Patients with breast cancer may be at higher risk of colorectal neoplasia

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Abstract

Background The risk of colorectal neoplasia in breast cancer survivors is unclear. This study aimed to determine the colonic adenoma detection rate (ADR) in patients with breast cancer.

Methods We conducted a retrospective study of patients with breast cancer who underwent a colonoscopy between 2000 and 2017. A control group (n=3295), comprising cancer-free patients undergoing their first screening colonoscopy, was used for comparison.

Results Of 62,820 breast cancer patients, 3304 met the inclusion criteria. The mean age at the time of first colonoscopy was 59 years. ADR was 55%; 1803 patients had adenomas. High-grade dysplasia was evident in 28% of polyps and invasive adenocarcinoma was detected in 172 patients (5%). The median time from breast cancer diagnosis to adenoma detection was 3 years. The ADR was 21% in patients aged <40 years (n=63) and 39% in patients aged 40-50 years (n=314). The ADR was 26% in patients <50 years with a body mass index (BMI) lower than 30 kg/m^2 or no family history of colorectal cancer. Multivariate logistic regression analysis revealed that the following independent factors were associated with a greater risk of colon adenoma: older age, higher BMI, family history of colorectal cancer, and personal history of breast cancer.

Conclusion In patients with breast cancer, the ADR was higher than the reported rates for the general population. Screening colonoscopy should be considered soon after breast cancer diagnosis in patients <50 years of age. Further prospective studies investigating our findings are warranted.

Keywords Breast cancer, colorectal neoplasia, colorectal cancer, colon adenoma, screening, surveillance

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Introduction

With advances in cancer therapeutics and the development of early screening and cancer detection, as well as a multidisciplinary approach to therapy, the 5-year survival rates of patients with localized breast cancer and breast cancer spread to regional lymph nodes have improved to 98.7% and 85.3%, respectively; this translates into 2.8 million breast cancer survivors [1]. With such a significant proportion of survivors, it is imperative to ensure that the long-term well-being of these patients is ensured, particularly by active surveillance for the long-term consequences of breast cancer and the cancer therapies these patients were exposed to. One of the most concerning potential threats to the long-term well-being of cancer survivors is the occurrence of a second *de novo* malignancy.

Colorectal cancer (CRC) is among the most common cancers affecting the American population. With more than 140,250 Americans diagnosed annually and a 5-year survival of 64.5%, CRC remains a challenge for clinical oncologists and imposes a significant burden on the patients' well-being [2]. There has been speculation regarding the incidence of non-breast malignancies, and particularly CRC, among patients with a history of breast cancer, though the literature on this topic has been conflicting [3-5]. A positive correlation between breast cancer and CRC was found after pooling the findings of 5 cross-sectional and case-control studies, with a pooled relative risk of 1.74 (95% confidence interval [CI] 1.27-2.21) [6]. On the other hand, more recent case-control studies have questioned the validity of a presumed higher risk of CRC among breast cancer survivors [7-9].

The greater risk of CRC in breast cancer survivors has been attributed to conditions such as obesity, hormonal influences, and the potential genetic commonality in the origin of breast and colon oncogenesis, as is seen among patients with familial cancer syndromes such as hereditary nonpolyposis CRC [10-12]. However, none of these factors addresses the incidence of adenomatous polyps and their progression to CRC among patients with a history of breast cancer. The adenoma detection rate (ADR) in our institution for patients 50-70 years old (38%) is higher than the reported ADR in the general population (25-35%). Preliminary evidence in the form of case-control studies reveals conflicting results concerning the risk of developing adenomatous polyps in patients with a history of breast cancer [13-18]. Additionally, the current literature consists of studies with small sample sizes, and the body of evidence addressing this issue is limited.

The aim of this study was to determine the incidence of adenomatous polyps and CRC among patients with a history of breast cancer in a tertiary cancer center, which receives a high volume of breast cancer patients.

