
Female	261(47)
Reason for referral	
Family history	62(11)
Symptoms	8(1)
Polyp at sigmoidoscopy	23(4)
Earlier adenoma	33(6)
Unknown	427(77)
Histology of adenomas at initial examination	
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. 34% had 0 examinations, 31% of the patients had at least one surveillance examination, 20% 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 caecum 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, and 26% occurred more than 3 years after initial examination. Adenomas were found in 24% of the surveillance examinations.

Five colorectal cancers were diagnosed during the follow-up period. Table 2 shows the characteristics of these patients. The number of adenomas removed at the initial examination was not known for all of the 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 visualise the ascending colon and caecum. A radiological examination was performed shortly afterwards at which no lesions were detected. A metastasised tumour was diagnosed in the caecum 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. 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 caecum. 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 years 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 years, 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.

Colorectal cancer incidence in adenoma patients was 0.86 (0.3–2.0) of the expected incidence in the general population ($n = 5$).

3.2. Literature search

The literature search identified seven other studies that compared estimates of the colorectal cancer risk after initial colonoscopic polypectomy with the rate in the general population. The design of the studies is described in Table 3 and the results of each study are presented in Table 4. The results of the studies 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 [4] and the study of Citarda [6] excluded patients with large ($\geqslant 3$ 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 with the general population in studies that included patients with large sessile polyps ranged from 0.5 (0.2–1.0) in the study of Bertario [7] to 1.3 (0.6–2.3) in the Funen Adenoma Surveillance Study [11]. The total number of colorectal cancers observed in the studies that included patients with large sessile adenomas, including the Amsterdam study, was 48 where 57 cancers were expected in the general population, a relative risk of 0.8 (0.6–1.1).

Table 2
Characteristics of colorectal cancer cases in the Amsterdam study

Patient no.	1	2	3	4	5
Gender	Male	Male	Female	Male	Male
Age at cancer diagnosis (years)	59	60	83	85	73
Histology of adenomas at initial examination	Unknown	Tubulovillous	Unknown	Tubular	Tubulovillous
Number of adenomas removed at initial examination	4	2	3	7	2
Number of surveillance examinations after initial examination	0	1	2	1	1
Time between initial examination and cancer diagnosis (years)	2.0	3.4	6.0	8.3	2.9
Time between last examination and cancer diagnosis (years)	2.0	1.9	4.1	6.9	2.0
Anatomical site of cancer	Caecum	Caecum	Ascending colon	Rectum	Sigmoid
Dukes' stage	D	C	A	A	A

Table 3
Literature review: design of studies on colorectal cancer incidence in patients in whom adenomas were removed. Mean follow-up time in each study is presented in Table 4

Study/author [Ref.]	Population and exclusion criteria	Initial examination	Surveillance colonoscopy schedule	End of follow-up
National Polyp Study [4,5]	Adenoma patients excluding family or personal history of familial polyposis, IBD, personal history of polypectomy or colorectal cancer. No polyps detected, non-adenomatous polyps only, End of the study in 1990 colorectal cancer or sessile adenoma with a base larger than 3 cm	Complete initial colonoscopy with all detected polyps removed	Arm A: at 1, 3, 6 years after initial colonoscopy Arm B: at 3 and 6 years after initial colonoscopy	
Citarda [6]	Patients with at least one adenoma larger than 5 mm excluding patients with genetic syndromes, previous adenomas or colorectal cancer, previous colonic resection, IBD or sessile adenomas more than 3 cm in diameter	Complete colonoscopy or (incomplete) colonoscopy and double contrast enema	74% had surveillance in the last 4 years of the study	End of the study in December 1996 with results of last surveillance examination or by telephone interview
Bertario [7]	Adenoma patients detected at programme screening, excluding patients with hyperplastic or inflammatory polyps, previous adenoma or colorectal cancer or histories of FAP or HNPCC	Colonoscopy	Surveillance at 1 year after initial colonoscopy, if negative, subsequently every 3 years	Date of first recurrence of polyps or colorectal cancer or last information/ death
Lund [8]	Adenoma patients, no exclusion criteria published	Complete colonoscopy or (incomplete) colonoscopy and barium enema. Flexible sigmoidoscopy at 6 months after initial examination	Randomised to surveillance by flexible sigmoidoscopy or colonoscopy at varying intervals	Follow-up until March 1998 for patient in screening trial and last surveillance visit for patients not in this trial
Meagher [9]	Adenoma patients, excluding patients with colorectal cancer, a history of colorectal cancer, IBD, FAP or hyperplastic polyps only and patients who did not attend surveillance examinations within 1 year of the date they were advised to return.	Colonoscopy	Advised surveillance: at 1 year after initial examination and at 3 years if no further polyps were found	Most recent colonoscopic examination for each patient
Atkin [10]	Adenoma patients with symptoms, excluding patients who had undergone colonoscopy or surgical excision of colonic adenomas	25-cm rigid sigmoidoscope	No surveillance	Development of colorectal cancer, death, colonoscopy, patient's 86th birthday or May 1988
Funen Adenoma Surveillance Study [11]	Adenoma patients with symptoms or positive in ongoing FOBT screening study, excluding patients with FAP, HNPCC or colorectal neoplasia in personal history	Mainly complete colonoscopy	Surveillance intervals varying from 6 to 48 months.	Most recent examination or death, refusal to follow-up or emigration
Amsterdam study	Adenoma patients, excluding patients with cancer, no adenomas or non-adenomatous polyps only, patients with IBD	Colonoscopy (93%) or barium enema and sigmoidoscopy (7%)	Surveillance within 1 year. Thereafter 3–5 yearly, depending on number of adenomas	October 1998 or occurrence of cancer

