Pathologic Features of Initial Adenomas as Predictors for Metachronous Adenomas of the Rectum

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Background: **Colorectal cancer is the third most common cancer in the world, arising mostly from pre-existing adenomatous polyps (adenomas) of the large bowel. Patients with colorectal adenomas are at increased risk of colorectal cancer because of a high recurrence rate for adenomas. We followed a cohort of 1490 patients with rectal adenomas to determine whether recurrence might be related to pathologic characteristics of the initial adenomas.** ***Methods:*** **The patients were identified in Haining County, China, from 1977 through 1978 by means of examination with a 15-cm rigid sigmoidoscope. They were followed by endoscopic examination at years 2, 4, 6, 11, and 16 after their initial polypectomy. New adenomas in the rectum were identified in 280 patients in these follow-up examinations.** ***Results:*** **Statistically significant twofold to threefold elevated risks of metachronous (recurrent) adenomas were observed for patients who had more than two initial adenomas or whose most advanced initial adenoma was more than 1.0 cm in size, was of villous/tubulovillous type, or showed moderate to severe dysplasia. Much stronger associations were observed for advanced metachronous neoplasms, which are defined as cancers or adenomas with severe dysplasia, with multivariate adjusted relative risks (95% confidence interval) of 4.2 (1.8–9.9) for a large initial adenoma (>1.0 cm), 8.1 (4.2–15.6) for villous/tubulovillous architecture, and 14.4 (5.0–41.3) for severe dysplasia. In particular, patients who had a large (>1.0 cm) adenoma with severe dysplasia at baseline had a relative risk of 37 (7.8–174.7) of developing advanced metachronous neoplasms compared with patients who had small adenoma(s) with mild dysplasia.** ***Conclusions:*** **The risk of metachronous adenomas is closely related to the pathology of initial adenomas, thus allowing identification of a high-risk group of adenoma patients for close surveillance after their initial polypectomy.** **[J Natl Cancer Inst 1998;90:1661–5]**

Colorectal cancers, the third most common cancer in the world *(1,2)*, arise mostly from pre-existing adenomatous polyps (adenomas) of the large bowel *(1–4)*. Removal of adenomas reduces the morbidity of and mortality from colorectal cancer *(5,6)*. About 30%–60% of patients will develop metachronous (recurrent) adenomas in 3–5 years from their initial polypectomy *(7);* thus, they are at an elevated risk of developing colorectal carcinoma *(1,2,8–12)*. Therefore, effective follow-up surveillance, such as repeated colorectal endoscopic examination, is needed in this high-risk population to detect subsequent adenomas and/or carcinomas in a timely manner *(4,5,13)*. The appropriate surveillance interval, however, has been debated, because only a small proportion of adenomas proceed to carcinomas *(5,7,11,13,14)*. It is, therefore, important to identify those adenoma patients who are at a particularly high risk of developing metachronous adenomas for more intensive follow-up.

Pathologic features of the initial adenomas have been implicated as useful predictors for recurrent adenomas *(2,13,15,16)*. The results from previous studies *(13,15,16)*, however, have been inconsistent. Studies to evaluate predictors for recurrent adenomas are expensive because they require that colorectal endoscopic examination be systematically repeated over a long period of time, and thus they are not often practical. From 1977 through 1978, 1490 patients with rectal adenomas were identified, by examination with a rigid 15-cm sigmoidoscope, in a population-based rectal cancer-screening program in Haining County, China. These individuals were followed systematically for 16 years. This cohort provides the opportunity to assess baseline predictors for recurrent adenomas.