Patients and methods

This was a retrospective study of patients with a diagnosis of breast cancer who had undergone a colonoscopy after their breast cancer diagnosis between 2000 and 2017. This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Eligible patients were identified from our institutional tumor registry and endoscopy unit database. All patients had confirmed malignancy of the breast by histopathology. Patients with benign breast lesions or a personal history of CRC prior to breast cancer diagnosis were excluded. Our control cohort included all patients without a personal history of any type of cancer who underwent colonoscopic screening between 2008 and 2017.

Natural language processing and electronic medical chart review were conducted to extract information pertaining to demographics and medical and oncologic history. Demographics included age, sex, race/ethnicity, and body mass index (BMI) at the time of colonoscopy. Medical and oncologic history consisted of history of smoking, a first-degree relative with a history of CRC, breast cancer treatment modality, site of breast cancer and histologic type of breast cancer. The hormonal status of breast cancer (i.e., estrogen and progesterone positivity) was extracted from the breast cancer departmental database.

Colonoscopy data

The index colonoscopy performed after breast cancer diagnosis was recorded. Patients with poor preparation for the colonoscopy were excluded. The time from breast cancer diagnosis to first colonoscopy was calculated. Data regarding the colonoscopic assessment included the size of the polyp, the site of the polyp, the morphology of the polyp, and the method of polyp removal. The size of the polyp was divided into small (≤10 mm) or large (>10 mm). The site of the polyp was described as left colon if it was located distal to the splenic flexure and as right colon if it was located proximal to the splenic flexure. Sessile, pedunculated, flat, and diminutive or indeterminate were the morphological categories of the polyps.

Histologic evaluation was performed for all colonic lesions. The histologic subgroups of the colonic adenoma consisted of tubular, tubulovillous, villous, or serrated. The presence of high-grade dysplasia or advanced adenocarcinoma features in the colonic tissue was reported. Patients with inadequate histologic specimens were excluded. ADR was defined as the percentage of procedures where colonic adenomas were detected divided by the total number of procedures.

For patients in whom adenoma was detected during index colonoscopy, data regarding subsequent surveillance colonoscopies were also recorded and the ADR for all subsequent colonoscopies was documented. For these patients, the adenoma recurrence-free time was defined as the period from the index colonoscopy to the first subsequent colonoscopy with adenoma or the last subsequent colonoscopy without adenoma, whichever was earlier.

Statistical analysis

Descriptive statistical measures using means and standard deviations or medians with interquartile ranges for continuous variables were conducted. Categorical variables were summarized using frequencies and percentages. Fisher's exact and χ^2 tests were used to compare categorical variables. Wilcoxon rank sum and Kruskal-Wallis tests were used to compare continuous variables. To assess for factors associated with adenoma and adenoma recurrence on the repeat colonoscopy, univariate and multivariate logistic regression analyses were conducted. To assess predictors of early adenoma recurrence, we performed Cox regression model. Statistical tests were two-sided. P-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS (version 9.4; SAS Institute, Cary, NC, USA) and SPSS (version 24.0; IBM Corporation, Armonk, NY, USA) software.

Results

Patient characteristics

Of the 62,820 patients who had a breast cancer diagnosis during the study period, 3304 met the inclusion criteria. Most were female (99.6%), the mean age was 59 years (standard deviation, 10 years) and the majority were white (68.2%). A first-degree relative with a history of CRC was reported in 43.0% of patients and a history of smoking in 36.7% (Table 1). The clinical characteristics of patients in the control group (n=3295) compared with those of patients with breast cancer are listed in Supplemental Table 1.

Breast cancer history

Most patients had their breast lesion removed surgically without adjuvant therapy (56%). Of the patients who did receive adjuvant therapy, 10% received cytotoxic chemotherapy only and 38% received hormonal therapy in addition to cytotoxic therapy. Ductal carcinoma was the most common histologic type (65%), followed by lobular carcinoma (12%).

