newer, noncytotoxic, standard-of-care agents. Finally, palliative care often amounts to little more than a few doses of morphine that are woefully inadequate for alleviating symptoms.

I find it unacceptable that the most basic, decades-old elements of oncology care are absent in Malawi, while cancer-related expenditures are skyrocketing in other parts of the world to levels that are unsustainable even in high-income countries. Allowing such disparities to persist is an ethical choice.

Fortunately, investments are gradually increasing, and our work with partners in Malawi is largely supported by the U.S. National Cancer Institute, which, along with other funders, has substantially escalated its commitment to addressing cancer globally. But funding cancer programs solely through research grants can have distorting effects on agendas, skewing activities toward the production of research articles rather than effective treatment or palliation for patients. "Scholarship" can sometimes amount to little more than repeated recitations of the challenges faced or shipping of tumor tissue to international laboratories for assays with little immediate relevance to local populations; however important they may be, mechanistic insights will not benefit Malawians in the short or medium term if medicines against "druggable" targets remain unavailable and the supply of even very old drugs is inconsistent. It is incumbent on us as a scientific community to generate not just citations but better outcomes for the poorest patients in the world.

Moreover, clinicians and scientists are not enough. Science was essential but insufficient to catalyze the international movement that transformed HIV from an existential threat in sub-Saharan African countries to a prototypical global health success story. What was ultimately required was not just research but broad civil-society activism and political will. Malawians with HIV can now live normal lives, for which we thank protesters who stormed international meetings over many decades to demand action. A similar energy now drives our moonshot dreams for cancer, but I believe we must also commit ourselves to expending a small fraction of that energy to control cancer, using proven methods, in places like Malawi. Shooting for the moon is important, but so is shooting for a world that is just and equitable.

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Colorectal Cancer on the Decline — Why Screening Can't Explain It All

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Unlike screening for breast or prostate cancer, screening for colorectal cancer promises not only to find cancer early, but also to prevent it from occurring. In the 1960s, Gilbertsen first suggested that polypectomy could turn colorectal cancer into a preventable disease.[1] Two decades later, Vogelstein envisioned the polyp-to-cancer progression as a stepwise process and detailed the genetic alterations that occur at each step.[2] Colorectal cancer became widely viewed as having a long latency period — providing ample time for both early detection and prevention. Conditions were thus considered ideal for screening to reduce related mortality.

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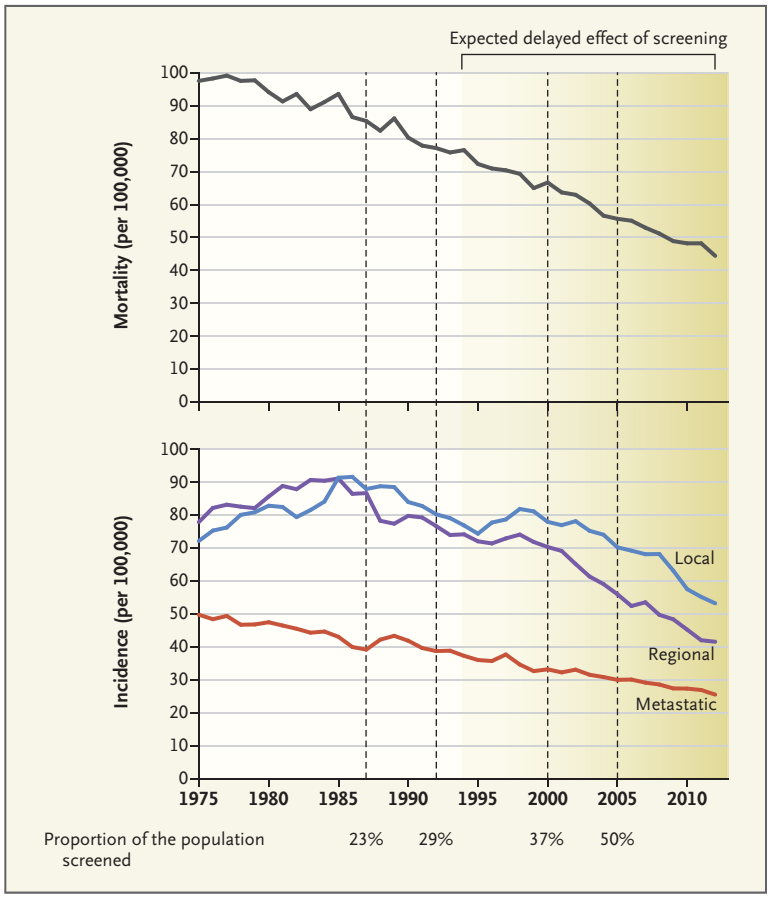

Colorectal-Cancer Mortality (Top) and Stage-Specific Incidence (Bottom) among People 50 Years of Age or Older in the United States, 1975–2012.

Data are from the Surveillance, Epidemiology, and End Results Program 9 and are age-adjusted to the 2000 U.S. standard population. Total incidence is the sum of local, regional, and metastatic incidence.