FAP, familial adenomatous polyposis coli; IBD, inflammatory bowel disease; HNPCC, hereditary non-polyposis colorectal cancer.

Table 4
Literature review: reported colorectal cancer incidence in patients in whom adenomas were removed and relative colorectal cancer risk compared with the age- and gender-matched general population

Study/author [Ref.]	No. patients	Sessile included	Mean follow-up time (years)	Person years	Cases	Relative risk (95% CI)
National Polyp Study [4,5]	1418	No	5.9	8401	5	0.2 (0.1–0.6) [a]Win: (0.05–0.70)
Citarda [6]	1693	No	10.5	14211	6	0.3 (0.1–0.7)[b]
Bertario [7]	1096	Yes	10.5	11393	10	0.5 (0.2–1.0)[c]
Lund [8]	776	Yes	6.6	5138	6	0.7 (0.2–1.4)[d]
Meagher [9]	645	Yes	4.4	2847	3	0.8 (0.2–2.3)
Atkin [10]	1618	Yes	13.9	22462	14	1.2 (0.7–2.1)[e]
Funen Adenoma Surveillance Study [11]	1056	Yes	4.3	Not published	10	1.3 (0.6–2.3)
Amsterdam study	553	Yes	5.3	2924	5	0.9 (0.3–2.0)

95% CI based on the exact Poisson distribution. Win: [5], the data differ slightly because the exact Poisson distribution was not used.
[a] Relative risk is 0.3 (0.1–0.8) if cancers ($n = 0$) and person-years in the first 2 years of follow-up are excluded.
[b] Cancers in the first 2 years of follow-up are excluded ($n = 3$). Relative risk is 0.5 (0.2–1.0) if included.
[c] Cancers in the first 2 years of follow-up are excluded ($n = 2$). Relative risk is 0.6 (0.3–1.1) if included.
[d] Relative risk is 0.4 (0.1–1.1) if two malignant polyps are excluded.
[e] Relative risk in the distal part of the colon. Cancers ($n = 3$) and person-years in the first 2 years of follow-up are excluded.