Colon polyps

Colon adenomas were detected in 1803 patients (55%) with breast cancer (Supplemental Table 2). Of these, 575 patients had more than one adenoma. Patients with colonic adenomas were older (P=0.001), had higher BMI (P=0.004), and reported a history of CRC in a first-degree relative more frequently (P<0.001) compared to patients without adenomas (Table 1). The median time from breast cancer diagnosis to first colonoscopy was 3 years (interquartile range, 1-6). The ADR for the control group was 29%.

Features of the colonic adenomatous polyps (n=2720 polyps) found in breast cancer patients are listed in Table 2.

Table 1 Characteristics of breast cancer patients with and without adenomatous polyps detected by colonoscopy (N=3304)

Characteristic	Polyps, n (%), (N=1803)	No polyps, n (%), (N=1501)	P
Age, years, mean (SD)	60.6 (9.1)	58.1 (9.9)	<0.001
Female	1796 (99.6)	1494 (99.5)	0.792
Race			0.716
White	1235 (68.5)	1018 (67.8)	
Black	255 (14.1)	223 (14.9)	
Hispanic	204 (11.3)	158 (10.5)	
Asian	90 (5.0)	80 (5.3)	
Other	19 (1.1)	22 (1.5)	
BMI, kg/m², mean (SD)	30 (7)	29 (7)	0.004
BMI>30 kg/m²	710 (43.4)	523 (40.0)	0.065
Family history of colorectal cancer	827 (45.9)	595 (39.6)	<0.001
Smoking	668 (37.0)	544 (36.2)	0.638
Breast cancer treatment			0.394
Surgery only	982 (54.5)	853 (56.8)	
Chemotherapy	115 (6.4)	90 (6.0)	
Endocrine therapy	706 (39.2)	558 (37.2)	
Type of breast cancer			0.284
Ductal	1166 (64.7)	983 (65.5)	
Lobular	220 (12.2)	166 (11.1)	
Mixed	192 (10.6)	137 (9.1)	
Inflammatory	21 (1.2)	21 (1.4)	
Other	204 (11.3)	194 (12.9)	
Breast cancer hormonal status (n=2617)			
Estrogen positive	1149 (79.8)	929 (78.9)	0.593
Progesterone positive	957 (66.9)	760 (65.2)	0.382
Either or both	1171 (81.3)	951 (80.8)	0.763

BMI, body mass index

Most polyps were located in the right colon (64%); of these, 135 (5%) were larger than 10 mm. Tubulovillous features were detected in 8% and villous features in 1% of polyps. Serrated adenoma was detected in 176 polyps (7%). High-grade dysplasia was evident in 28% of polyps. Invasive adenocarcinoma was detected in 172 patients (5%).

ADR by age and time from breast cancer diagnosis to colonoscopy

The ADR was 21% in the 63 patients younger than 40 years, 39% in the 314 patients between 40 and 50 years, 54% in the 1420 patients between 51 and 60 years, and 60% in the 1507 patients older than 60 years. ADRs of patients stratified by age and time from breast cancer diagnosis to colonoscopy are shown in Fig. 1. In patients 50 years or younger, the ADR was the highest if the colonoscopy occurred more than 10 years after breast cancer diagnosis. Among the same age group, the ADR was only 26% in patients who did not have a family history of CRC or a BMI higher than 30 kg/m^2 (Supplemental Fig. 1).

Factors associated with adenoma

On multivariate logistic regression analysis that included both patients with a history of breast cancer and the control group, older age, higher BMI, family history of colorectal cancer in a first-degree relative, and a personal history of breast cancer were associated with a higher risk of colon adenoma (Table 3).

