2017 Emily Couric Memorial Lecture: Colorectal Cancer: Polyps, Prevention, and Progress

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Colorectal cancer remains the second-leading cause of cancer death in the United States—but efforts over the past two decades have resulted in tremendous progress in understanding the biology of how this disease develops, increasing screening rates, and decreasing incidence and mortality in those age 50 years and older. The drivers of this movement have been outstanding leadership, innovation, and collaboration. As we move forward to tackle issues such as the increasing incidence of this disease in younger adults, the need to address disparities in care and outcomes, and our shared goal to reach 80% screening rates, it's important to understand and appreciate the story of our past success in order to advance our future efforts.

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It's an honor to present the Emily Couric Memorial Lecture this year. It's also a privilege to be speaking on the important topic of colorectal cancer screening and prevention, especially since this cause meant so very much to Emily. Indeed, Emily was one of the early champions in the fight to effect the legislative changes needed to make screening more available to more people.

Together, we have made tremendous progress over the past 20-plus years in our efforts to end colorectal cancer as a major cause of cancer death in the United States. Countless lives have been saved with the decreasing incidence and mortality we have seen in the United States from colorectal cancer. And yet, there is so much more to be done. We need to continue Emily's fight to ensure access to care, increase screening rates, strive continually to improve our quality initiatives, address disparities, and determine why incidence rates are rising in our young adults. I believe a major key to tackling these issues successfully in the future lies in our understanding of our history—and in our appreciation of what has made us successful thus far.

The story of polyps, prevention, and progress in colorectal cancer truly is one of leaders, of innovators, collaborators, even one of heroes. And it's one that started long ago at a time when discussions about the colon and colon cancer were considered impolite at best—and colonoscopy and colonoscopes were tools used only for diagnosis. Using these same tools to prevent cancer is where this story begins.

POLYPS AND PREVENTION: HIGHLIGHTS FROM HISTORY

Before the availability of the fiberoptic colonoscope, gastroenterologists were dependent on barium enemas to visualize the

colon, and when polyps were seen, they could only be removed surgically. Innovations in technology improved the colonoscope and colonoscopy technique so that one could examine the inside of the colon and remove polyps. Indeed, if you ask Jerry Wayne and others, they will tell you stories about making their own snares with wire and hemostats. But it was William Wolff and Hiromi Shinya who described the technique of colonoscopy with polypectomy in the *New England Journal of Medicine* in 1973 [1]. This publication brought the concept and the procedure to widespread awareness in the medical field. However, it was not until 1985, at the time of President Ronald Reagan's diagnosis of colon cancer, that the subject of colon polyps and cancer first reached mass public awareness. After noting that the President's hematocrit had been dropping after December 1984 but showing no further deterioration (Reagan appeared to be in great health), a fecal occult blood test (FOBT) in March 1985 produced a positive result. Only a flexible sigmoidoscopy was performed to evaluate this finding and a benign polyp was discovered. It was not until after his brother was diagnosed with colon cancer and the President's doctor enlisted the help of First Lady Nancy Reagan that the President underwent a complete colonoscopy in July 1985. During the procedure, a malignant mass in the right colon was detected. He subsequently was diagnosed with a T2N0Mx (Dukes B) malignancy after he underwent a right hemicolectomy the next day [2, 3]. This news at the time generated a floodtide of calls from the public, with Irving Rimer of the American Cancer Society noting that “the taboo against talking about colon and rectal cancer...has been broken” [4]. But the spotlight did not last as long as we would have liked—and we still had a long way to go, both in public awareness and in the science of how this disease develops.

