A Colorectal Cancer Moonshot

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Conflict of interest disclosure: None.

This is the author's manuscript of the article published in final edited form as:

Kahi, C. J. (2017). A Colorectal Cancer Moonshot. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 15(6), 910. https://doi.org/10.1016/j.cgh.2017.01.005

In 2016, President Barack Obama appointed Vice President Joe Biden to lead a “Cancer Moonshot” initiative to accelerate and consolidate efforts to prevent, diagnose and treat cancer. The Cancer Moonshot Task Force delivered its report [1] in October 2016, and laid out its vision to transform cancer research and care, and “achieve a decade’s worth of progress in 5 years”. Colorectal Cancer (CRC) was prominently featured in the report: Strategic Goal 4 aims to advance health programs, policies, and outreach to help Americans reduce their cancer risk, strengthen understanding of environmental determinants of cancer, and enhance the cancer screening continuum-concepts which are at the core of CRC prevention. Specifically, the report focuses on the expansion of CRC screening in the US, the removal of insurance barriers, and recognizes the National Colorectal Cancer Roundtable’s “80% by 2018” initiative [2] (to increase CRC screening rates of eligible adults to 80 percent by 2018) as a driving force for state-and local-level initiatives to increase CRC screening.

CRC is a quintessential example of a “screenable” disease [3]: It is common and in general has a long latency period, early detection can decrease mortality, accurate screening modalities and effective treatment options are available, resources are available to screen and to provide diagnostic tests in those with positive screening, screening is cost-effective, and modalities to screen are accepted by patients and providers. It should also be reemphasized that a fundamental attribute of CRC, and one which distinguishes it from other cancers for which screening is recommended and widely practiced, is that it is amenable to primary prevention. Fletcher and colleagues [4] remind us that prevention is “the act of keeping from happening”, and outline the levels of prevention based on timing during disease course: primary prevention keeps the disease from occurring at all, by removing its causes and controlling risk factors; secondary prevention detects disease early at the asymptomatic stage and when treatment can halt progression; tertiary prevention is focused on reduction of complications after disease has become clinically evident. Screening for CRC is, to a certain extent, secondary prevention:

CRC-related mortality is related directly to disease stage at diagnosis; thus, early detection identifies at-risk patients before symptoms occur and increases the chances of a favorable outcome. Unlike other cancers though, for which early detection (secondary prevention) is the only option, screening for CRC relies to a great extent on primary prevention, predominantly through the detection and removal of precancerous colorectal polyps. This concept is not new: in the 1960s, Gilbertsen [5] suggested that CRC could be a preventable malignancy through polypectomy, before the Vogelstein model [6] provided the biologic framework (adenoma to carcinoma sequence with long latency) supporting the rationale for more widespread screening. CRC screening with current modalities has been shown to decrease cancer occurrence and death, and concrete benefits of screening are discernible at the population level: a recent large German population-based study [7] showed that cancers detected by screening colonoscopy had a lower stage than those diagnosed by colonoscopy in patients with symptoms; the magnitude of stage shift was comparable to patients undergoing screening by fecal occult blood testing.

Where do we stand globally with regards to CRC incidence and mortality? In the US, there have been significant long-term declines in overall CRC rates since a peak in the mid-1980s, and the declines have been more pronounced for those 65 years or older [8]. There has been vigorous debate [9] regarding the mechanisms driving these downward trends, with some attributing the benefit primarily to mass screening, and others to improved risk factors. There is a reasonable rationale for both sides of the argument. The observed declines started before widespread screening for CRC, and the timing of decreased mortality at the population level is not consistent with an effect of screening[9], because of the significant time lag (up to a decade) between receipt of screening and measurable impact on CRC death rates [10,11] coupled with the relatively slow uptake of screening in clinical practice [9]. On the other hand, the more recent accelerated declines of proximal colon cancer are more plausibly driven by increased use of screening colonoscopy and polypectomy, and CRC incidence and mortality have *increased* in

persons younger than 50 years, for whom screening is not routinely recommended. Similarly, the “risk factor” hypothesis cannot explain the whole picture. A lot has been written about the nefarious effects of the Western lifestyle, and the associations between obesity, the metabolic syndrome and its components, lack of physical activity, cigarette smoking, and the risk of colorectal neoplasia. Disentangling the effect of these factors on CRC risk at a population level is more complex than that of screening: while screening is a defined event which can be isolated in time, the lifestyle risk factors interact with one another, are influenced by individual predisposing genetic and other factors (such as aspirin/NSAID and calcium use), and exert their effect over many years. In addition, some of these factors would be expected to influence CRC risk in opposite directions; for example, increasing rates of obesity versus decreasing prevalence of cigarette smoking. Screening is likely driving the decline in CRC incidence to a greater extent than that of CRC mortality, because CRC-related deaths are also affected by earlier detection of symptomatic disease, and improvements in cancer therapy. However, ascribing the decreasing CRC rates primarily to screening *or* improved risk factors oversimplifies the issue, as it is likely that both are contributory, albeit to a different extent depending on time frame.

