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REVIEW

The History of Colorectal Cancer Screening: A Personal Perspective

Sidney J. Winawer

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Abstract The present explosive interest in screening for colorectal cancer (CRC), one of the most prevalent and preventable cancers, had its beginnings at a hospital in London and an Internist's office in Ohio. Demonstrated there were the concepts that CRC did not occur de-novo but arose from a premalignant polyp, that detection of the resultant cancer at an earlier stage was associated with better survival and that cancer could be detected at an early presymptomatic stage by screening. Many years later, the introduction of colonoscopy and colonoscopic polypectomy provided the opportunity for randomized trials to prove that these concepts were true. The sequence of rigorous science followed by guidelines consensus and then multilevel national efforts of screening implementation has resulted in a decline in the CRC incidence and mortality worldwide, most significantly in the USA. Campaigns have been initiated to maximize population screening and further investigate its optimal approach. Some historical details of this success story and many of the key participants are presented in this paper.

Keywords Colorectal cancer screening · History of colorectal cancer screening · Polyp-cancer sequence and screening · Colorectal cancer · Colon polyps · Colonoscopy · Stool blood testing

The adage that "we see more clearly when we stand on the shoulders of others" rings true for colorectal (CRC) screening. The outstanding opportunities we now have to save lives from this highly preventable disease evolved over many years and from the efforts of many people. It has been a great privilege for me to be directly involved in much of the evaluation of CRC screening. This is a review of its history from a very personal perspective.

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The Beginning

In May 1927, Lockhart-Mummery and Dukes published a paper in Surgery, Gynecology and Obstetrics entitled, "The Precancerous Changes in the Rectum and Colon" (Fig. 1). They clearly demonstrated that CRCs were associated with residual adenomatous tissue. Thus, began the concept that CRC did not arise de-novo from the colonic mucosa but from a preexisting lesion [1, 2]. In subsequent studies during the 1930s, Dukes and colleagues developed the first staging system for CRC and showed that better patient survival accompanied a diagnosis and surgery at an earlier stage. These amazing discoveries were made at St. Marks Hospital in London, an institution that was dedicated first to the relief of the poor afflicted with rectal fistulae and later to the full spectrum of gastrointestinal diseases including inflammatory bowel disease and familial polyposis (as it was then called) and other benign disorders as well as cancer. Their early discoveries opened the door to the concept of detection of early-stage curable cancer and cancer prevention through polypectomy. Morson coined the term "polyp-cancer" sequence for CRC (Fig. 2) [3]. Vogelstein and colleagues later demonstrated the somatic mutations that accompanied this sequence (Fig. 3) [4]. The polyp-cancer sequence was challenged by many for 76 years [5] until it was finally proven in 1993 by the National Polyp Study (Fig. 11) [6].

In the early years, clinical methods to achieve these goals through screening were suboptimal. It was suspected

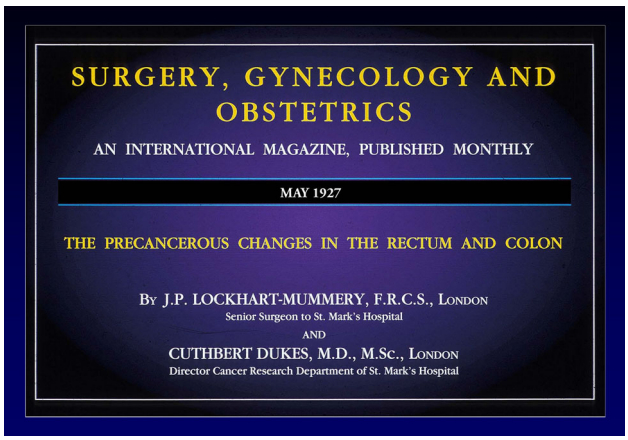

Fig. 1 Lockhart-Mummery and Dukes discovered the relationship of CRC to preexisting adenomas, a concept that was challenged until the NPS later demonstrated that CRC was prevented by identifying and removing adenomas

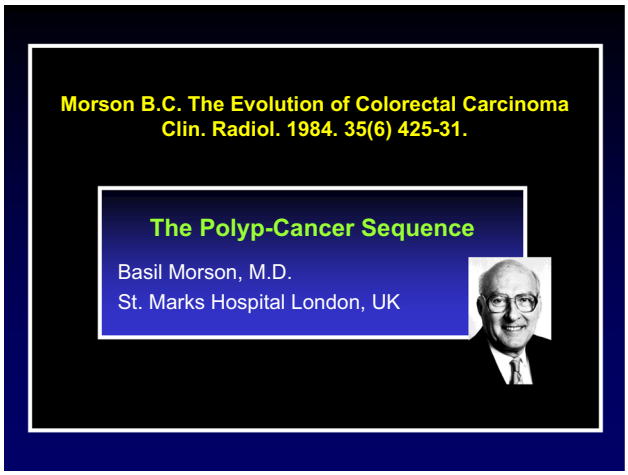

Fig. 2 Basil Morson was a preeminent gastrointestinal pathologist at St. Marks Hospital in London, who coined the term polyp-cancer sequence based on the eloquent work there of several clinical scientists including Lockhart-Mummery, Dukes and Muto

that occult bleeding preceded gross bleeding and the other symptoms of CRC but reliable detection of occult blood was not available. Patients were asked to bring in whole stool specimens for laboratory testing with benzidine, later shown to be carcinogenic to users, or bench guaiac testing with a series of three reagents, which was not very reproducible.

The rigid sigmoidoscope was not a very popular alternative either among patients or physicians. First developed at Hopkins by Kelly in 1895, it evolved into an instrument 25 cm in length, but only the most experienced colorectal surgeons could insert it up to its full length, usually with considerable patient discomfort (Fig. 4).

Some colorectal surgeons, such as the group at the Memorial Cancer Hospital in New York (later to become Memorial Sloan Kettering Cancer Center), could insert longer rigid scopes to the splenic flexure—sometimes, and with general anesthesia. This was usually prompted by an abnormal finding on barium enema somewhere in the distal colon up to the splenic flexure. It was not a joyful experience and not widely practiced.

However, not to be discouraged, two colorectal surgeons felt that rigid sigmoidoscopy could be used for CRC screening in asymptomatic people, the first effective clinical application of the concept of CRC screening. Gilbertsen initiated a rigid sigmoidoscopy screening study at the University of Minnesota in 1948, enrolling a staggering 21,500 people, and demonstrated an 85 % lower than expected incidence of CRC compared to the general population, and a 64 % 5 year survival in detected CRCs. These were amazing results. Although the study had many flaws; it was not randomized, with no control group, and follow-up was not complete and pathology of removed polyps not always known, but still it was a tour de force (Fig. 5) [7]. Hertz and Deddish at the Strang Clinic in New York City duplicated Gilbertsen's results in collaboration with Memorial Hospital. In 1960, they reported the feasibility of sigmoidoscopy screening in 26,000 asymptomatic people and a 90 % survival in 58 patients with detected CRC, followed for over 15 years [8].

