



Unrequited Returns in Asymptomatic Colorectal Cancer Detection

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Abstract

Aim: Colonoscopy has become the favored screening test for colorectal cancer. Measures have been identified since 2000 to enhance the quality of colonoscopy and to increase screening for at-risk persons. This study was designed to determine if changes in the rates of detection of colorectal cancer in asymptomatic persons are occurring. **Methods:** this is an observational study of a database of 887 patients taken from the colorectal cancer registry between 2006 and 2015. Participants were between 50 and 89 years of age and had initial detection of colorectal neoplasia by screen-detection or symptom-detection, and the clinical characteristics were compared. Rates of detection of colorectal cancer in asymptomatic and symptomatic persons were evaluated over five consecutive, two-year segments.

Results: 417 persons met the inclusion criteria. Screen-detected colorectal cancer occurred in 66 (16%) and symptom-detected in 351 persons and indicated the following: average age was 62.7 years vs. 71.3 years ($p=0.001$), men represented 66.2% vs. 49.6% ($p=0.014$), and early stage of disease was found in 69.7% vs. 43.9% ($p=0.001$). Race, family history, and location of disease were not different. Evaluation of the five two-year segments for changes in the rates of detection of screen-detected colorectal cancer did not demonstrate a significant change ($p=0.803$).

Conclusion: Persons with colorectal cancer who were detected by screening were significantly younger, more often men, and had lower stages of disease. Rates of screen-detected colorectal cancer remained stagnant over the decade of study, implicating a rejection by at-risk persons to undergo screening or a lack of referral for screening.

Introduction

Colorectal cancer mortality in the United States has been declining since 1975, yet in 2017 135,000 persons will be discovered to have colorectal cancer and 50,000 will die [1]. The decline in mortality from colorectal cancer since 1975 is attributed to 3 factors: 1) screening, accounting for 53% of the decline, 2) improved life style, accounting for 35%, and improved treatment, accounting for 12% [1,2]. Most of the benefit from screening is attributed to increased application of optical colonoscopy [1-3]. Colonoscopy has the advantage of being preventive by removing precancerous adenomas as well as by detecting early-stage cancer [4-7]. However, less than 30% of colorectal cancer cases are reported as being diagnosed before having symptoms [8-10], indicating that screen-detection approaches have not been reaching most persons with early-stage colorectal cancer. Increased public health emphasis on screening, including fecal occult blood testing, and improvements in the quality of colonoscopy [4-7,11], began over a decade ago as screening goals for all parameters were increasing from 25% in 2005 to 70% in 2015 [1,11]. The success of these efforts in increasing screen-detected colorectal cancer has not been demonstrated. This study was designed to evaluate the impact these measures had on the number of screen-detected cases of colorectal cancer between 2006 and 2015 as they relate to a large medical group practice in southwestern United States.

Methods

This is an Internal Review Board-approved, observational study of patients with colorectal cancer taken from the colorectal cancer registry of the Scripps Green Hospital in La Jolla, CA. Participants diagnosed between January 1, 2006 and December 31, 2015 with ages between 50 and 89 years were evaluated for initial detection of colorectal cancer based on screening measures versus diagnosis by symptom detection. Colorectal cancer was defined as adenocarcinoma between the cecum and the dentate line. The age of inclusion began with the age at which average-risk persons are first

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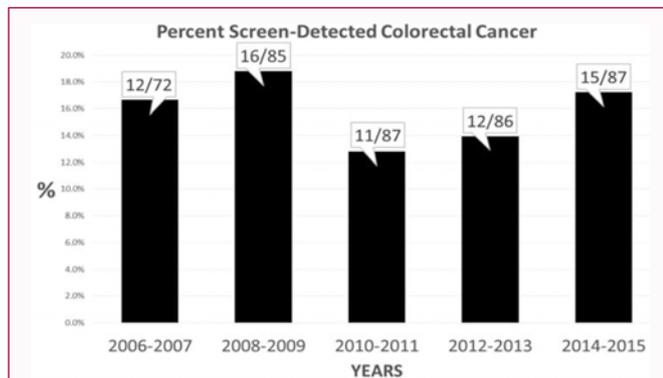


Figure 1: Time trend of percent of persons with screen-detected colorectal cancer compared to total study persons with colorectal cancer by two-year intervals.