Subjects and Methods

As a part of a population-based rectal cancer-screening program, conducted from 1977 through 1978, 185 851 adult residents of Haining County, China, aged 30 years and older, were examined for rectal neoplasms by use of a rigid 15-cm sigmoidoscope *(17)*. Suspected lesions within the reach of the sigmoidoscope were removed endoscopically or, when required, surgically. All pathologic material was reviewed independently by three senior pathologists who used criteria from the World Health Organization *(18)*. A final diagnosis was recorded for each patient when a consistent diagnosis from at least two pathologists was reached. Of these individuals, 1490 subjects (detection rate, 0.82%) were diagnosed as having one or more adenomas in their rectum and constitute the cohort for this report. The distributions of the pathologic features of the most advanced initial adenoma for each patient, along with some patient characteristics, are presented in Table 1. Most patients (91.4%) had a single adenoma. The predominant histologic type of the most advanced adenoma (hereafter referred to as the initial index adenoma) for each patient was tubular adenoma (91.6%). Only 3.4% of index adenomas were found to have severe dysplasia. Except for the shape of the index adenoma, other characteristics of the index adenoma were similar in men and women. Women had more pedunculated adenomas than men, and the difference was statistically significant ($P<.001$).

All patients with adenomas were followed by examination with a rigid sigmoidoscope at years 2 (in 1979), 4 (1981), and 6 (1983) and by examination with a flexible sigmoidoscope at years 11 (1988) and 16 (1993). The proportions of patients examined were 78.3% in year 2, 57.7% in year 4, 77.1% in year 6, 88.5% in year 11, and 61.0% in year 16. Virtually all patients (99.1%) received at least one follow-up examination, and 94.5% of the patients received at least two follow-up examinations. Two hundred sixty-nine patients died over the 16-year follow-up period.

All suspected lesions were removed at the follow-up endoscopic examinations. Pathology slides from these lesions were reviewed by a protocol identical to that used in the initial screening, and pathologists were blinded to the diagnosis of the initial adenomas. During the 16-year follow-up period, 280 patients had metachronous adenomas identified at a location in the rectum that could be reached by a rigid sigmoidoscope (<15 cm from the anal verge), 236 (84.3%) patients had a metachronous adenoma identifed at only one examination, 37 patients had a metachronous adenoma identified at two examinations, and seven patients had a metachronous ade

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See ''Notes'' following ''References.''

Table 1. Distributions of cohort members by selected patient characteristics and pathologic features of most advanced adenoma removed at the baseline screening

Indicator	Men (n = 948) No.	Men (n = 948) %	Women (n = 542) No.	Women (n = 542) %
Age groups, y*				
30–39	360	38.0	223	41.1
40–49	220	23.2	121	22.3
50–59	234	24.7	128	23.6
⩾60	134	14.1	70	12.9
No. of adenomas at baseline				
1	865	91.2	497	91.7
2	27	2.9	7	1.3
⩾3	56	5.9	38	7.0
Histology of index adenoma†				
Tubular	866	91.4	499	92.1
Tubulovillous	72	7.6	34	6.3
Villous	10	1.1	9	1.7
Dysplasia of index adenoma†				
Mild	493	52.0	315	58.1
Moderate	418	44.1	214	39.5
Severe	37	3.9	13	2.4
Size of index adenoma, cm†				
⩽0.5	765	80.7	431	79.5
0.6–1.0	137	14.5	84	15.5
>1.0	45	4.7	27	5.0
Shape of index adenoma†				
Pedunculated	450	47.5	331	61.1
Sessile	498	52.5	211	38.9

*Adenoma detection rates were 1.16%, 0.85%, 1.08%, and 0.93% among men in the age groups of 30–39, 40–49, 50–59, and ⩾60 years, respectively. The detection rates among women in the corresponding age groups were 0.68%, 0.48%, 0.64%, and 0.46%, respectively.

†Pathology of the most advanced initial adenoma.

noma identified at more than two examinations. Any new adenomas detected in areas 15 cm or more from the anal verge in the follow-up examinations were not considered to be metachronous adenomas in the current analysis. Among those individuals with metachronous adenomas, 15 patients were diagnosed with rectal cancer.