There were major problems with the sigmoidoscopy approach. Not only was it labor-intensive and not very well accepted around the country, but it resulted in major surgery. A barium enema performed in people with a rectosigmoid polyp showed additional polyps higher up in the colon in 50 % of people. This necessitated hospital admissions, laparotomy and multiple colotomies to remove the demonstrated polyp and to search each colon segment intraoperatively with a rigid scope for additional polyps. The mortality and morbidity were significant.

The Modern Era

The CRC screening landscape changed dramatically with several technological advances. In 1967 Greegor reported finding early-stage CRC by means of a new guaiac card test that could be prepared at home (gFOBT) (Fig. 6) [9]. He was an Internist working by himself in a primary care practice. Greegor observed that patients with CRC usually had gross rectal bleeding and that it was intermittent and worsened by a diet rich in fiber. He postulated that perhaps he could detect the cancers earlier by using the cards to detect occult blood from the cancers at an early stage. The test was done at home on a high-fiber diet, over 3 days with restriction of meat, peroxide-rich foods and medicine such

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GENETIC ALTERATIONS DURING COLORECTAL-TUMOR DEVELOPMENT

BERT VOGELSTEIN, M.D., ERIC R. FEARON, B.A., STANLEY R. HAMILTON, M.D., SCOTT E. KERN, M.D., ANN C. PREISINGER, B.A., MARK LEPPERT, PH.D., YUSUKE NAKAMURA, M.D., PH.D., RAY WHITE, PH.D., ALIDA M.M. SMITS, B.S., AND JOHANNES L. BOS, PH.D.

Abstract Because most colorectal carcinomas appear to arise from adenomas, studies of different stages of colorectal neoplasia may shed light on the genetic alterations involved in tumor progression. We looked for four genetic alterations (*ras*-gene mutations and allelic deletions of chromosomes 5, 17, and 18) in 172 colorectal-tumor specimens representing various stages of neoplastic development. The specimens consisted of 40 predominantly early-stage adenomas from 7 patients with familial adenomatous polyposis, 40 adenomas (19 without associated foci of carcinoma and 21 with such foci) from 33 patients without familial polyposis, and 92 carcinomas resected from 89 patients.

We found that *ras*-gene mutations occurred in 58 percent of adenomas larger than 1 cm and in 47 percent of carcinomas. However, *ras* mutations were found in only 9 percent of adenomas under 1 cm in size. Sequences on chromosome 5 that are linked to the gene for familial adenomatous polyposis were not lost in adenomas from the patients with polyposis but were lost in 29 to 35 percent of adenomas and carcinomas, respectively, from other patients. A specific region of chromosome 18 was deleted frequently in carcinomas (73 percent) and in advanced adenomas (47 percent) but only occasionally in earlier-stage adenomas (11 to 13 percent). Chromosome 17p sequences were usually lost only in carcinomas (75 percent). The four molecular alterations accumulated in a fashion that paralleled the clinical progression of tumors.

These results are consistent with a model of colorectal tumorigenesis in which the steps required for the development of cancer often involve the mutational activation of an oncogene coupled with the loss of several genes that normally suppress tumorigenesis. (N Engl J Med 1988; 319:525-32.)

Fig. 3 Vogelstein reported observations on somatic mutations that occurred in the polyp-cancer sequence. Although not directly related to screening, initially it provided the foundation for later studies of DNA mutation stool tests and laid the groundwork for understanding CRC biology, and targeted treatment of CRC

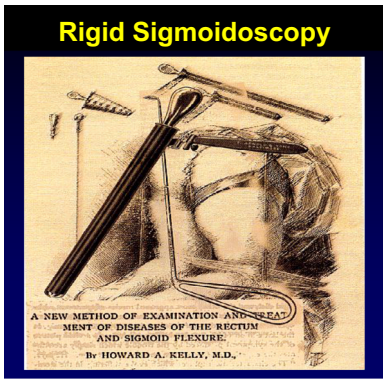


Fig. 4 The rigid sigmoidoscope was initially introduced at Johns Hopkins by Kelly in 1895

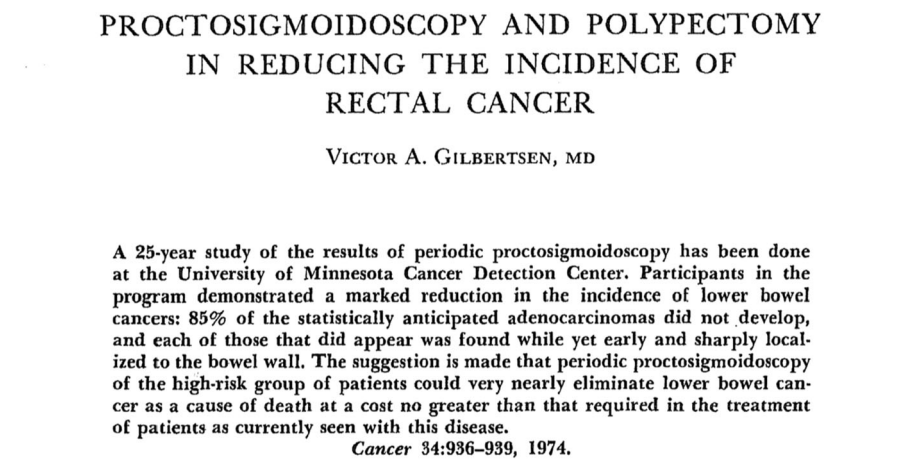
as aspirin that could produce bleeding. He followed up positive patients with a barium enema, did yearly testing of negative patients and continued to follow all of his patients in his office for many years. Dr. Gregor was an excellent clinical investigator as evidenced by the high adherence and good follow-up of his patients. He said that he did not think that he missed a cancer in his patient population. Commercialization of Hemoccult by Smith Kline Diagnostics led by Kay paved the way to widespread use.

The Challenge of Screening Bias

The effectiveness of gFOBT in CRC screening was challenged. A predominance of early-stage cancers could have resulted from length bias, detecting slow growing cancers with a long natural history, and thus a greater likelihood of being found by a one time test. Many of the detected cancers might never have surfaced clinically (overdiagnosis), and the cancers that did surface may have been detected earlier resulting only in a longer identification of the presence of the cancer but with no change in the natural history and outcome (lead time bias). The only way to eliminate the impact of these biases was to conduct a randomized control trial (RCT) to determine whether CRC screening reduced CRC mortality in the entire cohort.

There were, however, several concerns in mounting such trials. They would require large cohorts, and screening would have to be done periodically rather than once in order to "catch" the intermittent bleed from cancers. This would require high patient adherence.