advised to have a screening examination for colorectal cancer and ended at 3 years after the last age at which screening is recommended in select persons [1,3,4]. All persons were diagnosed and treated at the Scripps Green Hospital and satellite facilities. The electronic medical record for each person was reviewed by the author to verify the primary results. Persons were excluded who were diagnosed at an outside institution and transferred to Scripps Green Hospital, as were persons with a history of colorectal cancer, colon adenomas, prior colonoscopy, inflammatory bowel disease, non-adenomatous colon cancer, Lynch and other familial colorectal cancer syndromes, or an incomplete record. Stage of disease was divided into early or late at the inflection point between Stage II-A and Stage II-B, which separates those not recommended for adjuvant therapy from those who are [12]. Symptomatic persons were evaluated for the dominant sign or symptom, which was included in 1 of 5 categories; rectal bleeding, iron deficiency anemia, abdominal pain, persistent change in bowel habit, or miscellaneous, the latter encompassing weight loss, ascites, prolonged fatigue or fever. The subjects underwent bowel preparation with a minimum of 24-hr, clear liquid diet and standard laxation with sodium phosphate or polyethylene glycol (Suprep, Go-LYTELY, NULYTLY, Braintree Laboratories; Moviprep, Salix Pharmaceuticals). All colonoscopy examinations were performed by one of sixteen experienced, board-certified gastroenterologists or gastroenterology fellows-in-training under direct supervision in either an accredited hospital or an outpatient endoscopy room in 30 min to 45 min time slots. Each staff examiner had a minimum experience of 500 to over 5000 colonoscopies at the outset of the study and met benchmark rates for adenoma detection, cecal intubation, duration of withdrawal time and low rate of complications. Each examiner performed an average of 600-1000 endoscopic examinations per year. All examiners were fully aware of the need for examination withdrawal time of at least 6 or more minutes, the importance of reaching the cecum in all cases, meeting or exceeding minimum adenoma detection rates, the utility of retroflexed evaluation of the proximal colon and rectum, and the necessity of a well-prepared colon for a quality examination. Any cases not meeting these requirements were to have a repeat evaluation in the immediate future. Compliance was determined during periodic assessments by the Quality Assurance Team of Scripps Green Hospital and the satellite facilities. The examination rooms were equipped with high-definition Olympus colonoscopes with narrow band imaging beginning in 2005 and reaching comparable equipment with Olympus 180 colonoscopes in all rooms by 2013. All pathology readings were by experienced board-certified pathologists who held daily conferences

for group review of complicated cases. Fecal occult blood tests used the guaiac method from 2006-2009 and fecal immunochemistry test (Polymedco) from 2010 through 2015. The participants were divided by two primary end-points: 1) persons who were asymptomatic and deemed screen-detected by colonoscopy, with or without a current positive screening fecal occult blood test; and 2) persons diagnosed based on symptoms and deemed symptom-detected. These two categories were compared for age, sex, race, positive family history of colorectal cancer in at least one first degree relative, location of disease, and early versus late stage of disease. The location of disease was divided between proximal colon (cecum to splenic flexure) and distal colon (descending colon to rectum). Demographics and clinical characteristics of the study population were summarized using a mean and standard deviation for the continuous variable (age) and frequencies for the categorical variables (sex, race, family history, cancer location, and stage of disease). An independent sample t-test and chi-square tests were used to assess differences in demographics and characteristics between screen-detected and symptom-detected persons. Chi-square tests were used to compare the overall ratio of screen-detected vs. symptom-detected persons across all years, as well as between each of the five consecutive, two-year segments. SPSS version 13.0 was used for all analyses (SSPS Inc, Chicago, Illinois). Statistical significance was set at $p < 0.05$.