Relative risks (RRs) were used to measure the strength of the associations between the risk of metachronous adenomas and the characteristics of initial adenomas. Because some subjects had metachronous adenoma detected at two or more follow-up examinations, a generalized Cox regression model (MULCOX) was used in the analyses to account for possible dependency of multiple events *(19,20)*. The hazard function is defined as $\lambda k(t;Z_{ik}) = \lambda_{0k}(t)e^{\beta 1Zik(t)}$, where $k = 1, \ldots, K$, the number of events for each patient. This model was used to control potential confounders and to derive adjusted RRs and 95% confidence intervals (CIs). We also used a simple Cox regression model in the analysis to examine the consistency of the results from these two Cox regression models and found that consistency was very good. Because the MULCOX regression model takes into account multiple events, we elected to use this method in our data analysis. Persons were considered at risk for metachronous adenomas until the time of death, the identification of colorectal cancer, or the end of the study. A test for dose–response relationships across levels of study variables was performed by treating each ordinal score variable as a continuous variable in the Cox model. Proportional hazards assumption for using the Cox regressions was examined and found to be valid for all major analyses. All *P* values reported are two-sided.

RESULTS

Multiplicity of initial adenomas was positively associated with the risk of metachronous adenomas (*P* for trend <.001), with an age- and sex-adjusted RR of 2.7 (95% CI = 2.0–3.7) for those who had three or more initial adenomas detected (Table 2). The age- and sex-adjusted RRs of metachronous adenomas were also statistically significantly elevated for those whose initial index adenoma was tubulovillous/villous type, was larger than 1.0 cm, or showed moderate or severe dysplasia. These RRs remain essentially unchanged after additional adjustment for the number of initial adenomas. No statistically significant associations were observed between metachronous adenomas and the patient's age and sex or the shape of the patient's index adenoma. Results from the simple Cox regression model that included the first metachronous adenoma as the event were very similar to those presented in Table 2. The adjusted RRs of metachronous adenomas ranged from 1.8 to 2.8 for patients who had more than two initial adenomas (RR = 2.8; 95% CI = 2.0– 3.9) or those whose initial index adenoma

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) for metachronous adenomas associated with selected characteristics of the initial adenomas*

Indicator	No. of person-years	No. of new adenomas	Age- and sex-adjusted RR (95% CI)	Multivariate† RR (95% CI)
No. of initial adenomas				
1	18 467.9	269	1.0 (referent)	
2	468.3	8	1.2 (0.6–2.6)	N/A
⩾3	1230.9	56	2.7 (2.0–3.7)	
Trend test			*P*<.001	
Histopathology of index adenoma‡				
Tubular	18 656.7	275	1.0 (referent)	1.0 (referent)
Villous/tubulovillous	1510.4	58	2.7 (2.0–3.5)	2.6 (2.0–3.4)
Dysplasia of index adenoma‡				
Mild	11 249.6	142	1.0 (referent)	1.0 (referent)
Moderate	8281.1	177	1.8 (1.5–2.3)	1.8 (1.4–2.2)
Severe	636.5	14	1.9 (1.2–3.2)	1.9 (1.1–3.2)
Trend test			*P*<.001	*P*<.001
Size of index adenoma, cm‡				
⩽0.5	16 318.4	254	1.0 (referent)	1.0 (referent)
0.6–1.0	2890.0	52	1.2 (0.9–1.5)	1.2 (0.9–1.6)
>1.0	942.8	27	1.8 (1.2–2.7)	1.6 (1.0–2.6)
Trend test			*P* = .005	*P* = .01
Shape of index adenoma‡				
Pedunculated	10 672.1	158	1.0 (referent)	1.0 (referent)
Sessile	9495.0	175	1.2 (1.0–1.5)	1.2 (1.0–1.5)

**P* values are two-sided.

†Adjusted for age, sex, and number of initial adenomas. N/A = not applicable.

‡Pathology of the most advanced initial adenoma.

was 1.0 cm or more (RR = 1.8; 95% CI = 1.2–2.9), was of the villous/tubulovillous type (RR = 2.8; 95% CI = 2.0–3.9), or showed severe dysplasia (RR = 2.3; 95% CI = 1.3–4.1).