Repeated colonoscopy evaluation

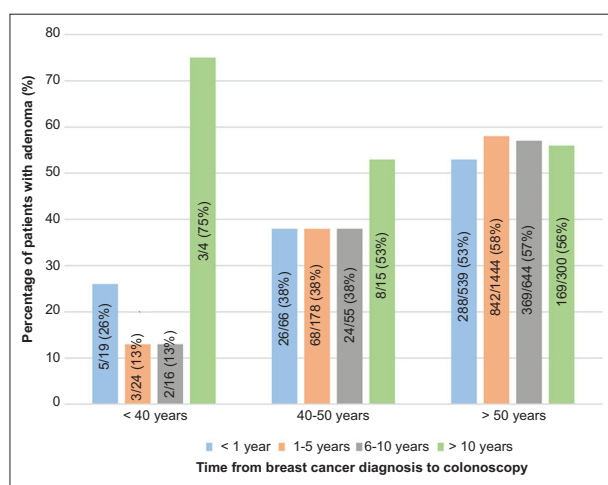A subsequent colonoscopy for any indication was performed in 831 patients in whom adenomas had been detected on the

initial colonoscopy. The ADR for the repeated colonoscopy was higher for patients whose second colonoscopy occurred more than 5 years after the first than for patients with shorter intervals (Table 4). The ADR for the repeated colonoscopy was higher (54%) for patients whose polyps had high-risk features for adenoma recurrence (i.e. more than 2 polyps,

Table 2 Polyp characteristics among patients with breast cancer

Characteristic	Polyps, n (%)(N=2720)
Site	
Right colon	1737 (63.9)
Left colon	983 (36.1)
Size	
>10 mm	135 (5.0)
≤10 mm	2585 (95.0)
Morphology	
Pedunculated	203 (7.5)
Sessile	1088 (40.0)
Flat	238 (8.8)
Diminutive	1191 (43.8)
Endoscopic removal	
Biopsy/forceps	1799 (66.1)
Hot snare	362 (13.3)
Cold snare	387 (14.2)
En bloc EMR	138 (5.1)
Piecemeal EMR	34 (1.3)
Histologic features	
Tubular	2305 (85.7)
Tubulovillous	225 (8.3)
Villous	14 (0.5)
Serrated	176 (6.5)
High grade dysplasia	752 (27.6)
Cancer	172 (6.3)

EMR, endoscopic mucosal resection

Table 3 Multivariate logistic regression: risk factors of adenoma (all patients, n = 6599)

Characteristic	Adenoma	
	OR (95%CI)	P
Age	1.04 (1.03-1.05)	<0.001
Male sex	0.60 (0.19-1.93)	0.393
BMI	1.01 (1.00-1.03)	0.022
Family history of colorectal cancer	1.30 (1.10-1.53)	0.002
Smoking	1.08 (0.91-1.28)	0.363
Breast cancer	2.97 (2.68-3.28)	<0.001
Positive hormonal status	0.94 (0.76-1.18)	0.608

BMI, body mass index; OR, odds ratio; CI, confidence interval

Figure 1 Adenoma detection rate among patients with breast cancer stratified by age and time from breast cancer diagnosis to colonoscopy

polyps larger than 10 mm, and histological confirmation of high-grade dysplasia or tubulovillous or villous features) than for patients without high-risk features (41%; P<0.001). Furthermore, the median adenoma recurrence-free time was 3 years (interquartile range 2-5), and it was shorter for patients whose polyps had high-risk features (3 years; interquartile range 2-4) than for patients whose polyps did not have such features (4 years; interquartile range 2-5; P<0.001).

Factors associated with adenoma recurrence

A first-degree relative with a history of CRC, a personal history of breast cancer, more than one polyp detected on the initial colonoscopy, and a polyp larger than 10 mm on the initial colonoscopy were factors associated with a high risk of adenoma recurrence (Table 5).

Factors associated with earlier adenoma recurrence

Old age, more than two polyps detected on initial colonoscopy and large (>10 mm) polyps on initial colonoscopy were associated with early adenoma recurrence (Table 6).

Discussion

This single-center retrospective study from a tertiary cancer center study assessed the incidence of adenomatous polyps in patients who had a history of breast cancer. Adenomatous polyps were detected in 55% of the study population, higher than the median ADR at our institution (38%). The ADR in patients younger than 40 years and between 40 and 50 years was 21% and 39%, respectively. Among patients younger than 50 years, the ADR was highest (>50%) among patients whose colonoscopy occurred 10 years after the breast cancer diagnosis. Our multivariate logistic regression analysis comparing patients with breast cancer to a control cohort also identified breast cancer as an independent risk factor for colon adenomas.