Results

The Scripps Green Hospital colorectal cancer registry contained 887 entrants between January 1, 2006 and December 31, 2015, of which 417 met the inclusion criteria. Of the 470 persons excluded from the analysis, 154 had had prior colonoscopy evaluation, 115 were non-analytic cases originally evaluated at other institutions, 102 were too young, 34 were too old, 23 had neuroendocrine cancers, 13 had synchronous colorectal cancer, 11 had an incomplete record, 7 had squamous cell cancers, 7 had Lynch syndrome, and 4 had inflammatory bowel disease. Persons with screen-detected colorectal cancer numbered 66 out of 417 persons (16%). Within the two years preceding diagnosis of colorectal cancer, 14 of the 66 screen-detected persons had a positive screening fecal occult blood test (21%), which initiated the pre-symptomatic colonoscopy examination, 10 had a negative fecal occult blood test (15%), and 42 were not tested (64%). The 66 diagnoses by screening colonoscopy were randomly shared among the 16 examiners with a range of 1-9 diagnoses per examiner, which generally corresponded to the number of screening examinations performed. The dominant sign or symptom leading to symptom-detected colorectal cancer in 351 persons was rectal bleeding in 125 (36%), iron-deficiency anemia in 115 (33%), abdominal pain in 75 (21%), persistent change in bowel habit in 21 (6%), and miscellaneous in 15 (3%). An abdominal computerized Tomographic scan was abnormal in 74 of the 351 symptomatic persons prior to the diagnosis of colorectal cancer. A comparison of the age, sex, race, family history, location of disease, and stage of disease of the 66 screen-detected persons to the 351 symptom-detected persons with CRC led, respectively, to the following: the average age was $62.7 + 9.6$ years vs. $71.3 + 11.0$ years ($p < 0.001$), men represented 66.2% vs. 49.6% ($p < 0.014$), race was predominantly Caucasian at 92.3% and 91.4% ($p < 0.805$), positive family history for at least one first degree relative was present in 13.3% vs. 18.9% ($p < 0.303$), the cancers were distributed equally between the proximal and distal colon, and early stage of disease was found in 69.7% vs. 43.9% ($p < 0.001$) (Table 1).

After dividing the cases into five consecutive 2-year partitions,

Table 1: Demographics and characteristics of screen-detected and symptom-detected persons with colorectal cancer.

	Screen-detected (N=66)	Symptom-detected (N=351)	p-value
Age	62.7 ± 9.6	71.3 ± 11.0	< 0.001
Sex			0.014
Male	66.20%	49.60%	
Female	33.80%	50.40%	
Race			0.805
Caucasian	92.30%	91.40%	
Other	7.70%	8.60%	
Family history [†]			0.22
Yes	8.30%	14.20%	
No	91.70%	85.80%	
Cancer location ^{**}			0.529
Proximal colon	51.50%	47.30%	
Distal colon	48.50%	52.70%	
Stage of disease [†]			< 0.001
Early	69.70%	43.90%	
Late	30.30%	56.10%	

the data indicated no significant change within the partitions for screen-detected cases, which were evenly distributed over the 5 biennial segments ($p=0.803$) and the ratio did not exceed 18%. There was no significant difference between the results within the 5-year segments (all p values >0.05), and the number of persons having screen-detected colorectal cancer remained relatively consistent over the decade of study, never exceeding 20% of the total (Figure 1).

Discussion

Colonoscopy is recognized as the only screening technique which offers early detection of asymptomatic colorectal cancer as well as prevention of colorectal cancer by removal of precancerous adenomas [4-7]. The application of colonoscopy for colorectal cancer screening proliferated dramatically over the past 17 years, increasing from 34% in 2000 to 63% in 2015 [1]. These results were propelled by two main factors, the clinical demonstration of benefit and the cost coverage of screening colonoscopy by private insurance and Medicare [1,2]. Randomized studies of fecal occult blood testing and flexible sigmoidoscopy demonstrate significant, albeit modest, reductions in the incidence and mortality of colorectal cancer [13-15], while colonoscopy takes its mantle from observational, case-control and prospective cohort studies which estimate reductions in colorectal cancer incidence and mortality to lie between 20% and 50% [1,15,16]. The numeric extent of the benefits for colonoscopy in randomized, controlled trials remains to be quantified, as several studies are underway evaluating variations of annual fecal immunochemistry test or colonoscopy *vs.* no screening and fecal immunochemistry test *vs.* one-time colonoscopy on incidence and mortality [18-20].