A catalyst for the RCTs was the introduction of the colonoscope into clinical practice in the early 1970s. Prototypes were developed in the USA by Overholt [10] and in Japan by Niwa [11]. By 1973, excellent scopes were available, and there was expertise in the community albeit limited. For the first time, patients with a positive gFOBT could have an accurate diagnostic workup. In addition, in 1973, the feasibility of removing polyps through the colonoscope was reported by Wolff and Shinya thus adding a new and potentially huge preventive factor to CRC screening [12]. The combination of gFOBT with at-home stool cards for screening together with the diagnostic and therapeutic potential of the colonoscope provided the basis for launching the first CRC screening RCTs (Figs. 7, 8).



PROCTOSIGMOIDOSCOPY AND POLYPECTOMY IN REDUCING THE INCIDENCE OF RECTAL CANCER

VICTOR A. GILBERTSEN, MD

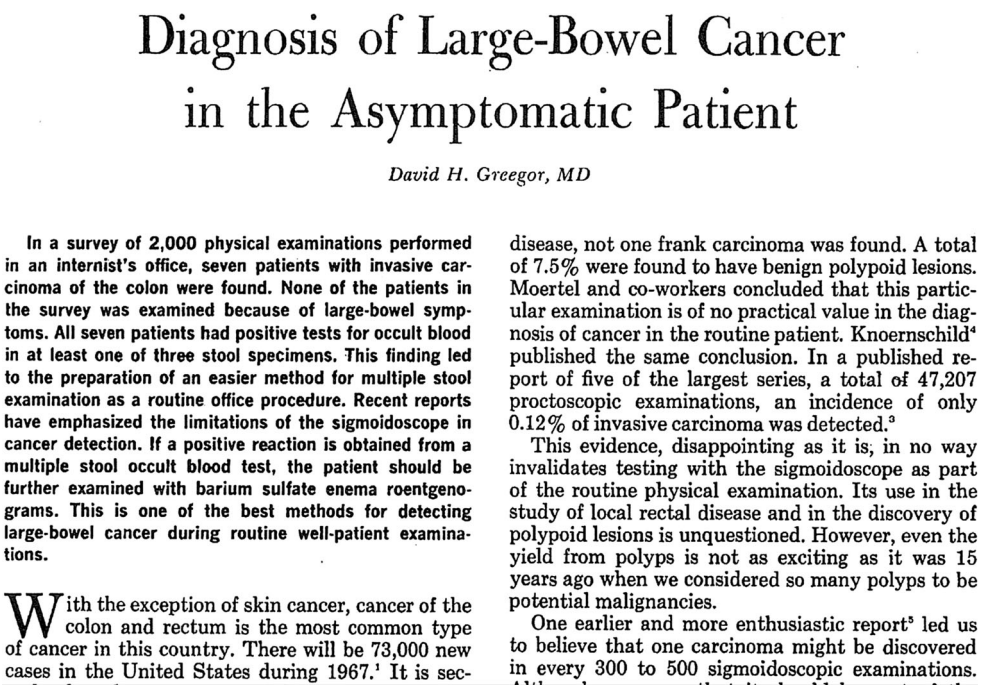
A 25-year study of the results of periodic proctosigmoidoscopy has been done at the University of Minnesota Cancer Detection Center. Participants in the program demonstrated a marked reduction in the incidence of lower bowel cancers: 85% of the statistically anticipated adenocarcinomas did not develop, and each of those that did appear was found while yet early and sharply localized to the bowel wall. The suggestion is made that periodic proctosigmoidoscopy of the high-risk group of patients could very nearly eliminate lower bowel cancer as a cause of death at a cost no greater than that required in the treatment of patients as currently seen with this disease.

Cancer 34:936–939, 1974.

PROBLEMS ASSOCIATED WITH TREATMENT OF patients with cancers of the large intestine continue to be of substantial concern in efforts for more adequate cancer control. This is one of the very most common visceral cancers. Half or more of those who develop intestinal cancer die of the disease, and a large proportion of patients continue to be seen only after their cancers have spread to such

at the Cancer Detection Center at the University of Minnesota.[2] Our findings suggest that substantial reduction is possible in the morbidity from intestinal cancer and that the risk of death from cancer of the lower bowel—the proctosigmoidoscopic area—can be virtually eliminated. Our studies are now of 25 years' duration, 18,158 patients have participated in the study, and 103,645 examinations

Fig. 5 The first large population screening study was launched at the University of Minnesota by Victor Gilbertsen in 1948, who was also a key visionary in the subsequent gFOBT RCT conducted at that institution



Diagnosis of Large-Bowel Cancer in the Asymptomatic Patient

David H. Greegor, MD

In a survey of 2,000 physical examinations performed in an internist's office, seven patients with invasive carcinoma of the colon were found. None of the patients in the survey was examined because of large-bowel symptoms. All seven patients had positive tests for occult blood in at least one of three stool specimens. This finding led to the preparation of an easier method for multiple stool examination as a routine office procedure. Recent reports have emphasized the limitations of the sigmoidoscope in cancer detection. If a positive reaction is obtained from a multiple stool occult blood test, the patient should be further examined with barium sulfate enema roentgenograms. This is one of the best methods for detecting large-bowel cancer during routine well-patient examinations.

With the exception of skin cancer, cancer of the colon and rectum is the most common type of cancer in this country. There will be 73,000 new cases in the United States during 1967.[1] It is sec-

disease, not one frank carcinoma was found. A total of 7.5% were found to have benign polypoid lesions. Moertel and co-workers concluded that this particular examination is of no practical value in the diagnosis of cancer in the routine patient. Knoernschild[4] published the same conclusion. In a published report of five of the largest series, a total of 47,207 proctoscopic examinations, an incidence of only 0.12% of invasive carcinoma was detected.[3]

This evidence, disappointing as it is, in no way invalidates testing with the sigmoidoscope as part of the routine physical examination. Its use in the study of local rectal disease and in the discovery of polypoid lesions is unquestioned. However, even the yield from polyps is not as exciting as it was 15 years ago when we considered so many polyps to be potential malignancies.

One earlier and more enthusiastic report[5] led us to believe that one carcinoma might be discovered in every 300 to 500 sigmoidoscopic examinations.

Fig. 6 The first significant clinical application of FOBT stool testing was conducted by David Greegor an Internist working by himself in a busy office practice using the newly available guaiac cards

RCTs Provide Validity for CRC Screening

Three RCTs were initiated in the 1970s in the USA first by Mandel, Bond, Church, and colleagues [13] and later in Europe, by Hardcastle [14] and Kronborg [15] and their colleagues. These trials used the gFOBT cards in a program of periodic testing with colonoscopy in positive patients. All three demonstrated that CRC screening reduces CRC mortality. Overall, mortality was of course not affected since CRC only contributes a small part to overall mortality. There was even a small reduction in CRC incidence demonstrated in the USA (UMinn) study.

