Digestion

Increased Prevalence of Colorectal Adenomas in Women with Breast Cancer

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Abstract
Background: The frequency of colorectal adenomas and carcinomas was investigated in a large cohort of women with breast cancer in comparison with matched controls, since data on the occurrence of second tumors in women with breast cancer is controversial. *Design:* In a cohort study, 188 consecutive women (median age 57 years) with primary breast cancer and 376 age-matched women who served as controls were examined by total colonoscopy. Breast cancer patients and controls were compared for the frequency of colorectal adenomas and carcinomas. *Results:* Women with breast cancer showed a higher risk of colorectal adenomas than controls (14.9 vs. 9.3%, p = 0.047, OR 1.7, 95% CI 1.0–2.9). This increased prevalence resulted primarily from an increased prevalence in the age group 65–85 (31 vs. 10%, p = 0.004, OR 3.8, 95% CI 1.6–9.3). Colorectal carcinomas were found infrequently in both groups (2 in each group). Women with breast cancer receiving anti-estrogen therapy showed a trend towards a lower risk of adenomas compared to women without anti-estrogen therapy (3.7 vs. 17.2%, p = 0.053, OR 0.16, 95% CI 0.0–1.1). *Conclusions:* Women with breast cancer above the age of 65 years have an increased risk of colorectal adenomas compared to women without breast cancer. Women with a diagnosis of breast cancer should especially be encouraged to participate in colorectal cancer-screening programs which, in most countries, call for screening of all average-risk individuals over the age of 50 years.

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Introduction

Epidemiological studies suggest an association between the incidence of breast cancer and the incidence of colorectal cancer [1–3]. Relatives of patients with breast cancer have been shown to develop colorectal tumors more frequently than controls [4]; conversely, families with a high risk of colonic cancer have breast cancers more frequently than controls [5]. Furthermore, first-degree relatives of patients with primary carcinomas of the breast or of the colon more frequently develop breast can-

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cer or colon cancer than controls [6], altogether suggesting a common susceptibility for colorectal and breast cancer.

Cross-sectional cohort studies for the risk of colorectal carcinomas in women with breast cancer would need very large numbers of patients due to the low incidence of colorectal cancer. On the other hand, using adenomas as an endpoint limits the predictive power of such a study due to the fact that most individuals with adenomas will not develop colorectal cancer in their lifetime. Nevertheless, colorectal adenomas are precursors of colorectal cancer and are much more frequent and hence, offer a better approach to address the question whether women with breast cancer bear a higher risk of colorectal tumors. However, studies on this matter have so far revealed conflicting data [7–16] and found odds ratios for the risk of subsequent colorectal adenomas as low as 0.7 or as high as 3.0 [9, 11–16]. This wide range might be explained by age differences, small numbers of patients studied, and the fact that mostly only the rectum and the sigmoid colon were studied. This prompted us to conduct a cross-sectional cohort study on the frequency of colorectal adenomas or carcinomas by performing total colonoscopy in women with breast cancer, and to compare it with the frequency of colorectal adenomas in age-matched controls.

Patients and Methods

Patients with a recent history of breast cancer were included in the study group. The study patients consisted of all those attending the Department of Gynecology of the University Hospital Munich-Grosshadern for follow-up after breast cancer therapy over a 24-month period. For each study patient, 2 age-matched controls (± 2 years) were recruited from women undergoing colonoscopy at the Department of Medicine II of the University Hospital Munich-Grosshadern during the same time period. The indications for colonoscopy in the control group are summarized in table 1.

Colonoscopy was offered to all consecutive patients in the study and control groups during the 2-year study period. In both groups, medical and family histories were obtained, and data on height and weight were collected. The exclusion criteria are summarized in table 2. Those women who gave their informed consent were then submitted to total colonoscopy. The study complied with the Helsinki declarations. The protocol was approved by the ethical committee of the University of Munich. Written informed consent was obtained from all patients studied.

Colonoscopy
In both study groups, the colonoscopies were performed by the same group of experienced endoscopists at the Department of Medicine II of the University Hospital Munich-Grosshadern. Any polyps or tumors were biopsied if smaller than 5 mm, or removed endoscopically or surgically if larger than 5 mm.

Table 1. Indications for colonoscopy in the control group

	n
Occult or overt blood in the stools (but not acute intestinal bleeding)	55
Abdominal pain of unknown origin	122
Diarrhea	51
Constipation	46
Suspected neoplasia	53
Abdominal mass	49

Table 2. Exclusion criteria in the study (n = 158) and the control (n = 1,362) groups

	Study group	Controls
Previous colorectal adenoma or carcinoma	24	154
Second primary carcinomas other than breast cancer	7	496
Chronic inflammatory bowel disease	0	165
Family history (one or more first-degree relatives) of breast cancer or colorectal cancer	3	8
Partial or total colectomy	1	159
Previous colonoscopy within the last 5 years	49	78
Reluctance to participate	59	0
Incomplete colonoscopy	9	97
No appropriate age-match	6	205

Adenomas and carcinomas were classified histologically as tubular, tubulo-villous or villous, in accordance with the criteria of the WHO [17].