Nine randomized trials summarized in a Cochrane review provide empirical evidence of an effect of screening on both colorectal-cancer incidence and mortality.[3] Four trials revealed a 14% reduction in colorectal-cancer mortality and a 5% reduction in colorectal-cancer incidence with fecal occult blood testing, suggesting that early cancer detection is primarily responsible for the reduction in mortality associated with that method. Five trials demonstrated a 28% reduction in colorectal-cancer mortality and an 18% reduction in colorectal-cancer incidence with sigmoidoscopy, suggesting that cancer prevention is the predominant mechanism for its effect. The trial data confirm colorectal cancer's long latency period by revealing a substantial delay — on the order of a decade — between screening and reduced cancer incidence and mortality.

Against this backdrop, we considered trends in colorectal-cancer incidence and mortality among U.S. adults 50 years of age or older. The big picture is unambiguous "good news": overall colorectal-cancer incidence has dropped by almost 40% since 1975 and by more than 45% since its peak in the mid-1980s. More important, colorectal-cancer mortality has fallen by more than half (see graph).

These trends are often attributed to screening. But the magnitude of the changes alone suggests that other factors must be involved. None of the trials of colorectal-cancer screening has shown a 50% reduction in mortality — nor have trials of screening for any type of cancer.

More important, the timing of the trends isn't consistent with this explanation. Population-wide colorectal-cancer screening has been slow to disseminate into clinical practice. According to the National Health Interview Survey, in 1987 only about 23% of the U.S. population 50 years of age or older had been recently screened.[4] Nearly two decades later, in 2005, that rate had increased only to 50%. Given the slow uptake of screening and its expected delayed effect on mortality, it's hard to imagine a substantial screening effect at the population level showing up much before this new millennium started.

If not screening, what explains the decrease in colorectal-cancer mortality? We believe there are three categories of plausible explanations. First, the treatments available for colorectal cancer today are better than they were 30 years ago. Improved surgical technique, standardization of preoperative and postoperative care, and an increasing reliance on high-volume providers have probably combined to reduce operative mortality. And the addition of adjuvant chemotherapy for patients with regional (node-positive) disease has been demonstrated

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to reduce longer-term mortality. Even patients with widespread disease can now undergo resection of distant metastases, and a quarter of them survive 5 years or more.

Second, earlier detection of symptomatic disease and subsequent reductions in mortality can occur even in the absence of widespread screening. Patients with colorectal-cancer symptoms are most likely presenting earlier and being diagnosed earlier than they were in the past. The widespread availability and use of endoscopy has lowered the threshold for directly examining the colon in people with symptoms that might represent cancer. Upticks in the incidence of local and regional disease in the late 1970s and early 1980s and again in the late 1990s may reflect the increasing use of sigmoidoscopy and colonoscopy, respectively. The decreasing incidence of metastatic disease — the rate at which patients initially present with metastatic colorectal cancer — is compatible with earlier detection of progressive cancers and is an important intermediate step for reducing mortality.

Finally, there could be fewer cases of colorectal cancer occurring in the first place. The incidence of metastatic disease has fallen steadily and substantially — by 45% since 1975. The decrease in overall incidence began well before the expected effect of polypectomy. In the absence of overdiagnosis, decreased incidence will reliably lead to decreased mortality.

A number of factors may be responsible for the decrease in colorectal-cancer incidence. For a gastrointestinal cancer, an obvious candidate would be a change in diet. Reduced consumption of smoked and cured meats has presumably resulted in lower exposure to carcinogenic nitrosamines. Changes in the gastrointestinal microbiome are another obvious candidate. The widespread use of antibiotics has probably led to changes in gut flora, as evidenced by the decreasing prevalence of *Helicobacter pylori*. Finally, the use of nonsteroidal antiinflammatory drugs (including aspirin), hormone-replacement therapy, and statins may have played a role, given their association with reduced colorectal neoplasia.

All of which is not to say that screening has had no effect on colorectal-cancer mortality. The steeper decline in the incidence of both local and regional disease in the past few years may reflect the preventive effects of increased rates of polypectomy. The rate of screening colonoscopy nearly doubled between 2000 and 2005 — from 20% to 39% among U.S. adults 50 years of age or older[5] — which could well explain this trend.

Nevertheless, we believe it's important for clinicians to have some humility regarding the effect of screening on disease trends. Although it's tempting to take credit for good news, doing so may exaggerate the perceived benefits of screening the general population and distract from the more important activities of promoting health — for example, by encouraging a healthful diet and exercise — and caring for the sick. Furthermore, overstating the benefits of colorectal-cancer screening may divert attention from colonoscopy's downstream effects and potential harms. The majority of people undergoing screening are neither identified as having cancer nor protected from its developing, but they often endure repeated colonoscopy for surveillance of small polyps. Certainly, aggressive efforts to screen and perform follow-up colonoscopy in persons who are most likely too old or infirm to benefit has real potential to cause harm. In questioning the argument that screening is the dominant explanation for decreasing colorectal-cancer incidence and mortality, the example of gastric cancer may be salient: since 1930, without any screening effort, gastric-cancer incidence and mortality have decreased by almost 90%.

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