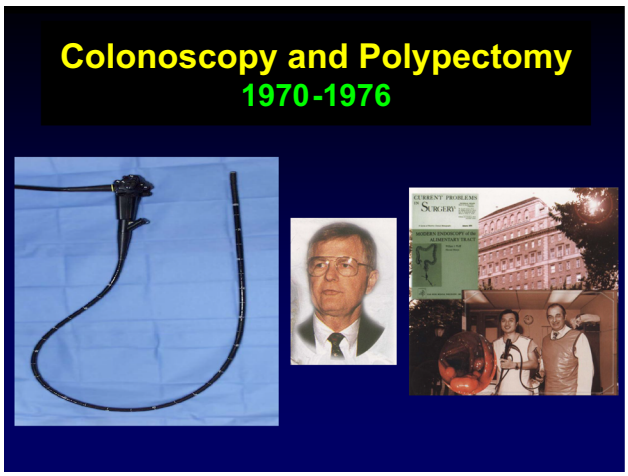


Fig. 7 Technological developments changed the landscape of CRC screening, diagnosis and treatment (polypectomy) following the pioneering work of Overholt who introduced colonoscopy in the USA along with Niwa in Japan, and the pioneering work of Wolff and Shinya who introduced the feasibility of colonoscopic polypectomy

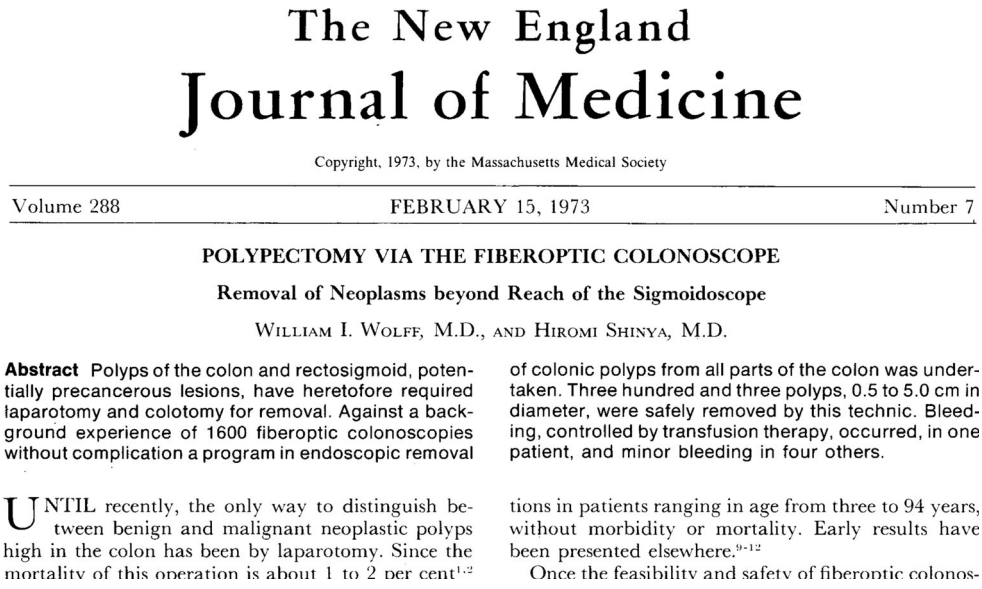
The trial results were an investigator's dream come true. Not only did they all demonstrate an effect in the same direction, but the results were consistent with each other. The largest mortality reduction (33 %) was seen in the Minnesota Trial in which the most sensitive slides were used annually (Fig. 9). Two European trials that used less-sensitive slides biennially showed a lower mortality reduction (13–15 %). The Minnesota second arm using a sensitive slide biennially had an effect intermediate between the European trials and the Minnesota annual arm. All very consistent!

Science Leads to a Consensus in Guidelines

After the trials were reported (1993–1996), a consensus appeared throughout the world literature that CRC screening is effective and should be offered to all people age 50 and older who are at average CRC risk. These trials put CRC screening on the map. In addition, because of the consistency of the results, future stool test methodology had an excellent yardstick for comparison. The guidelines [16–20] incorporated all available evidence and also strongly relied on mathematical modeling. The CISNET group led by Zauber was particularly important [19]. Most of these guidelines recommended a menu of options including gFOBT, flexible sigmoidoscopy or barium enema at varying intervals.

The guidelines distinguished between average-risk people and people at increased risk including those with a family history of CRC (and later the close relatives of patients with a pathologically documented adenoma, especially an advanced adenoma), those with familial syndromes (HNPCC, FAP), IBD and/or a past personal history of CRC or adenoma. Early studies by St. John in Australia documented very well the increased risk of close relatives of patients with CRC, inversely related to age of diagnosis [21]. A similar inverse risk was later reported in patients with adenomas by NPS investigators including Bishop from the UK [22] and by Burt [23]. FAP and Lynch syndrome were addressed individually in the guidelines (Fig. 10) [16, 24, 25].

Fig. 8 Wolff and Shinya reported the feasibility of colonoscopic polypectomy in over 200 patients in this landmark paper in the NEJM in 1973



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POLYPECTOMY VIA THE FIBEROPTIC COLONOSCOPE

Removal of Neoplasms beyond Reach of the Sigmoidoscope

WILLIAM I. WOLFF, M.D., AND HIROMI SHINYA, M.D.

Abstract Polyps of the colon and rectosigmoid, potentially precancerous lesions, have heretofore required laparotomy and colotomy for removal. Against a background experience of 1600 fiberoptic colonoscopies without complication a program in endoscopic removal of colonic polyps from all parts of the colon was undertaken. Three hundred and three polyps, 0.5 to 5.0 cm in diameter, were safely removed by this technic. Bleeding, controlled by transfusion therapy, occurred, in one patient, and minor bleeding in four others.

UNTIL recently, the only way to distinguish between benign and malignant neoplastic polyps high in the colon has been by laparotomy. Since the mortality of this operation is about 1 to 2 per cent[1,2] tions in patients ranging in age from three to 94 years, without morbidity or mortality. Early results have been presented elsewhere.[9-12]

Once the feasibility and safety of fiberoptic colonos-

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REDUCING MORTALITY FROM COLORECTAL CANCER BY SCREENING FOR FECAL OCCULT BLOOD

JACK S. MANDEL, PH.D., M.P.H., JOHN H. BOND, M.D., TIMOTHY R. CHURCH, PH.D., DALE C. SNOVER, M.D., G. MARY BRADLEY, M.D., LEONARD M. SCHUMAN, M.D., AND FRED EDERER, M.A., FOR THE MINNESOTA COLON CANCER CONTROL STUDY*

Abstract *Background.* Although tests for occult blood in the feces are widely used to screen for colorectal cancers, there is no conclusive evidence that they reduce mortality from this cause. We evaluated a fecal occult-blood test in a randomized trial and documented its effectiveness.