This analysis had one primary objective: to determine if enhanced colonoscopy techniques, made apparent over the past 12 years, in conjunction with intensified advocacy of colonoscopy, fecal occult blood tests, and any other screening for at-risk persons were leading to increased numbers of persons with screen-detected colorectal cancer as opposed to symptom-detected colorectal cancer. The results indicated no demonstrable rise in the number of screen-detected colorectal cancer between 2006 and 2015. At no point in the study did

the needle move to indicate screen-detected cases even reaching 20%. Consequently, the remaining 80% to 85% of persons with colorectal cancer had established symptoms before diagnosis. These results overlap and extend data from the Massachusetts General Hospital which evaluated 1071 persons with colon cancer, (not including rectal cancer), between 2004 and 2011 and reported 217/ 1071 persons (20.3%) having screen-detected colon cancer, (having excluded 1.9% of persons with a positive Hemoccult test for blood as a screening examination) [8]. The combined reports document the stagnant nature of the 20% to 30% ceiling for screen-detected colorectal cancer with the current study extending data another 4 years to 2015. One might have predicted a gradual rise in screen-detected colorectal cancer over the decade of evaluation due to improved colonoscopy technique. A reciprocal fall in interval cancers is associated with endoscopists who demonstrate high or improved adenoma detection rates over time [21,22] or have a longer withdrawal time [23]. However, reports from one of these centers that has employed systematic quality assessments of adenoma detection rates since 2000 also noted only a modest rise in screen-detected cases from 0.8 to 0.9% between 2000-2004 and 2004-2008 [22,24]. No rise occurred in the present study.

The dismal results found in the current study implicate the rate-limiting step for a timely diagnosis as the failure of patients to receive an initial deep screening test at a pre-symptomatic stage that might have been accomplished by a fecal occult blood test or direct referral for colonoscopy. The fault may lie at several areas, including a lapse in appropriate referral, reluctance, procrastination or rejection by the patient, or extensive co-morbidities [4-7]. Inadequate quality of endoscopy, unavailability of resources, and undue costs did not appear applicable to this population. When taking into account the attendance rates in several large, no-cost screening studies of persons being invited to have either fecal immunochemistry test or colonoscopy that show uptakes of about 40% and 25% [18,26,27], the results suggest that most of the failure lies with the persons-at-risk not agreeing to participate, simply procrastinating, or not being referred.

Over the decade of this study the average age of the unscreened, symptom-detected persons was 71.3 +11.0 years, representing 8.6 years more than the average age of the screen-detected persons. A concern might be the appropriateness of screening for the upper range of this group that has reached an older age without screening and is now facing increased risks for other fatal diseases. However, this study and others confirm intuitive expectations that early detection of colorectal cancer leads to an earlier stage of disease [8-11], and an early stage of disease is associated with a concomitant reduction in morbidity and mortality with longer survival, reduced requirements for treatment, less suffering, and lower costs [8-11,28,29]. Leading experts have recommended that unscreened persons in this age category who are physically fit be carefully considered for screening, with colonoscopy being the preferred test [4-6,25]. This analysis has several strengths as well as limitations. The strengths include the use of primary data representing quantitative information obtained from the electronic medical records from a single institution that was collected for scientific purposes. Each case was evaluated individually by the author, and the clinical management represented a standard of care that was stable over the decade of evaluation. The colonoscopy examinations were performed by a consistent team of experienced endoscopists each of whom averaged between 600 and 1000 endoscopic examinations per year. Although the denominator for the total number of patients at risk for colorectal cancer for this

institution was not available, the comparative number of total cases in each of the five 2-year partitions documented remarkable stability during this decade, and the total number of colorectal cancer cases per year was almost identical to that in a report from previous years [30]. Limitations include that the examinations were not individually assessed for quality nor were all video photos reviewed leaving the possibility that some examinations were incomplete, although this would not likely have changed the primary results. A remote possibility remains that cases in this southwestern United States area had differences in life-style, occupations, and education that make it unaccountable to a broader population. Likewise, confounding biases may have been present which were unrecognized.

The outcomes from this and related analyses suggest that the causes for reduction in the incidence and mortality of colorectal cancer are less related to screening than previously thought and that efforts toward increased screening have an appreciable margin for improvement [1,31-33]. Although colonoscopy remains an established asset for its ability to detect and remove precancerous adenomas, the full value of early detection of colorectal cancer has been muted, and the expectations for screening colonoscopy have not been required. This study indicates the apparent sources of the defaults, thus identifying targets for improvement.

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