Statistics
Breast cancer patients and controls were compared for the frequency of colorectal adenomas and carcinomas using the χ^2 test or the Student's t test. Women with breast cancer who had received the necessary therapies were compared for the frequency of colorectal adenomas using the two-sided Fisher's exact test. p values of <0.05 were regarded as significant. Values are given as mean ± SD or as median and range.

Results

Patients
Of 346 consecutive women with breast cancer who were evaluated for participation in this study, 158 were excluded. The reasons for exclusion were: previous colorectal adenomas (n = 9); previous colorectal carcino-

Table 3. Demographic and clinical characteristics of women with breast cancer and controls

	Breast cancer (n = 188)	Controls (n = 376)
Age, years (mean ± SD)	56.6 ± 12.2	56.9 ± 12.9
Age range, years	34–84	32–84
White Caucasian, %	100	100
Body mass index (mean ± SD)	25.0 ± 4.3	24.6 ± 4.6
Smokers	24 (13%)	41 (11%)
Parity		
0	34 (18%)	94 (25%)
1–2	113 (60%)	214 (57%)
>2	41 (22%)	68 (18%)
Menstrual status		
Regular/irregular cycle	20 (11%)	55 (15%)
Perimenopausal	57 (30%)	140 (37%)
Postmenopausal	111 (59%)*	181 (48%)*

* $p < 0.02$.

Table 5. Age-related prevalence of adenomas in women with breast cancer and in controls

Age years	Patients with adenomas in the study group		Patients with adenomas in the control group	
	n	%	n	%
<36	0/2	0.0	0/2	0.0
36–45	0/20	0.0	5/75	6.7
46–55	9/77	11.7	13/136	9.6
56–65	4/40	10.0	7/67	10.4
66–75	11/39	28.2*	4/54	8.9*
76–85	4/10	40.0*	6/42	14.3*
Total	28/188	14.9	35/376	9.3

Between the combined age groups 66–85 a significant difference was observed (*): OR 3.79 (95% CI 1.43–10.20) and RR 2.94 (95% CI 1.43–6.05).

Table 4. Endoscopic results in women with breast cancer and controls

Finding	Breast cancer (n = 188)	Controls (n = 376)
No adenoma or cancer	158 (84.0%)	339 (90.2%)
Tubular adenoma <1 cm	12 (6.4%)	20 (5.3%)
Tubular adenoma >1 cm	7 (3.7%)	3 (0.8%)
Tubulo-villous adenoma	9 (4.8%)	12 (3.2%)
High-grade dysplasia or cancer	2 (1.1%)	2 (0.5%)
Total adenoma	28 (14.9%)**	35 (9.3%)**
Total neoplasia	30 (16.0%)*	37 (9.8%)*

* $p < 0.04$; ** $p < 0.05$.

mas (n = 15); second primary carcinomas other than breast (n = 7); a family history of breast or colorectal cancer (n = 3); partial colectomy (n = 1); previous colonoscopy within the last 5 years (n = 49); reluctance to participate (n = 59), and incomplete colonoscopy (n = 9). Six women were not included in the evaluation because no appropriate age-matched controls were available. Thus a total of 188 women with breast cancer were studied.

1,738 consecutive women undergoing colonoscopy during the same period were evaluated for matching with the breast cancer patients. Excluded were: 554 women with previous or current malignant disease; 96 with previous colorectal adenomas; 165 with chronic inflammatory bowel disease; 159 with prior partial colectomy; 8 with a family history of breast or colorectal cancer, and 97 women because of incomplete colonoscopy. 78 women were excluded because of a previous colonoscopy within the last 5 years. 205 women were not included in the evaluation because no appropriate age-matched partner could be found. Hence, 2 each of the appropriate 376 control women were age-matched to each study patient.

The patients' characteristics are described in table 3. The mean age of the patients was 56.6 ± 12.2 years for the study group, and 56.9 ± 12.9 years for the control group (p = 0.79). The mean body mass index (calculated as weight in kilograms divided by the square of the height in meters) was similar in both groups: 25.0 ± 4.3 in the study group and 24.6 ± 4.6 in the control group (p = 0.35).