Methods. We randomly assigned 46,551 participants 50 to 80 years of age to screening for colorectal cancer once a year, to screening every two years, or to a control group. Participants who were screened submitted six guaiac-impregnated paper slides with two smears from each of three consecutive stools. About 83 percent of the slides were rehydrated. Participants who tested positive underwent a diagnostic evaluation that included colonoscopy. Vital status was ascertained for all participants over 13 years of follow-up. A committee determined causes of colorectal cancer, the primary study end point, were monitored with the sequential log-rank statistic.

Results. The 13-year cumulative mortality per 1000 from colorectal cancer was 5.88 in the annually screened group (95 percent confidence interval, 4.61 to 7.15), 8.33 in the biennially screened group (95 percent confidence interval, 6.82 to 9.84), and 8.83 in the control group (95 percent confidence interval, 7.26 to 10.40). The rate in the annually screened group, but not in the biennially screened group, was significantly lower than that in the control group. Reduced mortality in the annually screened group was accompanied by improved survival in those with colorectal cancer and a shift to detection at an earlier stage of cancer.

Conclusions. Annual fecal occult-blood testing with rehydration of the samples decreased the 13-year cumula-

Fig. 9 The first RCT on CRC screening was reported in 1993 by Mandel and colleagues at the University of Minnesota. This was followed in 1996 by reports from two European RCTs that confirmed the validity of CRC screening

The Paradigm Shifts

In 1997, screening colonoscopy was added to the guidelines menu by the GI Consortium co-chaired by Fletcher and me [16], and subsequently the American Cancer Society (ACS), CRC Committee led by Byers and Levin [26] and many other organizations also recommended colonoscopy as an option. Inclusion of colonoscopy in the 1997 Guidelines was based primarily on two studies: a study in 1992 by Selby that reported a reduction in CRC mortality following rigid sigmoidoscopy presumably due to the removal of adenomas in the rectosigmoid [27], and the National Polyp Study that reported in 1993 a reduction in CRC Incidence as a result of colonoscopic polypectomy (Fig. 11) [6]. These studies provided evidence for the long standing belief that CRC arose from preexisting adenomas and that interrupting the adenoma—carcinomas sequence prevented CRC.

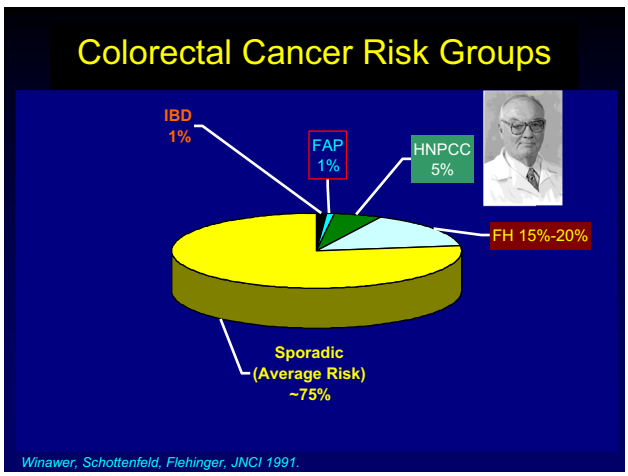

Fig. 10 Henry Lynch, a GI oncologist in Omaha, Nebraska, tracked high-risk CRC families and characterized Hereditary non-polyposis CRC (Lynch syndrome). This accounts for approximately 5 % of CRCs, and a smaller percentage is associated with Inflammatory Bowel Disease (IBD) and Familial Adenomatous Polyposis (FAP). Non-syndrome family history accounts for 15–20 % of CRCs, and the majority are average-risk people (75 %)

When screening colonoscopy was introduced into guidelines, it was recommended that the interval between screening colonoscopy exams should be 10 years in average-risk people. This interval was based on the 10–15 year expected average "dwell" time for a small polyp to grow and transform into CRC, the 10 year protective effect observed in Selby's sigmoidoscopy study, the long period observed in the NPS for new advanced adenomas to occur, and an older study by Stryker in the pre-colonoscopy era, that showed a long period of time before large (>1 cm) adenomas developed into cancer in patients who refused to have a laparotomy for removal of their polyps [28]. Hoff's studies on sigmoidoscopy also suggested a long polyp dwell time [29]. In addition, the GI Consortium Guidelines Committee that first introduced screening colonoscopy understood that they were recommending a more invasive test. They wanted to be as conservative as possible with this recommendation and therefore recommended a 10-year interval. It was of interest that the generalists,

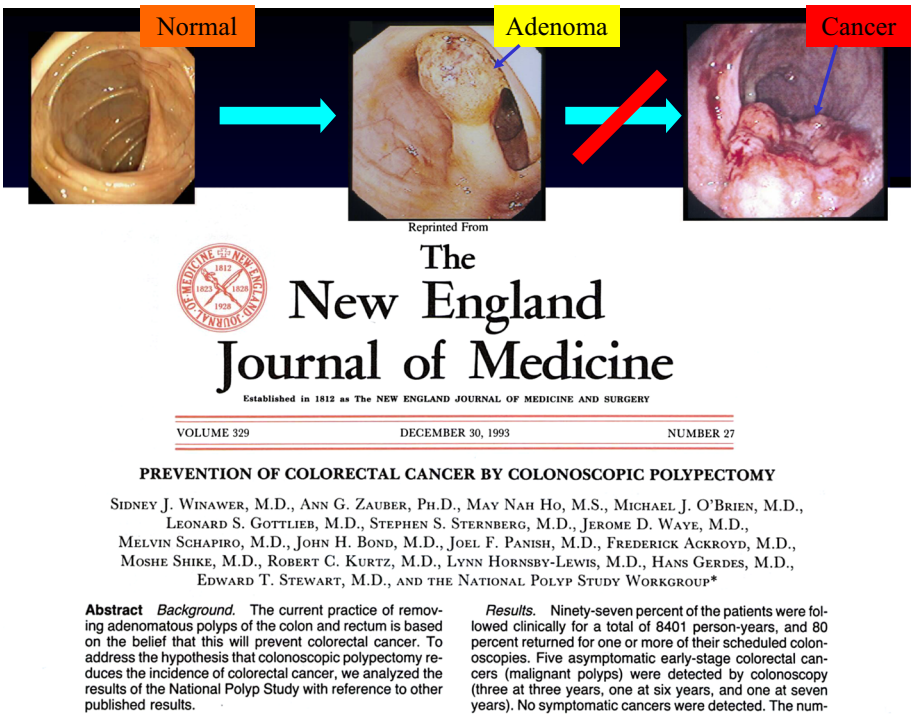

Fig. 11 The National Polyp Study demonstrated a reduction in expected CRC incidence following colonoscopic polypectomy, comparing observed NPS CRCs over a 6-year time period with expected CRCs in two cohorts with polyps that were not removed (pre-colonoscopy era) and the general population (SEER)

nurses and patient advocates on the committee were the folks who suggested colonoscopy as a screening option.