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Fig. 1 Virginia State Senator Emily Couric (bottom row, left) and Dr. David Johnson (bottom row, second from right) and Nancy Schlossberg (bottom row, right) smile as Governor Jim Gilmore (bottom row, second from left) signs the bill that requires coverage for colorectal cancer screening

Biology

Then in 1988, Bert Vogelstein and colleagues published a landmark article identifying the genetic alterations that occur over a period of years in the development of colorectal cancer [5]. They described what is now the “Vogelstein Model,” or a pathway of chromosomal instability, marked by a predictable sequence of genetic mutations that led to the development of an adenoma and its progression to carcinoma. These scientists defined for us a window of prevention, from benign polyp to malignancy. Fast forward to 2006, we saw others like Weisenberger and colleagues continuing the important work in uncovering how colorectal cancer develops [6]. Ultimately multiple pathways are now thought to lead to the development of colorectal cancer, including genetic and epigenetic chromosomal instability progressing to advanced adenomas and cancer; inherited genetic mutations of the mismatch repair genes, as in the Lynch syndrome, resulting in microsatellite instability (MSI) and accelerated polyp to carcinoma transformation; and finally a sessile serrated polyp-cancer pathway such as seen with BRAF mutation and MSI due to acquired mismatch repair gene defects from hypermethylation of CpG islands in the *MLH1* promoter [5–7]. This important knowledge would prove to be invaluable in understanding the genetic basis of colorectal cancer, act as a template for studying other carcinomas, and help inform future recommendations in screening and surveillance.

Screening

In the 1990s, the benefits of screening tests also began to crystallize, with randomized, controlled studies by Mandel and colleagues, Kewenter and colleagues, Hardcastle and colleagues, and Kronborg and colleagues showing 15%–33% reductions in colorectal cancer mortality with the use of simple annual guaiac FOBT screening [8–12]. These findings were confirmed later, in 2013, by Shaikat and colleagues in a 30-year follow-up Minnesota Colon Cancer Control study, which showed a 32% reduction in colorectal cancer mortality [13]. While we knew anecdotally

from the experiences of President Reagan and many others, these researchers showed us definitively that FOBT works and screening saves lives. Importantly, these stool tests were done at home and not done during a digital rectal examination. We learned later from Collins and colleagues in 2005, that FOBT during a digital rectal exam is not effective for colorectal cancer screening [14].

Around the same time as the FOBT studies were showing these encouraging results, Sidney Winawer, Ann Zauber, and colleagues from the National Polyp Study Workgroup published their groundbreaking analysis on the prevention of colorectal cancer by polypectomy [15]. In analyzing data on nearly 1500 patients with adenomatous polyps, these authors showed a 76%–90% reduction in the expected colorectal cancer incidence after polypectomy. Fast forward to almost 20 years later, and Zauber, Winawer, and colleagues, using the same post-polypectomy cohort, would now demonstrate the long-term result of colonoscopy and polypectomy, showing a 53% reduction in deaths from colorectal cancer [16]. That initial 1993 landmark National Polyp Study publication, showing the preventive value of polypectomy, was essential in laying the groundwork for what was to come.

Indeed, in 1997, Winawer and associates released updated national colorectal cancer screening guidelines—which for the first time included colonoscopy as one of the recommended screening tests [17]. This meant that physicians could now offer colonoscopy as a screening option to their patients, and insurances were more likely to cover this procedure. In this same year, the American Cancer Society and Centers for Disease Control and Prevention (CDC) would join forces to form the National Colorectal Cancer Roundtable (NCCRT), led by founding Chair Bernard Levin and Co-Chair Robert Smith, along with Marion Nadel, senior epidemiologist, Division of Cancer Prevention and Control, at the CDC. It was the beginning of a nationwide coalition to coordinate efforts to increase colorectal cancer screening and end this disease.

Public awareness

Unfortunately, 1997 also brought a devastating diagnosis for attorney and MSNBC legal correspondent Jay Monahan. Jay had presented in acute pain, and I was deeply saddened to have to tell him he had widely metastatic colon cancer. With very few treatments available at the time, Jay died just nine months later at age 42. This was a tragic and devastating loss to his wife Katie Couric, their two little girls, and their family and friends. At Jay’s wake, Katie remarked to a group of us that something had to be done about this terrible disease. She did not want this same tragedy happening to other families. We told Katie that, as the recognized and respected co-anchor of the morning “*Today*” show, she may be able to do more to fight colon cancer than any physician could. In retrospect, that was an understatement. Katie would go on to join forces with the Entertainment Industry Foundation in establishing the National Colorectal Cancer Research Alliance (2000) and later Stand Up To Cancer (2008). And it was not long after Jay’s untimely death that she began a public awareness effort that would make colorectal cancer personal and get people talking about it.

