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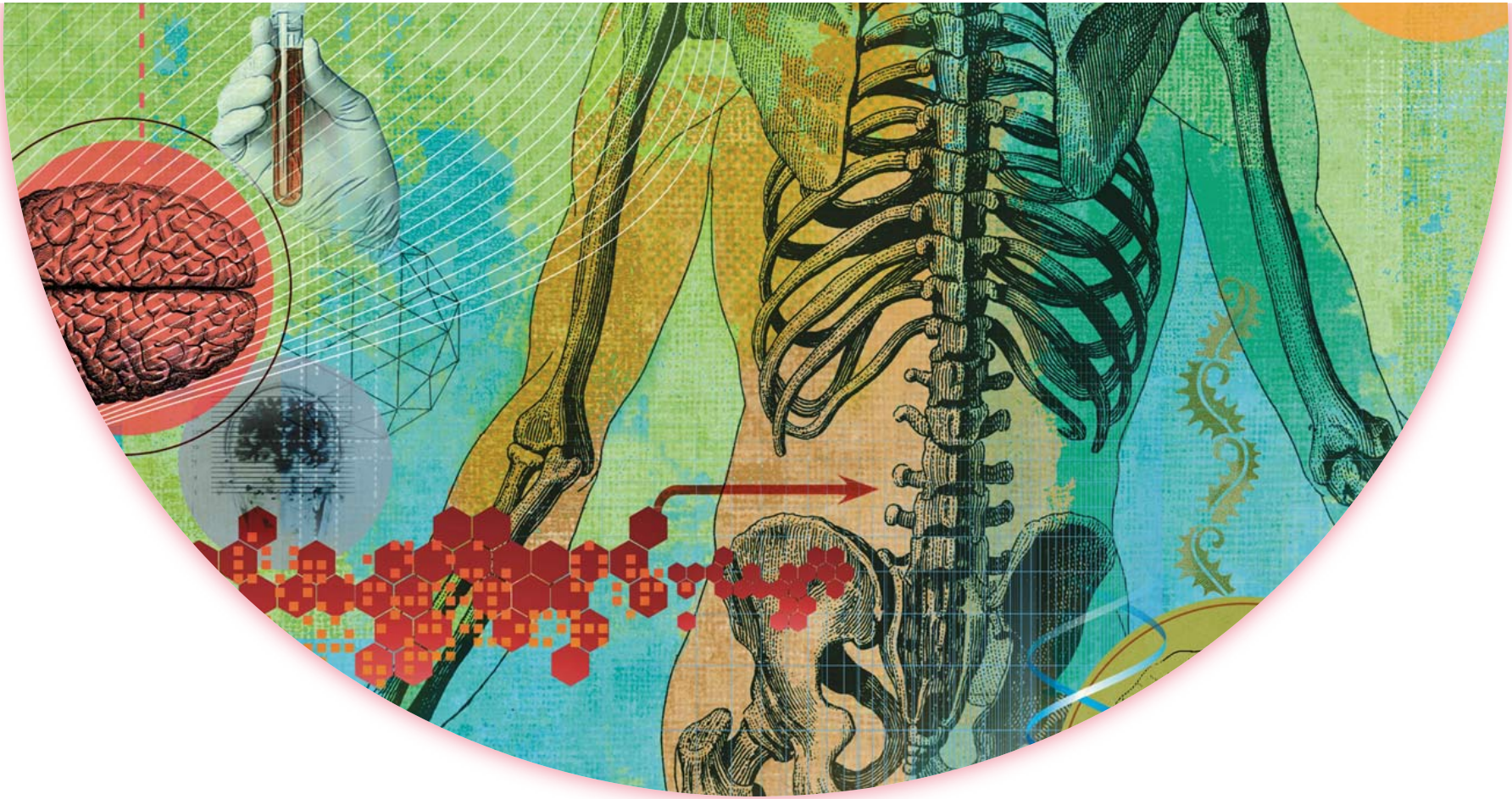
Il miracolo del cancro non è una

cura.



È Prevenzione.

Non possiamo curare la nostra via d'uscita dal crescente carico di casi di cancro. L'unica soluzione è una difesa su vasta scala, in modo che

nessuno soffra la malattia in primo luogo.