Raising the Bar

Recent US guidelines have made a distinction between the goal of early-stage cancer detection and cancer prevention [18]. It is, of course, important for screening tests to have a high sensitivity for early-stage CRC. However, it is critical for screening tests to also have a high sensitivity for advanced adenomas [30], especially with high-grade dysplasia which is the bridge to invasive cancer [31]. In 2012, a mortality reduction following polypectomy was reported by Zauber, Winawer, O'Brien and colleagues from the NPS indicating that the CRCs prevented by the detection and removal of adenomas were lethal and not an over diagnosis bias [32]. These findings compel an expectation that any screening test should find adenomas especially the advanced type (Fig. 12).

The high sensitivity of colonoscopy for advanced adenomas coupled with polypectomy and the elimination of annual or biennial repeat stool testing have made it the most commonly used screening test in the USA. A two-step approach with colonoscopy targeted to people who have a positive first-step screening test such as FOBT (gFOBT or FIT) or flexible sigmoidoscopy has been advocated by some, especially when colonoscopy resources are more limited than in the USA This is a concept that is evidence-based but resource-driven. In other words, do what you can with what you have [33]. The European Union Guidelines have advocated a 2-step approach, most commonly with FIT as the first step primarily for resource reasons [20]. RCTs have demonstrated that the 2-step approach using either FOBT or flexible sigmoidoscopy (FS) results in a CRC mortality reduction. The CRC incidence and mortality reduction from screening colonoscopy have been reported to be greater than that provided by colonoscopy driven by either FOBT or FS, but these data are based on observational studies [13–15, 34–37]. Several screening colonoscopy RCTs, now in progress, will in several years provide more precise measurement of the magnitude of the screening colonoscopy mortality effect in the general population as compared to fecal immunochemical tests (FIT) for blood in the stool [38].

Surveillance: The Downstream Effect of Screening

Regardless of the screening method used, adenomas are the most common outcome. This requires follow-up surveillance [39]. After the feasibility of colonoscopic polypectomy was reported in 1973, the practice after polypectomy was to have the patient return for annual colonoscopy or barium enema examinations. The National Polyp Study demonstrated in an RCT of surveillance intervals that the first follow-up colonoscopy could be deferred for 3 years and that the barium enema

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REPORT AFFIRMS LIFESAVING ROLE OF COLONOSCOPY

DEATH RATE CUT IN HALF

20-Year Study Is Seen as Best Evidence Yet on Screening Test

By DENISE GRADY

A new study provides what independent researchers call the best evidence yet that colonoscopy — perhaps the most unloved cancer screening test — prevents deaths. Although many people have assumed that colonoscopy must save lives because it is so often recommended, strong evidence has been lacking until now.

In patients tracked for as long as 20 years, the death rate from colorectal cancer was cut by 53 percent in those who had the test and whose doctors removed precancerous growths, known as adenomatous polyps, researchers reported on Wednesday in The New England Journal of Medicine. The test examines the inside of the intestine with a camera-tipped tube.

"For any cancer screening test, reduction of cancer-related mortality is the holy grail," said Dr. Gina Vaccaro, a gastrointestinal oncologist at the Knight Cancer Institute at Oregon Health and Science University who was not involved in the research. "This study does show that mortality is reduced if polyps are removed, and 53 percent is a very robust reduction."

Colorectal tumors are a major cause of cancer death in the United States and one of the few cancers that that can be prevented with screening. This year, more than 143,000 new cases and 51,000 deaths are expected. Incidence and death rates have been declining for about 20 years, probably because of increased use of screening tests and better treatments. But only about 6 in 10 adults are up to date on getting screened for colorectal cancer, according to federal estimates.

Cancer screening tests have come in for greater scrutiny recently. A government panel recommended in October that men

Continued on Page A3

Study Affirms Lifesaving Role of Colonoscopy

From Page A1

Ann Zauber, a statistician, and Dr. Sidney J. Winawer, a gastroenterologist, both at Memorial Sloan-Kettering Cancer Center, followed patients who had polyps removed in colonoscopies.

A study is declared the best evidence yet of the benefits of a screening test.

Evidence That a Dreaded Test Prevents Deaths

CUMULATIVE DEATHS FROM COLORECTAL CANCER

A camera on the tip of a device used to view the large intestine.

was inaccurate [40]. The latter was discontinued subsequently as a surveillance method. Additional NPS studies indicated that patients could be stratified into low or high risk of subsequent advanced adenomas, the outcome metric introduced in the NPS studies. Risk satisfaction was also demonstrated in the UK by Atkin in a long-term follow-up of Morson's cohort of patients with retrosigmoid adenomas [41]. The GI Consortium Guidelines beginning in 1997 [16] and extending to 2012 by the US Multi-Society Task Force [18] integrated these data. Other guidelines committees also incorporated these observations so that today there is a consensus for baseline risk stratified surveillance recommendations. The most recent USMSTF guidelines have also made recommendations for surveillance following removal of serrated polyps [18].

Fig. 12 The New York Times picked up the NPS study by Zauber, Winawer, O'Brien et al. published on February 12, 2012, in the NEJM which demonstrated a reduction in CRC mortality following colonoscopy polypectomy. The NPS cohort CRC deaths were compared to that expected in the general population (SEER) using the National Death Index to follow up the NPS Cohort

The Screening Landscape Today

The latest report by the CDC indicated that approximately 65 % of at risk men and women in this country are up to date with screening, 90 % with colonoscopy and 10 % with FOBT of one type or another [42], a remarkable improvement from the 20 % screening rates in the early 1990s. In the USA, gFOBT has been more commonly used than FIT up until now. However, FIT has been gaining acceptance throughout the Western world and is gaining a foothold in the USA since it has a higher CRC and advanced adenoma sensitivity than gFOBT with as good specificity, does not require dietary restriction and can be done in 1 or 2 days rather than 3 [43, 44]. The sensitive gFOBT now used also has a better performance than the older Hemoccult II. Newer tests such as CT colonography (CTC) and stool DNA may make inroads into CRC screening in the future [45, 46]. A recent report of the stool DNA mutation test, which also had FIT as part of it, has shown a higher sensitivity for advanced adenomas than a comparison test of only FIT (42 vs. 22 %) and also had a high sensitivity for adenomas with high-grade dysplasia (69 %).