To examine the consistency of the observed associations between pathologic features of the initial adenomas and the risk of metachronous adenomas over a 16-year follow-up period, we performed separate analyses for the periods from July 15, 1977, to July 14, 1983, and from July 15, 1983, to July 15, 1993, according to the years of detection of metachronous adenomas. No appreciable difference in the strength of the associations was observed in these two periods. To evaluate whether certain pathologic characteristics of the initial adenomas can be used to predict the risk of metachronous adenomas detected in more than one follow-up examination, we performed separate analyses for patients with metachronous adenomas detected at a single or at multiple time points. The strengths of the association between baseline pathologic characteristics and the risks of metachronous adenomas were generally stronger in patients with multiple occurrences than in those with a single occurrence. For example, in the former group, the adjusted RRs (95% CI) were 3.1 (1.6–5.9) for those with two or more initial adenomas, 2.8 (1.4–5.7) for those whose initial index adenoma was of the villous/tubulovillous type, 3.1 (1.2–8.0) for those who had a large (1.0 cm) initial adenoma, and 3.4 (1.4–8.0) for those whose initial adenoma showed severe dysplasia. The corresponding RRs (95% CI) for the latter group were 2.2 (1.4–3.3), 2.4 (1.6–3.5), 1.6 (0.9–2.6), and 1.9 (1.3–2.9).

To assess whether the associations observed above were affected by incomplete excision of the initial adenomas or synchronous adenomas that were missed at the baseline screening, we performed similar multivariate analyses after excluding all adenomas (n = 106) detected at the first follow-up examination. Most of the positive associations remained statistically significant. The adjusted RR (95% CI) of recurrent adenomas was 2.3 (1.6–3.3) for individuals who had three or more adenomas detected at baseline. For those whose initial index adenoma was of the villous/tubulovillous type, the RR (95% CI) was 1.7 (1.2–2.5); for those whose initial index adenoma was larger than 1.0 cm, it was 1.1 (0.7–1.9); and for those whose initial index adenoma showed severe dysplasia, it was 2.3 (1.4–3.6). With exclusion of recurrent adenomas (n = 119) detected at the same locations as those of the initial adenomas, the corresponding RRs (95% CIs) were 2.7 (1.9–3.8) for three or more adenomas detected at baseline, 1.9 (1.3–2.6) for villous/tubulovillous type of index initial adenoma, 0.8 (0.4–1.5) for initial index adenoma larger than 1.0 cm, and 1.5 (1.0–2.2) for initial index adenoma that showed severe dysplasia. These results indicate that the associations observed in this study cannot be accounted for by the effect of incomplete excision of the initial adenomas or synchronous adenomas. It should be noted that not all adenomas excluded above are those that were missed or incompletely removed at the initial screening. Therefore, the above analyses represent a very conservative approach to evaluate the potential bias, and the RRs from these analyses may be substantially underestimated.

We further assessed whether pathologic features of the initial adenomas could be used to predict future risk of advanced metachronous neoplasms, defined as a carcinoma or an adenoma with severe dysplasia. The advanced metachronous neoplasms included in the analysis were mostly larger than 0.5 cm, and 15 of these lesions were rectal cancers. The risk of advanced metachronous neoplasms was found to be strongly associated with histologic type, size, and the degree of the dysplasia of the initial index adenoma but less so for the number of initial adenomas (Table 3). Older patients were more likely to develop advanced metachronous adenomas than were younger patients; the RR was 3.1 (95% CI = 1.3–6.7) for the age group of 60 years or older versus the age group of 30–39 years. We also analyzed the associations with large (>1.0 cm) metachronous adenomas and found that the results were similar to those for advanced metachronous adenomas.