At a time when colons and colon cancer were still not discussed, Katie and her producers began in 1998 working on health segments to inform the public about this disease, the second-leading cause of cancer death in the country. Then in March 2000, she underwent her well-known televised colonoscopy, performed by Kenneth Forde, demystifying the procedure and encouraging people to talk to their doctors about colorectal cancer screening and prevention. Katie responded to her own family's tragedy by turning it into a mission to save the lives of countless others. We did not know it then, but she would never stop.

Around the time that Katie's colon made its television debut, Katie's sister, Virginia Democratic Party Co-Chair and State Senator Emily Couric, was hard at work, along with David Johnson (American College of Gastroenterology President, 2006–2007), advocating for legislation in Virginia. They succeeded. Emily and David were both present when Governor Jim Gilmore signed the first bill that would require insurance companies to cover colorectal cancer screening, including colonoscopy, as of July 2000 (Fig. 1). This ensured that many more Virginians would have access to screening—and would spark similar legislative efforts across the country [18].

A few years later, in 2003, Cram and colleagues would report on the “Katie Couric Effect,” showing a nearly 19% sustained increase in colonoscopies nationwide following Katie's broadcast colonoscopy in 2000 [19]. Never before had colorectal cancer screening had a champion who had the will and the platform to connect with the American people and move the screening needle forward like this.

While public demand for colorectal cancer screening was growing, gastroenterology leaders were proactively talking about quality, something we had all along taken for granted. Doug Rex and colleagues had pointed out the surprising and controversial observations in 1997 that colonoscopy can miss polyps in an operator-dependent manner, finding an overall adenoma miss rate of 24%, varying from 17%–48% depending on which endoscopist was performing the exam [20]. This was followed in 2006, with then-ACG President Jay Popp and American Society for Gastrointestinal Endoscopy (ASGE) President David Bjorkman joining together to make quality a priority and issue joint ACG-ASGE quality indicators for colonoscopy [21, 22]. These guidelines, by Rex and colleagues, introduced us to adenoma detection rate (ADR), withdrawal time, cecal intubation, and other quality benchmarks. These champions recognized that it was our role, as leaders in the field, to proactively issue the recommendations needed to ensure that endoscopists provided the highest quality colonoscopy to their patients.

This was followed by the formation of a remarkable collaboration known as the GI Quality Improvement Consortium, or GIQuIC (giquic.gi.org). In 2009, under the leadership of Irving Pike, the ACG and ASGE launched GIQuIC to collect, track, and benchmark electronically the quality metrics for colonoscopy from physicians and institutions nationwide [23]. In September 2011, we saw inclusion of data from approximately 100,000 colonoscopies, increasing to over six million colonoscopies currently and climbing. About one third of U.S. endoscopists are now utilizing GIQuIC to benchmark their quality data.

From the data, we know that ADR increases with GIQuIC reporting [24]. We also know from Kaminski and colleagues that a

higher ADR is associated with lower interval colorectal cancer rates [25] and that increasing individual ADR with feedback reduces the risk of interval colorectal cancers and deaths [26]. Thus, paying attention to quality improves quality—and GIQuIC, currently led by President Glenn Eisen and Executive Director Laurie Parker, continues to play an important role in collecting and tracking the appropriate quality benchmarks. We know that using GIQuIC makes what we do even better and demonstrates to our patients our commitment to quality.