4. Discussion

Adenoma patients are considered to be at high risk for colorectal cancer, because adenomas are precursors of colorectal cancer. Therefore, once an adenoma is detected, colonoscopic polypectomy is performed and patients are regularly examined by colonoscopy. Meanwhile, the colorectal cancer risk in adenoma patients after removal of adenomas is not well known, and can only be measured by surveillance. The Amsterdam study shows a relative colorectal cancer risk after colonoscopic polypectomy of 0.9 (0.3–2.0) compared with the general population. A literature search identified seven other studies on the relative colorectal cancer risk in adenoma patients. The relative risks reported 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 inclusion or exclusion of patients with large sessile adenomas may partially explain the differences in the risk estimates. It is expected that patients with large sessile adenomas have an increased risk for subsequent colorectal cancer, because large adenomas may change to a malignant tumour and because it is difficult to remove sessile adenomas completely. The National Polyp Study and the study of Citarda, which excluded patients with large sessile polyps at the initial examination, found low colorectal cancer relative risk estimates, whereas higher estimates were found in studies that included patients with large sessile polyps (Table 4). This comparison suggests that patients with large sessile polyps are at high risk for colorectal cancer, even after polypectomy. Indeed, in a recent study, 166 patients with large sessile polyps were followed for a median of 36 months and two malignant polyps were diagnosed during that period [12]. This results in a colorectal cancer incidence in these patients of approximately 4/1000 person years, which is higher than the cancer incidence of 0.4 to 2.2/1000 in the reviewed studies. It is also supported by the finding of Atkin that the incidence of rectal cancer after removal of a rectal adenoma was strongly associated with a history of incompletely excised sessile adenomas [10].

Besides the inclusion or exclusion of patients with large sessile polyps, other factors may contribute to the differences in reported colorectal cancer risks. Firstly, the completeness of the initial and follow-up examinations may have influenced the reported risk. As an example, in the Amsterdam study, the initial colonoscopy did not visualised the caecum in Patient 1. Although the initial colonoscopy was followed by barium enema, a carcinoma was diagnosed in the caecum two years later. Patient 3 had an 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 been systematically followed by repeat colonoscopy, as was done in the National Polyp Study.

Secondly, the endpoint of the studies will have influenced the relative risk estimates. In some studies, follow-up of all or most patients ended with the results of the last surveillance examination [6,8,9,11], while in others, follow-up ended at the end of the study period [4,7,10]. Ending with a surveillance test will result in higher risk estimates, because asymptomatic cancers detected at the last surveillance examination are included, while the low-risk person-years in the years after the last surveillance examination are excluded. This effect will be

more pronounced in studies with a small number of follow-up years per person and thus may have played a role in the results of the Meagher and Funen studies and less so in the Citarda and the Lund studies.

Thirdly, the upper age of surveillance may have played a role, as in the Amsterdam study two cancers were diagnosed in patients (Patient 3 and Patient 4) who had stopped follow-up several years before diagnosis due to their older age (>75 years). These two Dukes' A cancers might 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 Amsterdam study had been prevented, the relative colorectal cancer risk would decrease to 0.5 (0.1–1.5).

In all of the studies reviewed, except the study of Atkin [10], the study population was subjected to surveillance. Therefore, the relative colorectal cancer risk in the studies reflect the effect of endoscopic polypectomy and subsequent surveillance. In the longer run, surveillance decreases colorectal cancer incidence by further removal of adenomas. By contrast, colorectal cancer incidence increases through the detection of asymptomatic cancers. A modelling study estimated that it takes approximately 6 years before the cumulative incidence is reduced [13]. Therefore, given the short follow-up time, surveillance may have raised rather than decreased cancer incidence in most studies. Surveillance may have reduced colorectal cancer incidence in the studies of Citarda and Bertario, because the mean follow-up time was significantly longer than 6 years and surveillance was performed. In the Bertario study, patients had an average of 5 surveillance endoscopies, while 74% of the patients in the Citarda study had a surveillance examination in the last 5 years of the study. However, the studies are too small to study the effect of surveillance interval on colorectal cancer risk.

There is a wide variation in the percentage of colorectal cancers detected at surveillance (asymptomatic cancers) and not by symptoms among the studies. This can be explained by the small number of cancer cases per study. Furthermore, the percentage of asymptomatic cancers is correlated with the average number of surveillance examinations per patient. In the Amsterdam study, none of the five cancers was 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, with an average of 1.2 surveillance examinations per patient, but some of the examinations consisted of several colonoscopies, because colonoscopy was repeated if the first colonoscopy was incomplete. The Citarda and Meagher studies did not publish the number of surveillance examinations performed, while the Bertario and Atkin studies did not publish the number of cancers detected at surveillance.

The present review shows that the relative colorectal cancer risk estimates in adenoma patients in the eight reviewed studies varies between 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 difference can be explained, at least partially, by differences in the inclusion of patients with large sessile polyps, completeness of colonoscopic examinations and other factors. Our 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, and that the risk for patients with non-sessile adenomas is probably lower than that in the general population.

Conflict of interest statement

None declared.

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