The Worldwide CRC screening activities are most thoroughly reviewed each year in possibly the best CRC screening meeting internationally, the World Endoscopy Organization/IDCA Colorectal Cancer Screening Committee. This was initially organized by Rozen, Crespi and others, under the leadership in recent years by Young and now by Rabineck, Kuipers and Sung [47]. After years of progressive increases, CRC mortality is now declining and incidence has flattened in many developed countries. In the USA, both CRC incidence and mortality have been decreasing steadily over the last 25 years, in large part due to increasing screening rates over this period.

A US national campaign led by Wender of the ACS has been initiated to try to increase screening rates from 65 to 80 % by 2018. Many barriers exist that prevent people from being screening, including personal and system barriers. In addition, there have been disparities in health care including CRC screening. In the past, screening rates have been observed to be lower in blacks and Latinos as compared to whites. In New York City, racial disparities in screening were recently eliminated as result of an aggressive citywide coalition for CRC Control (C5) that was organized by the NYC Department of Health to encourage screening colonoscopy [48]. It is desirable to eliminate screening racial disparities nationally since this has been thought to be a significant factor in the higher CRC incidence and mortality seen in blacks as compared to whites.

A major issue in CRC screening is in people who select FOBT rather than colonoscopy. The FOBT trials that demonstrated a reduction in CRC incidence and mortality had a high adherence to a program of annual testing. A single FOBT has a relatively low sensitivity for CRC and advanced adenomas, and the performance improves for repeated testing. High adherence to annual testing is critical for its benefit [17]. Community studies have reported a wide range of adherence for repeated testing [49].

Whether colonoscopy is done as a screening test or a diagnostic test in people with a positive screening test, it needs to be of high quality. Quality benchmarks have been reported in recent years. There is now a major emphasis on the quality of colonoscopy as measured by withdrawal time, adenoma detection rate and cecal intubation rate. As emphasized by Rex, Lieberman, Greenwald, Regula, Kaminski and others, colonoscopy needs to be of the highest quality to achieve its optimal level of effectiveness [50–52]. The "simple" FOBT also needs to be of high quality as shown by Fleisher [53] in the USA and Gnauck in Germany [54].

Physician and Public Awareness of CRC Risk

Physician awareness of CRC prevention began to take hold in the 1980s. Educational programs directed to primary care physicians were initiated although they probably did not have much effect until scientific reports and guidelines became more visible in the 1990s. The International Working Group on CRC began in 1979 and issued several reports, more presentations began to surface at medical meetings, and opinion leaders in CRC prevention began to get a platform at major meetings in the 1980s and 1990s. The power of national organizations began to weigh in including the AGA, ACG, and ASGE and also the ACS and CDC. The ACS organized the National Colorectal Cancer Roundtable which brought together many interested stakeholders for a concerted national effort, led by Smith, Levin, Weber and Doroshenk. Foundations added immensely to this effort such as the Prevent Cancer Foundation led by Aldige. Physician awareness of CRC as a preventable disease was becoming an established concept. The big hurdle was to get the message into the minds of the public.

It is important to have strong scientific evidence that screening is effective followed by guidelines that recommend screening. However, it is quite another challenge for this to filter into the consciousness of the public and to be implemented on a wide scale. Public awareness of CRC risk and its prevention has come a long way in just a brief time span. I remember being on a TV show in the 1970s where after 2 Viennese dancers and a facial cream demonstration I was asked, "What is colorectal, is it a new toilet cleaner?" The host fortunately was impressed with the data and quickly made a plea to the audience to "get

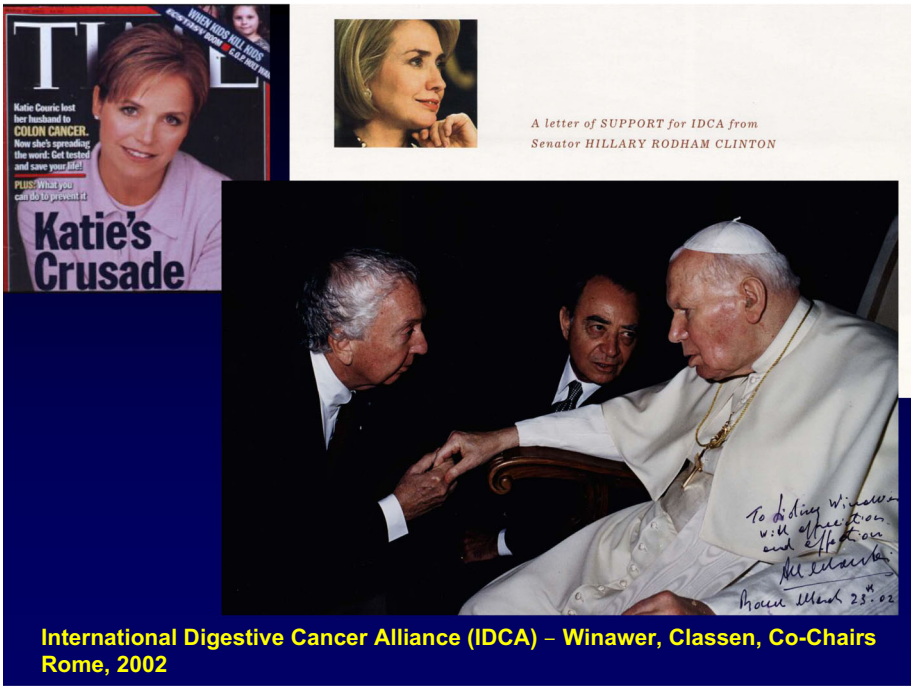

Fig. 13 Several people voiced support for colorectal cancer screening including Katie Couric, First Lady Hillary Rodham Clinton, and the late Pope John Paul II

tested" to prevent CRC. The media was so silent about CRC that the American Cancer Society in the 1980s came out with the slogan—"CRC; Silence is NOT Golden."

A small blip in screening occurred on the radar screen when then President Reagan had CRC discovered in 1985 at age 74. Reagan had a positive FOBT and had a colonoscopy which showed a proximal colon CRC. He had a hemi-colectomy for a Dukes B CRC (staging system in use then). His care provided the basis for considerable public education. Information about screening and diagnostic options and surgery, polyps and CRC was widely aired on TV channels and in the print media. This provided an opportunity for many CRC screening proponents.

A more recent catalyst to CRC public awareness resulted from the efforts of Katie Couric. Her husband, Jay Monahan, died of CRC in 1998 at age 42. I had the privilege of helping her organize a week-long series on CRC and be her "anchor doctor" each day. The series covered the polyp-cancer relationship, screening, diagnosis, surgery, epidemiology including familial and other risk factors, genetics, etc. This program was followed in 2000 by Katie having a colonoscopy live on TV by Forde at NY Presbyterian Hospital. What followed has been called the "Couric Effect." A paper in 2003 reported results from Lieberman's CORI database on 400 gastroenterologists in 22 states, which showed an increase in the average number of colonoscopies per physician from 15 over the 20 months before to over 18 in the 9 months after the TV colonoscopy [55]. Many patients who came into GI units and were asked why they were requesting a colonoscopy said, "Katie said I should have it done" (Fig. 13).