To help coordinate our multi-pronged efforts to increase screening and reduce the incidence and mortality associated with colorectal cancer, in 2014, under the leadership of NCCRT Chair Richard Wender and NCCRT Director Mary Doroshenk, the NCCRT launched a campaign to screen 80% of adults aged 50 and older by 2018 (known as the 80 by 18 campaign), providing a unified initiative under which health professionals, public health professionals, professional societies, government health agencies, advocacy groups, survivors, and families could join together and collaborate in achieving this common goal [27]. The message is to promote all recommended screening options, and to allow individuals and their doctors to choose the test that is right for them. All across the country, more and more cities, regions, hospitals, healthcare networks, and advocacy groups are working to reach 80% screening and beyond.

PROGRESS: OUR SUCCESSES AND AREAS IN NEED OF ATTENTION

Needless to say, the past 20 years have brought tremendous progress in the fight against colorectal cancer. In the *Morbidity and Mortality Weekly Report*, White and colleagues show the national colorectal cancer screening rate increasing from under 40% in 2000 to 62.4% in 2015 [28]. A more recent report by Joseph and associates notes an increase in those up to date in screening (ages 50 to 75) from 65.5% in 2012 to 67.3% in 2016 [29]. While we have more work to do in this area, these data show great improvement.

Perhaps even better news is that these efforts are producing extraordinary outcomes—indeed, they are saving lives. Siegel and colleagues show colorectal cancer incidence rates declining by 32% between 2000 and 2013, and death rates decreasing by 34% from 2000 to 2014 in persons age 50 and older [30]. This encouraging trend is due to increased screening and other factors—including the availability of several new and more effective treatments for those diagnosed with colorectal cancer. It is essential to underscore that an increase in screening, especially in preventive colonoscopy screening, has contributed significantly to this drop in colorectal cancer cases and deaths. There is no greater reward for our collaborative efforts to increase screening than lives saved, and we should all take a moment to feel a collective pride in this accomplishment.

It is important to reflect on this success, and the leadership, innovation, and collaboration that made it possible, as we address areas in need of further attention. In addition to continuing to increase screening rates, we need to double down on our efforts to eliminate disparities in colorectal cancer incidence and mortality. In African Americans, for example, we see a higher colorectal cancer incidence

and mortality [31], along with earlier onset of disease than in other racial/ethnic groups [32]. This is why, in 2017, the ACG, American Gastroenterological Association (AGA), and ASGE released new multi-society colorectal cancer screening recommendations indicating that African Americans, at otherwise average risk, need to begin screening at age 45, rather than age 50 [33]. It is important that we are aware of these guidelines and continue to pursue efforts to gain greater understanding and to eliminate such disparities wherever they exist.

Another area in great need of further evaluation is the increasing incidence of colorectal cancer in young adults in the United States. While these numbers in older adults are decreasing, Siegel and colleagues reported that colon cancer incidence has been increasing annually since the mid 1980s by 1.2%–2.4% per year for young adults aged 20–39 years, and since the mid-1990s increasing 0.5%–1.3% per year for adults aged 40–54 years. Even more alarming, they note that the increase in rectal cancer incidence rates for these younger adults have been increasing longer and more quickly [34]. Based in part on this disturbing trend and modeling that demonstrates improved life-years gained, the American Cancer Society issued new guidelines for colorectal cancer screening in May 2018, recommending that screening for individuals at average-risk for the disease begins at age 45 [35]. In addition to being aware of these new screening recommendations, we must also further evaluate the potential causes of the increase in incidence in younger people. A change in the microbiome (perhaps related to societal overuse of antibiotics); diet high in red meat, fat, and processed foods; increased obesity; and decreased physical activity have been hypothesized as potential risk or causative factors, but we do not have the answer. As a community, we need to up our research efforts to identify the risk factors or causes behind this alarming trend, so that we can take the necessary steps to bring an end to it and protect our young adults from developing this disease.

In terms of polyps, we know that sessile serrated polyps are responsible for 20%–35% of colorectal cancers [36]. These lesions can be more difficult to detect [37] and may be more difficult to remove completely [38]. In addition to continuing our overall quality efforts, we need to continue to evaluate the biology and timeline for sessile serrated polyps and their progression to cancer—and to innovate more effective ways to detect and remove these lesions.