Frequency of Colorectal Adenomas and Carcinomas

Women with breast cancer had a significantly higher incidence of colorectal adenomas than the control patients (n = 28 (14.9%) vs. n = 35 (9.3%), OR 1.7, 95% CI 1.0–2.9, p = 0.047; table 4). The age-related prevalence of adenomas in patients and controls showed a significant difference between the combined age groups of 66–85: 31 vs. 10%, p = 0.004, OR 3.8, 95% CI 1.6–9.3 (table 5). Colorectal carcinomas were found in only 2 women with breast cancer and in 2 of the controls (OR 2.0, 95% CI 0.3–14.4, p = 0.60; table 4). Women with breast cancer had a significantly higher incidence of colorectal tumors

Table 6. Adjuvant therapy in women with breast cancer, and prevalence of adenomas according to therapy

Therapy regimen	Patients	Patients with adenomas	
		n	%
No adjuvant therapy	57	7	12.3
Radiation	51	8	15.7
Chemotherapy + anti-estrogen	2	0	0.0*
Anti-estrogen + radiation	25	1	4.0*
Chemotherapy + radiation	49	12	24.5
Chemotherapy + radiation + anti-estrogen	4	0	0.0*
Total	188	28	14.8

No significant differences in terms of colorectal adenoma rates were observed between each group in comparison to the group without therapy. However, in women receiving anti-estrogen therapy (n = 31) only 1 woman had an adenoma, as compared to women receiving no anti-estrogen therapy (n = 157) of whom 27 had adenomas: * p = 0.053.

(carcinomas and adenomas) than control patients (n = 30 (16.0%) vs. n = 37 (9.8%), OR 1.7, 95% CI 1.0–2.9, p = 0.039; table 4).

No statistically significant difference was noted between the study group and the control group with regard to the site of adenomas. In the study group 6 women had adenomas in the right colon and 22 women in the left colon, whereas in the control group 2 women had adenomas in the right colon and 33 women in the left colon. The 2 carcinomas in each group were found in the rectum, and sigmoid in the study group and in the right colon and rectum in the control group, respectively.

There was no difference between the 2 groups in terms of the histological grading of the adenomas: of the adenomas found in the women with breast cancer 68% were tubular and 32% were tubulo-villous, while of those found in the control group 66% were tubular and 34% were tubulo-villous (table 4).

Time Interval, Adjuvant Therapy, Menstrual Status, Tumor Site, and Histological Grading

The interval between the diagnosis of breast cancer and colonoscopy was 3.5 ± 3.3 years for all women with breast cancer, and 4.9 ± 4.1 years for those with breast cancer and colorectal adenomas (n.s.).

In women with breast cancer receiving anti-estrogen therapy (n = 31) only 1 adenoma was observed as com-

pared to women who received no anti-estrogen therapy (n = 157) in whom 27 adenomas were detected. However, this trend failed to be significant (3.2 vs. 17.2%, p = 0.053, OR 0.16, 95% CI 0.0–1.1; table 6). Subsequent analysis of hormone receptor status revealed no difference between both groups. However, more women in the breast cancer group than in the control group were post-menopausal (59 vs. 48%, p < 0.02; table 3).

Prevalence of Adenomas with Regard to Indications for Colonoscopy

The prevalence of adenomas in the control group was analyzed with regard to the six indications for colonoscopy: most adenomas in the control group were found in patients with constipation (15.2%), followed by patients with abdominal pain (9.8%), occult or overt blood (9.1%), abdominal mass (8.1%), suspected neoplasia (7.6%), and diarrhea (5.9%). The two carcinomas in the control group were associated with the indication abdominal mass.

Discussion

In this cross-sectional study, women with primary breast cancer showed a higher risk of colorectal adenomas than matched controls with an OR of 1.7. The increased prevalence of adenomas in the breast cancer patients does primarily result from a significantly increased prevalence in the age group 65–85, in which 31% of the breast cancer patients have adenomas as compared to only 10% of the control group. Therefore, due to this observation and the fact that the time interval from breast cancer diagnosis to colonoscopy was similar in both groups, one could assume that the adenoma risk is predominantly increased in women with breast cancer who are older than 65 years.

So far, comparable cohort studies revealed conflicting data on this matter [9–16]. Studies with the result of an elevated risk did either not reach significance [13] or evaluated only the rectum and sigmoid colon [13–16]. In a study by Bremond et al. [14], a group of 145 women with breast cancer had a 2.5-fold higher incidence of colorectal adenomas than a control group (n = 144), when only the rectum and sigmoid were studied. Rozen et al. [15], and Jouin et al. [16], found colorectal adenomas to be 2.7–3.0 times more common in women with breast cancer than in controls. However, in most of their patients only a sigmoidoscopy was performed. On the basis of the increasing numbers of colorectal neoplasms found in the right colon in women [18], and the fact that women have a

higher incidence of right-sided colonic cancer than men [19], a complete colonoscopy as performed in our trial might be warranted. In one study, Murray et al. [12], were unable to find any increased adenoma rate (OR 0.7) in breast cancer patients, which, however, might be explained by the relatively small number (n = 43) of patients with breast cancer examined. These 5 studies [12–16] were summarized in a meta-analysis [9], revealing an increased risk of 1.7 for colorectal adenomas in women with breast cancer, a value similar to that observed in our study.