The above risk factors for advanced metachronous neoplasms were further analyzed to evaluate their combined predicting value (Table 4). The risks of advanced metachronous neoplasms were statistically significantly elevated among patients who were found at baseline to have index adenomas of the villous/tubulovillous type or index adenomas with severe dysplasia, regardless of size. Patients who had a large (>1.0 cm) index adenoma with severe dysplasia had an RR of 37 (95% CI = 7.8–174.7) of developing advanced metachronous neoplasms com-

Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) for advanced metachronous neoplasms* associated with characteristics of the initial adenomas†

Indicator	No. of events	Age- and sex-adjusted RR (95% CI)	Multivariate adjusted RR (95% CI)‡
No. of adenomas at baseline			
1	49	1.0 (referent)	
2	2	1.4 (0.4–5.2)	N/A
⩾3	7	2.0 (0.9–4.4)	
Trend test		$P = .06$	
Histopathology of index adenoma§			
Tubular	33	1.0 (referent)	1.0 (referent)
Villous/tubulovillous	25	8.3 (4.3–16.0)	8.1 (4.2–15.6)
Dysplasia of index adenoma§			
Mild	9	1.0 (referent)	1.0 (referent)
Moderate	40	5.9 (2.6–13.5)	5.8 (2.6–13.3)
Severe	9	14.4 (5.0–41.4)	14.4 (5.0–41.3)
Trend test		$P<.001$	$P<.001$
Size of index adenoma, cm§			
⩽0.5	33	1.0 (referent)	1.0 (referent)
0.6–1.0	11	2.4 (1.3–4.6)	2.4 (1.2–4.6)
>1.0	14	4.4 (1.9–10.2)	4.2 (1.8–9.9)
Trend test		$P<.001$	$P<.001$
Shape of index adenoma§			
Pedunculated	23	1.0 (referent)	1.0 (referent)
Sessile	35	1.6 (0.9–2.9)	1.6 (0.9–2.8)

*Cancer or adenoma with severe dysplasia identified at follow-up.
†*P* values are two-sided.
‡Adjusted for age, sex, and number of initial adenomas.
§Pathology of the most advanced initial adenoma.

Table 4. Relative risks (RRs) and 95% confidence intervals (CIs) for advanced metachronous neoplasms* by joint distribution of selected pathologic features of the initial index adenoma

Characteristic of index adenoma	Size of initial index adenoma: ≤1.0 cm — No. of patients	No. of events	RR† (95% CI)	>1.0 cm — No. of patients	No. of events	RR† (95% CI)
Histologic type						
Tubular	1321	32	1.0‡ (referent)	44	1	1.2 (0.2–8.8)
Villous/tubulovillous	97	12	7.3 (3.8–14.2)	28	13	13.2 (4.2–41.8)
Dysplasia						
Mild	784	9	1.0§ (referent)	24	0	—
Moderate	598	33	5.5 (2.4–12.7)	34	7	14.9 (4.6–48.4)
Severe	36	2	11.2 (3.3–38.2)	14	7	37.0 (7.8–174.7)

*Cancer or adenoma with severe dysplasia identified at follow-up.

†Adjusted for age, sex, and number of adenomas.

‡Reference group for all comparisons involving histologic types and size of initial adenoma.

§Reference group for all comparisons involving type of dysplasia and size of initial adenoma.

pared with those having small adenoma(s) with mild dysplasia. This RR was increased to 46.1 (95% CI = 11.7–181.6) after exclusion of new adenomas detected in the first follow-up examination as outcomes.