Other TV personalities pitched into the CRC media campaign in the 1990s. Timothy Johnson, an Internist in Boston, who was the science reporter on ABC had several interviews, and as a result of his efforts was invited as a keynote speaker to the American Gastroenterology Association (AGA) plenary session at Digestive Disease Week and to the New York City Citywide CRC Control (C5) Coalition. Barbara Walters made a striking comment when she substituted for Katie Couric on the Today Show on CBS. During her interview with me, she said that "Dr. Winawer" did my colonoscopy, and then we proceeded to talk about the risk in women. This was important, because for many years, until perhaps the 2000s, women did not think that CRC was their disease. They thought of CRC mainly in terms of rectal cancer and assigned the same male risk to that as they did for prostate cancer.

Congress approved CRC screening coverage for Medicare patients in 1998. All three national GI societies helped get this legislation passed. First Lady Hillary Clinton added to the public awareness when she hosted a large group of National Opinion leaders and others involved in CRC prevention to the White House in 1999. Levin was the AGA representative to this event. In 2000, President Clinton proclaimed March CRC month, and in 2001, colonoscopy was added to Medicare reimbursements. This

was just recently re-proclaimed by President Obama who had a CT colonography (CTC) done, which was widely reported and increased public interest in this modality. Considerable press coverage resulted in patients asking about CTC as a screening option.

Although celebrity-driven media is important, scientific evidence trumps everything. Rigorous studies have a major effect on guidelines and public policy, and both of these produce media attention that impacts public awareness. I remember in particular the attention that was attributed to the landmark paper by Wolf and Shinya in the NEJM in 1973 that showed the feasibility of colonoscopic polypectomy; the Mandel University of Minnesota FOBT trial that demonstrated a CRC mortality reduction published in 1993 in the NEJM [13]; the NPS studies that demonstrated a CRC incidence reduction in the NEJM 1993 [6]; and a mortality reduction in the NEJM in 2012 [32]. Guidelines also get a lot of media attention, especially the 1997 GI Consortium guidelines that introduced screening colonoscopy [16]. This was accompanied by a large press conference in Washington entitled "A Call for Action." It was the first multidisciplinary guidelines committee that made strong evidence-based recommendations for screening after publication of the UK and Danish FOBT trials were reported that showed a mortality reduction that was consistent with the earlier University of Minnesota trial. Introduction of new tests also make a big impression in the media. An example of this is the CTC series of reports by Pickhardt [46] and the recent large stool DNA mutation/FIT trial led by Imperiale [45].

When new data result in guidelines changes particularly when the guidelines are either from the US Preventive Services Task Force (USPSTF) or ACS, usually media coverage follows. This was the case for the evolving USPSTF guidelines which in 2008 gave CRC screening a Grade A for the evidence, strongly recommended screening, and added colonoscopy, and also recommended to consider stopping routine screening at age 75 and not to continue screening beyond age 85 [19].

International media coverage is also affected by US studies as well as by other worldwide studies and events. When the first International Digestive Cancer Alliance was organized in Rome at the Vatican in 2003, there was a lot of international media coverage, especially because the late John Paul II gave an audience and read a statement in support of the worldwide prevention of CRC. He called attention to statistics that there were more than 1 million new cases and more than 500,000 deaths from CRC annually worldwide. He also noted that CRC was on the rise in many developing countries, presumably because of the aging of the populations and their adoption of a western diet (Fig. 13).

The Future

The "Holy Grail of CRC Screening" is a term coined for a blood test that would identify people with an increased risk of advanced adenomas or CRC. There are many studies in this area, but thus far, we do not have the "Holy Grail." However, we do have many options for CRC screening. Those people who elect one of those options get a benefit—a lower risk of dying from CRC than those who do not get screened. Which option is the best? Of course, the best test is the one that gets done and done well!

For the near future, campaigns to increase screening worldwide will focus on stool testing while in the USA, the focus is on colonoscopy as the preferred test although increased screening in general is the overall goal. In the more distant future, with evidence of the effectiveness of colonoscopy and with evidence worldwide on adherence to sequential screening, recommendations may change. My personal view is that the concept that CRC screening is evidence-based but resource-driven [33] will prevail. In countries like the US colonoscopy, every 10 years will most likely continue because of the high colonoscopy resources here [18], but in most other countries, two-stage screening will prevail with FIT as the first stage, and colonoscopy targeted to positive patients as the second diagnostic/therapeutic step [20, 56]. Further clinical experience will likely clarify the role of other tests such as stool DNA and CTC as primary screening options. If the "Holy Grail" is discovered, that may trump all previous screening tests.

As new tests emerge, they will require vigorous evaluation as outlined by Young and the WEO workgroup [57]. This group has recommended a standardized approach to the evaluation of new tests. The international debate will continue regarding effectiveness of ad hoc screening versus national programs. However, it is now clear that the CRC opportunistic screening rate in the USA has exceeded all expectations and has outpaced by far screening in most other countries. This has been a phenomenon resulting from translating rigorous worldwide science into practical guidelines and then aggressively pursuing widespread population acceptance.

What We Have Learned from the Past?

- *Science trumps* A methodical sequence is critical: rigorous science followed by guideline recommendations based on evidence, then implementation based on resources.
- *The paradigm has shifted* CRC screening is no longer only screening for early-stage curable CRC, but also for

advanced adenomas, the removal of which will prevent lethal CRC. This message needs more public emphasis.

- *A nation engaged* Cooperation and collaboration by multiple disciplines and organizations including physicians, nurses, social workers, administrators, survivors, community workers and many others, all with a shared belief and purpose.
- *Media power* Involvement of the media, celebrities and public health officials magnifies the effect geometrically.
- *Legislation* Key for reimbursement of strategies.
- *Persistence and perseverance* To achieve anything requires hard work, committed over a long period of time, tirelessly. This is as true for population CRC screening as it is for any other endeavor.
- *An evolving field* Finally, we need to be open to new scientific, sociological, and other developments which will inevitably evolve and will dramatically alter our approach. Examples in the past are the polyp-cancer concept, colonoscopy, polypectomy, FOBT cards, FIT, DNA stool testing, CTC, the paradigm shift to detecting advanced adenomas, and in the future, the "Holy Grail" of blood tests or some preventive measure. They will come. It is only a matter of time, but people at risk should not wait for the "Holy Grail." Their future is now. Men and women need to do a test. Any test is better than none, and the best test is the one that gets done and done well.

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