Outside the US, the CRC landscape is less than encouraging. The GLOBOCAN 2012 data [12] depict wide geographical variation in incidence, with rates varying ten-fold in both sexes worldwide (highest estimated rates in Australia/New Zealand and lowest in Western Africa). Nearly 55% of the cases occur in more developed regions, while more CRC-related deaths (52% of the total) occur in less developed regions, reflecting the impact of delayed diagnosis and decreased access to modern therapeutic options. Contrary to the US trends, worldwide, CRC incidence has increased by more than 30% between 2008 and 2013 [13].

Two compelling studies in this month’s issue of *Clinical Gastroenterology and Hepatology* provide a more global perspective on the current and projected burden of CRC, and

offer insight into epidemiological trends. In the first study, Murphy and colleagues [CGH citation] determined the US age-standardized incidence of CRC from 1975 through 2013, using the population-based Surveillance, Epidemiology, and End Results program of cancer registries. CRC incidence peaked during 1980-89, with a subsequent decline beginning around 1990. The declines in incidence between 1980-84 and 2010-13 were limited to the screening-age population, and were more pronounced for whites (40%) than for blacks (26%). In persons aged 20-49 years, CRC incidence increased by 37% between 1990-94 and 2010-13 and was similar for whites and blacks. The study also reported that left-sided CRC incidence began to decrease much earlier (in the mid-1980s) than that of right-sided cancer (starting in 2000); this is consistent with temporal trends of CRC screening modality use in the US, with colonoscopy dominating the field in later years. These data provide a compelling argument to support the notion that widespread screening is responsible for declining CRC incidence, because it is biologically implausible that the same CRC risk factors would exert opposite effects in screening-eligible persons versus those younger than 50. The study cannot draw definitive conclusions regarding causality, and it has limitations inherent to registry research: CRC risk factors such as cigarette smoking, obesity, aspirin/NSAID use, personal and family history of polyps or CRC, inflammatory bowel disease, or Lynch syndrome are not accounted for. Nevertheless, the findings mirror those of a recent study from Germany[14]: after decades of steady rise, CRC incidence and mortality have begun to decrease, within 10 years after the addition of screening colonoscopy to the German national cancer screening program for adults ≥ 55 years old. The second study, by Tsoi and colleagues [CGH citation], utilized cancer incidence data and population statistics from the International Agency for Research on Cancer to project CRC rates in persons 65 years or older in selected countries through 2030, taking into account changing population age structures and national income levels. The US was the only country with projected declines in CRC incidence, from 227.7/100,000 in 2015 to 190.7/100,000 in 2030, while the UK and Sweden were projected to experience modest relative increases

(about 5%) in CRC incidence over the same time frame. Conversely, incidence projections for other developed regions such as Japan and Hong Kong and those from developing regions such as Croatia, Costa Rica, and Shanghai-China, predicted significant relative increases between 2015 and 2030, ranging from 18.5% to 60.5%. Limitations of this study are that the data required for the analysis restricted the selection of registries, raising concerns about generalizability and representativeness, and that long-term projections are subject to uncertainty and multiple possible confounding factors. Nevertheless, it is remarkable that of the selected countries, only the US had predicted long-term decline in CRC incidence, bucking global trends-including those of other developed nations with sophisticated health care systems.

Given the expanding evidence, it is reasonable to postulate that intensified CRC screening efforts could be the primary reason for declining CRC incidence in the US, particularly in more recent years. The 80% by 2018 campaign depends on grassroots initiatives, as it engages stakeholders including health care providers, health systems, communities, businesses, community health centers, state and local government, and cancer survivors, to support CRC prevention. The multi-tiered strategies emphasize both risk factor education and reduction, and actual screening. Why not build and support similar models beyond the borders of the US, under the auspices of the United Nations? We have multiple precedents of successful international collaborative efforts to combat and even eradicate communicable diseases; why not turn global attention and collaboration to a preventable cancer, one which is expected to claim millions of lives over the next 15 years? A global colorectal cancer moonshot is needed.

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