Our findings contradict the previously reported ADR among patients with a history of breast cancer. A meta-analysis of 6 case-control studies that reported ADR in patients with breast cancer revealed 67 and 47 incidences of polyp detection among cases and controls, respectively, translating into a pooled odds ratio of 1.5% (95%CI 0.97-2.2; P=0.07), with no heterogeneity (I^2=1%) [13-18]. It should be noted that this analysis only included polyps larger than 1 cm, an approach that would fail to account for smaller polyps, which according to our study constitute the majority of adenomatous polyps in breast cancer patients. Additionally, the ADRs in these case-control studies could have been influenced by a plethora of factors, including the recognized facets of a high-quality screening colonoscopy as well as the institutional ADR, not explicitly reported in these 6 studies. At our institution, the

Table 4 Adenoma detection rate by interval between first and second adenoma detection among patients with breast cancer

Time from first to second colonoscopy	No. of patients	Repeat colonoscopy ADR
<3 years	346	138 (39.9%)
3-5 years	279	138 (49.5%)
>5 years	206	109 (52.9%)

ADR, adenoma detection rate

Table 5 Logistic regression: risk factors for adenoma recurrence

Characteristic	Adenoma recurrence	
	OR (95%CI)	P
Age	1.01 (0.99-1.03)	0.223
BMI	1.01 (0.98-1.03)	0.563
Family history of colorectal cancer	1.68 (1.24-2.72)	0.001
Smoking	1.03 (0.76-1.39)	0.852
Number of polyps	1.84 (1.50-2.25)	<0.001
High-grade dysplasia	0.99 (0.67-1.48)	0.984
Polyp larger than 10 mm	1.24 (0.67-2.28)	0.490
Tubulovillous or villous features	1.55 (0.98-2.46)	0.061
Time from first to second colonoscopy	1.12 (1.05-1.21)	0.001
Breast cancer	1.92 (1.59-2.32)	<0.001

BMI, body mass index; OR, odds ratio; CI, confidence interval

Table 6 Cox regression: time to adenoma recurrence

Characteristic	Time to recurrence	
	OR (95%CI)	P
Age	1.01 (1.00-1.03)	0.044
Family history of colorectal cancer	1.17 (0.95-1.44)	0.137
Adenoma initially	1.30 (1.11-1.52)	0.001
High-grade dysplasia	1.01 (0.79-1.30)	0.926
Number of polyps	1.40 (1.29-1.51)	< 0.001
Polyp larger than 10 mm	1.73 (1.19-2.53)	0.004
Tubulovillous or villous features	1.19 (0.89-1.59)	0.250
Breast cancer	1.03 (0.89-1.19)	0.698

OR, odds ratio; CI, confidence interval

endoscopist turnover rate is low, which ensures consistency in the quality of endoscopy.

A significant proportion of the patients with adenomatous polyps had a first-degree relative with a history of CRC, were older, and had a higher BMI compared to patients without polyps. A higher BMI could act as a driver for their breast cancer and the development of adenomatous polyps. This finding conflicts with the hormonal aspect of colonic adenoma. Nonetheless, the hormonal status of breast cancer was not associated with a

greater risk of colorectal neoplasia in our cohort. Additionally, a history of CRC in a first-degree relative hints at a genetic susceptibility to the development of adenomatous polyps. The potential influence from obesity and a positive family history is further supported by the fact that, for patients younger than 50 years who were not obese or did not have a family history of CRC, the ADR was only 26%. However, since the majority of the patients were not referred for genetic counseling and testing, we were unable to evaluate the presence of genetic mutations and asymptomatic familial syndromes. This is reflective of real-world practice, in which the threshold for referral to conduct genetic testing for familial cancer syndromes or genetic susceptibility to the development of adenomatous polyps is high. Even among patients with a high risk of CRC, assessed by validated criteria for hereditary cancer syndromes such as hereditary nonpolyposis CRC, it has been reported that referral for genetic work-up and counseling is suboptimal [19,20].