THE FUTURE: WHAT'S ON THE HORIZON

We have come so far since making our own snare wires for colonoscopies—and since the discussion of all things colon was taboo. It's exciting to reflect on the progress we have made and recognize that we are moving the needle closer toward the eradication of colorectal cancer. An important part of our journey forward will be to focus on quality and improve our ability to detect and remove polyps with screening colonoscopy. In addition, we hope to develop better minimally invasive screening options.

Already, there have been multiple technologies—including multi-camera endoscopy; cuff-assisted, ring-assisted, balloon-assisted colonoscopy; and retroflexed/panoramic catheter devices—that have been studied and found to increase the detec-

tion of adenomas in comparison to the traditional forward-view colonoscopy [39–43]. Many of these devices improve our ability to visualize behind the folds of the colonic wall, thereby increasing our ability to detect these lesions, including flat lesions [44]. However, all new technology must be closely studied and compared to the current state of the art and, most importantly, technology must not act as a substitute for quality. Only through research will we know whether these devices make a difference in our ability to prevent or better detect cancers. While we continue to innovate and assess the benefit of these new devices, we must always concentrate on providing what we know works: vigilance and adherence to our recommended quality benchmarks.

So too, we also have less invasive options available. We have long known that take-home stool tests, used as recommended, are effective in the early detection of colorectal cancer. Today, the sensitivity of stool testing has greatly improved, with the availability of fecal immunochemistry test (FIT) and new multi-target FIT plus DNA tests that are more sensitive than the guaiac-based FOBTs of old.

In addition, studies evaluating the use of blood and breath tests are currently underway. A blood test utilizing the Septin 9 gene, which encodes for the protein involved in cytokinesis and cytoskeletal remodeling, was shown to have 48.2% sensitivity for colorectal cancer and 11.2% sensitivity for adenomas. In another study, the Septin 9 blood test performed better and showed slightly higher sensitivity than FIT testing (73% vs. 68%) but significantly less specificity (81% vs. 97%) [45, 46]. While we do not currently have a blood test recommended for the screening of colorectal cancer by the multi-society task force or other national guidelines, this area of study holds promise.

Finally, we know about PET scans and CAT scans, but it's the “DOG” scan that is under study today. When dogs are used to sniff breath and stool in samples of known colorectal cancer compared to controls, studies have shown a 91% sensitivity in breath and 97% sensitivity in stool. The specificity for both was 99% [47]. So what are these dogs smelling, what are they detecting—and how can we measure it? Researchers believe that they are detecting volatile organic compounds, or VOCs, and that these VOCs are expelled in both stool and breath. They believe that many diseases have a VOC signature, or breath print. Indeed, early preliminary studies have identified the VOC signature for colorectal adenomas, colorectal cancer, and other cancers [48–51]. In one pilot study, breath testing with gas chromatography and mass spectrometry using these signatures showed an 85% sensitivity for colorectal cancer and 94% sensitivity for adenomas [52]. Another study showed 85% sensitivity in detecting colorectal cancer in stool [53] and 86% sensitivity by breath test [54]. Although early, these promising results suggest that VOC analysis may prove valuable in the future of minimally invasive testing for diseases, such as colorectal cancer. Like all minimally invasive testing, any positive test would require a colonoscopy for definitive diagnosis.

Emily Couric once said, “An eager willingness to serve others is undoubtedly one of the most attractive attributes an individual can possess.” Our history shows that we have no shortage of health professionals, researchers, legislators, organizations, survivors, and family members willing to serve this cause. We must

take the lead of the many heroes who have brought us this far and continue our fight to increase our research in young adults, disparities, and other critical areas; improve access to care; and educate the public on why screening is so important. It's in this spirit of leadership, innovation, and collaboration that we have made so much progress—and that we will reach 80% screening and beyond. And it's with our increased screening rates, continued quality efforts, and more effective treatment options that we will see an end to colorectal cancer as a leading cause of cancer death in the United States.

CONFLICTS OF INTEREST

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