A more recent study analyzed the incidence of colorectal polyps in patients with a history of breast cancer in Taiwan [20]. The authors found colorectal adenomas and one carcinoma in 10 of 89 women. However, no control group was used.

The studies of Rozen et al. [15] and Rex et al. [11] analyzed population-based control groups, which are considered the most appropriate approach to the selection of a control group [9]. However, the volunteer group in the first study [15] was 5 years younger than the breast cancer group and, therefore, a bias due to the age dependence of colorectal tumors cannot be excluded. On the other hand, in the study of Rex et al. [11], the volunteer group was 5 years older than the breast cancer group. These points might explain why Rozen et al. [15] found a higher risk and Rex et al. [11] found a lower risk than in our study. Acquiring several hundreds of asymptomatic control patients for colonoscopy studies is difficult. Therefore, as in most other studies, we used in- and out-patients referred for colonoscopy. However, rather than using controls presenting with symptoms, it might have been better to have selected asymptomatic individuals presenting for colonoscopy screening, which is now widespread in Germany but was not when the study was initiated. However, it is also likely that small adenomas did not cause the symptoms. In order to exclude the bias of age, our study patients were age-matched with 2 control patients.

In our control group 40% of the women were examined for suspected neoplasia, abdominal mass, or occult or overt blood in the stools, indications with a high likelihood for colorectal neoplasias. Taking this fact into account, our calculated OR for the adenoma risk might rather be underestimated than overestimated. In this study, almost one third of the controls were excluded because of a prior malignant disease and of prior adenomas. Inclusion of these groups could have changed the findings significantly. On the other hand, the inclusion of patients with adenomas or malignomas as controls seemed even less appropriate.

Our study was not designed to establish the incidence of colorectal carcinomas in breast cancer patients since the number of expected cancer cases would be too small to show significant differences.

In a recently published paper, Newschaffer et al. [21] used the Surveillance Epidemiology and End Results (SEER) database to estimate the risk of colorectal cancer after a diagnosis of breast cancer in more than 200,000 women. Surprisingly they found that women with previous breast cancer were 5% less likely to develop colon cancer and 13% less likely to develop rectal cancer than women in a general population. The authors speculate that more vigilant screening in breast cancer patients might have lead to increased endoscopic removal of colorectal polyps and thus to less cancer development.

Although we did not intend to analyze differences in the respective breast cancer therapy groups we, interestingly, observed that women with breast cancer who received anti-estrogen therapy showed a trend towards a lower risk of adenomas than women who received no anti-estrogen therapy (table 6). The influence of anti-estrogen therapy on adenoma growth is a matter of speculation, but our data are consistent with recent observations [22]: anti-estrogen drugs prevent the development of cancer in patients who are at high risk of developing second primary tumors after surgical removal of the initial tumor. On the other hand, meta-analyses summing up studies on women with breast cancer who received tamoxifen showed that this drug had no apparent effect on the incidence of colorectal cancer [23, 24]. In addition, it is difficult to evaluate the effects of anti-estrogens in our study, if these patients received anti-estrogens with or without chemotherapy and radiation. Larger cross-sectional studies examining the chemopreventive effect of anti-estrogen drugs could possibly clarify their role in the prevention of colorectal adenoma growth.

Interestingly, more post-menopausal women were among the breast cancer patients than among controls. A recent paper showed that the menopausal status is considered a confounding risk factor (OR 1.5) for the development of colorectal cancer [25]. However, in that study the elevated cancer risk was only true for women who have never used hormone replacement therapy. We think that in our study the influence of the menopausal status is of only minor importance, since 43% of our breast cancer patients were treated with hormone replacement therapy and/or chemotherapy. Furthermore the most significant finding in our study, the difference between the adenoma rates in the age groups 65–85, was observed among women who were all post-menopausal.

A potential limitation of our analysis is that we have not analyzed genetic markers, like BRCA1, which could link breast with colorectal cancer [26]. However, other studies have not shown an increased colorectal cancer risk in *BRCA* mutation carriers [27, 28]. In addition, we excluded patients with a family history of one or more first-degree relatives with breast cancer or colorectal cancer. Other common pathogenetic factors that could explain differences, like obesity [29] or age, are unlikely as well, since both populations showed no differences with respect to age and body mass index (table 3).

In summary, our data suggest that women with breast cancer have about twice the risk of developing colorectal adenomas than women without breast cancer. This risk mainly seems to exist in those women with breast cancer who are older than 65 years. As a consequence of these observations, women with a diagnosis of breast cancer should especially be encouraged to participate in colorectal cancer screening programs, which, in most countries, call for screening of all average-risk individuals over the age of 50 years [30].

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