Most of the polyps in our study were smaller than 10 mm, and 40% were sessile. Both of these factors have been shown to contribute to the polyp miss rate [21,22]. Additionally, a majority of the polyps were located in the right colon, which can potentially amplify the polyp miss rate if a flexible sigmoidoscopy is chosen over a colonoscopy. These factors should be taken into account in order to improve the ADR of colonoscopy, since detection of such smaller and inconspicuous polyps may require a more thorough colonic assessment, which in turn increases withdrawal time [21]. Furthermore, 6.5% of the polyps had a serrated histologic appearance. Serrated polyp detection may also require thorough colonic inspection, which further underscores the importance of a thorough colonoscopy.

Our findings also have implications for the timing of screening colonoscopy in patients with a history of breast cancer. Because the ADR for patients younger than 40 years was highest when the colonoscopy occurred more than 10 years after a breast cancer diagnosis, screening should be performed less than 10 years from the date of breast cancer diagnosis, or when the patient is 40 years old at the latest. It should be noted that, as most patients younger than 40 years without a family history of breast cancer will probably have undergone colonoscopy for gastrointestinal symptoms, this might have led to underestimation of the ADR in this patient population undergoing colonoscopy within 10 years of breast cancer diagnosis. However, for patients 40-50 years old, the ADR within 1 year of breast cancer diagnosis was 38%. Hence, the appropriate timing for a recommendation of screening colonoscopy should be dictated by the patient's age at the time of breast cancer diagnosis, and a screening colonoscopy within 1 year of breast cancer diagnosis for patients older than 40 years could be deemed appropriate.

The ADR for repeat colonoscopy increased as the time from index polyp detection to repeat colonoscopy increased, ranging from 40% when performed within 3 years of the index polyp detection to 53% when performed more than 5 years from the index polyp detection. Factors associated with early adenoma recurrence should be taken into account when making recommendations regarding the optimal surveillance interval. Our analysis revealed an association between early adenoma recurrence and old age and large and multiple polyps at initial

colonoscopy. A personal history of breast cancer was a risk factor for adenoma recurrence. Because the median adenoma recurrence-free time in our study was 3 years, repeat colonoscopy should be performed within 3 years of the index polyp removal.

In our study, the incidence of CRC among breast cancer survivors was 5%, higher than the 1.33% rate predicted by SEER for CRC incidence among women [23]. The high rate of invasive CRC identified in our study is further grounds for suggesting early screening colonoscopy for patients with breast cancer. The authors of previous studies have advocated for early screening colonoscopy for CRC in patients with a history of breast cancer. However, the literature on this issue has been conflicting. A meta-analysis of 1,055,917 patients with breast cancer found the pooled event rate for CRC to be 0.7% [18]. The pooled event rate in an analysis of 10 studies from the United States revealed an incidence of 1.1%. It should be noted that there was significant heterogeneity among the studies included in this meta-analysis (I^2=97%). As a tertiary cancer center, we had the advantage of a larger sample size of local patients, as well as national and international referrals, potentially reflecting the real-world breast cancer population.

Our study has some limitations that should be noted. The flaws of a retrospective design are inherent to our study. Additionally, subgroup analysis stratifying patients according to ethnicity was not performed; hence, it is not evident whether ethnicity plays a role in the development of adenomatous polyps in patients with breast cancer. In certain subgroups, a small sample size limited our ability to draw meaningful conclusions. As a considerable number of our cohort had colonoscopy for indications other than CRC screening, the ADR could have been underestimated. Lastly, although our low gastroenterologist turnover assures consistency in the quality of colonoscopy, we did not assess the impact of specific quality indicators, such as cecal intubation and withdrawal time, on the ADR.