DISCUSSION

Our investigation has clearly shown that certain characteristics of the initial adenomas are useful in predicting subsequent risk of developing metachronous neoplasms, particularly cancer and advanced metachronous adenomas. These findings are supported by several previous studies *(2).* Three follow-up studies *(13,15,16)* have been published on this topic. The U.S. National Polyp Study *(13)* found that the size and number of the initial adenomas were associated with recurrent adenomas. The study, however, did not report the predicting value of the histologic type or degree of dysplasia of the initial adenomas. The second study *(15)* found that the multiplicity and the size of the initial adenomas were independent predictors, whereas the presence of villous elements and of severe dysplasia in the initial adenoma was not important in predicting metachronous polyps. Because a high proportion of patients received their initial examinations only 6 months before the follow-up examinations, it is likely that many of the adenomas detected at the follow-up examinations are those that were missed at the initial examination. This may affect the interpretation of the study results. The third study *(16)* suggested that the multiplicity of adenomas may be related to an increased risk of recurrent adenomas. This last association, however, was not statistically significant, perhaps as a result of a small sample size.

Because most metachronous adenomas are small, contain only tubular elements, or have low-grade dysplasia, they are, for the most part, pathologically unimportant *(5,7,13).* Severe dysplasia, the hallmark of malignant transformation of adenoma, is used synonymously with carcinoma *in situ (21).* It has been reported that the frequencies of the p53 and APC gene mutations are higher in adenomas with severe dysplasia than in those with mild or moderate dysplasia *(22–24).* Konishi and Morson *(21)* suggested that severe dysplasia per se may be the most selective marker of increased cancer risk. It is important, therefore, to predict the risk of cancer and metachronous adenomas with severe dysplasia. Our findings for the strong positive associations of pathologic features of the initial adenomas and the risk of advanced metachronous neoplasms are consistent with results from some previous studies *(5,11,25),* although the associations observed previously were weaker than those observed in this report. In a series of studies *(11,12,26)* from the Mayo Clinic, the risk of colorectal cancer was twofold to fourfold elevated among patients who had a large polyp. No information, however, was provided in those reports regarding the predictive value of the degree of dysplasia of the initial adenomas. In a cohort study *(5)* conducted in the U.K., the size, villous architecture, and dysplasia of the initial adenomas were found to be associated with the future risk of rectal cancer. In particular, a fivefold excess risk of rectal cancer was found among patients whose initial adenomas had severe dysplasia. In that study, the degree of dysplasia was graded with the same protocol used in this study *(18).* In the U.S. National Polyp Study *(13),* only the number of initial adenomas was found to be a strong predictor for advanced metachronous adenomas.

It is likely that some of the adenomas detected in the follow-up endoscopic examinations in our study were synchronous adenomas that were too small to be detected and removed in the initial polypectomy; the results were essentially unchanged, however, after all newly discovered adenomas in the first follow-up examination were excluded from the analyses. Although the strength of the associations was slightly reduced after we further excluded any recurrent adenomas detected at the same locations as those of the initial adenomas, the positive associations persisted, indicating that our findings cannot be explained entirely by the effect of incomplete excision of the initial adenomas or synchronous adenomas. Nevertheless, detection of synchronous and metachronous adenomas in the follow-up examinations should be viewed as equally important in clinical practice. In this context, it may be clinically unimportant to distinguish predictors for these two types of adenomas. Although virtually all patients (94.5%) received at least two examinations during the 16-year follow-up period, the participation rates were low at the year-4 (in 1981) and year-16 (in 1993) follow-up examinations. The low participation rates, particularly in the last follow-up examination, could introduce selection bias if participants and nonparticipants differed with regard to both exposure variables (characteristics of the baseline adenomas) and outcomes (risk of metachronous adenomas). We found, however, that patients who participated or did not participate in the last follow-up examination were very similar with regard to all pathologic features of the initial adenomas, indicating this bias may not be important in this study.

In summary, we have shown that the risk of metachronous adenomas, particularly carcinoma and adenomas with severe dysplasia, was closely associated with specific, easily ascertained, pathologic features of the initial adenomas. This study has provided strong evidence

that pathologic features of the initial adenomas are useful in predicting the risk of metachronous adenomas. This study is limited to adenomas detected in the rectum, and we are currently conducting a colonoscopic follow-up study among patients who were identified with adenomas to evaluate predictors for metachronous adenomas of the whole colorectum.

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NOTES

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