In conclusion, patients with a history of breast cancer have a high incidence of adenomatous polyps in all age groups and a 5% incidence of invasive CRC. Screening colonoscopy for adenoma should be considered within 5 years of breast cancer diagnosis or by the age of 40 years, whichever comes first, for patients younger than 40 years at the time of breast cancer diagnosis. For patients older than 40 years, a screening colonoscopy within 1 year of breast cancer diagnosis would be appropriate. For patients in whom adenoma is detected, a repeat colonoscopy should be performed within 3 years of the index polyp detection. For patients in whom no adenoma is detected, a surveillance interval of 5 years may suffice. Future prospective studies with adequate sample size should be performed to validate our findings regarding the risk of developing adenomatous polyps and invasive CRC among breast cancer patients compared with a well-matched control group.

Acknowledgment

Summary Box

What is already known:

- Breast cancer is among the most common malignancies
- It has been suggested that breast cancer and its treatment may be linked with colorectal neoplasia
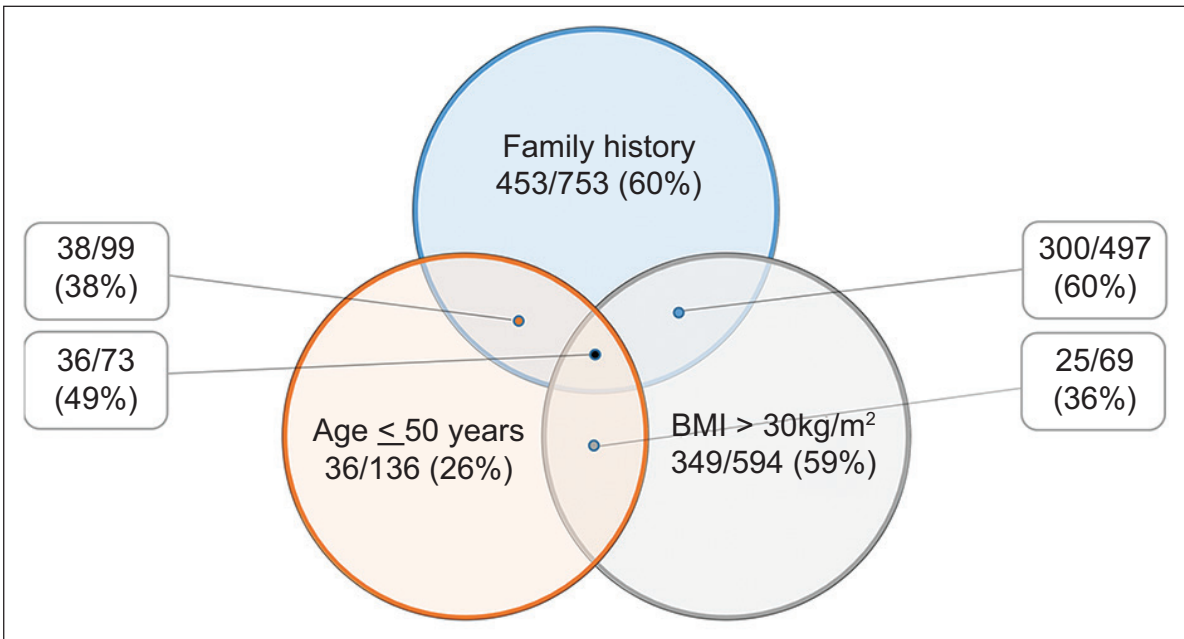- Studies have revealed conflicting results regarding this topic

What the new findings are:

- The rate of colon adenoma, a precursor for colorectal cancer, was higher in breast cancer survivors than in a cancer-free control cohort
- The rates of high-grade dysplasia and of colorectal cancer were also higher than in the control group
- Therefore, in breast cancer survivors, screening colonoscopy for colorectal cancer should be considered earlier than the age of 50 years, the age for colorectal cancer screening recommended by multiple societies

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Supplementary Figure 1 Venn diagram of adenoma detection rate according to the presence of risk factors (age, family history, and body mass index [BMI]) among patients with breast cancer