Di Madeline Drexler

Illustrazioni di Stephanie Dalton Cowan

Nei prossimi anni, il cancro diventerà la principale causa di morte negli Stati Uniti. Più avanti in questo secolo, è probabile che sarà la principale causa di morte in tutto il mondo. Il cambiamento segna una drammatica transizione epidemiologica: la prima volta nella storia che il cancro regnerà come il killer numero uno dell'umanità.

È una storia di buone/cattive notizie. Il cancro è principalmente una malattia dell'invecchiamento e la dubbia buona notizia è che stiamo vivendo abbastanza a lungo per subirne le devastazioni. La nuova classifica del cancro riflette anche gli impressionanti

guadagni della salute pubblica contro le malattie infettive, che hanno tenuto il primo posto fino al secolo scorso, e contro le malattie cardiache, l'attuale numero uno.

La cattiva notizia è che il cancro continua a portare dolore e dolore ovunque colpisca. Siddhartha Mukherjee ha intitolato la sua biografia magistrale sul cancro *L'imperatore di tutte le malattie* , citando un chirurgo del 19° secolo. Ha omesso la seconda parte dell'epiteto del chirurgo: "il re dei terrori". I moderni trattamenti mirati e l'immunoterapia in alcuni casi hanno portato a cure meravigliose e molte neoplasie vengono ora catturate abbastanza

presto in modo che i loro malati possano vivere una vita piena. Ma i progressi nel trattamento da soli non saranno mai sufficienti per arginare completamente il peso del cancro.

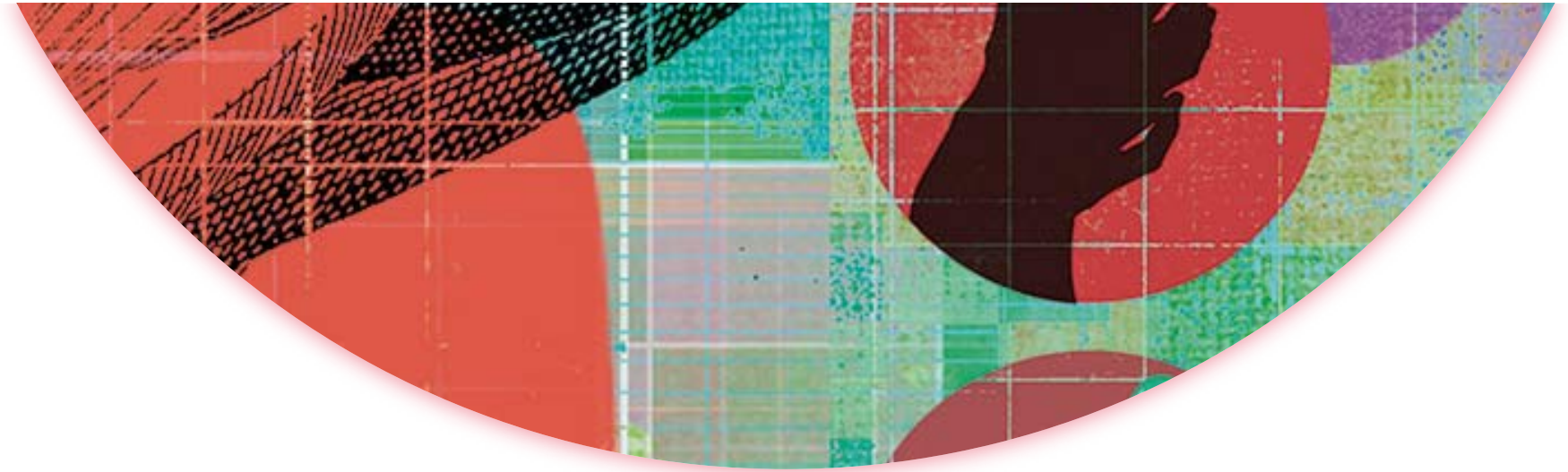
Come ogni professionista della sanità pubblica sa, a livello di popolazione, l'unico modo per ridurre sostanzialmente l'incidenza e la mortalità per qualsiasi malattia è attraverso la prevenzione. E su larga scala, abbiamo fatto molti meno progressi nella prevenzione del cancro che nella prevenzione delle piaghe precedenti. Abbiamo domato le infezioni con servizi igienico-sanitari e vaccini, favoriti dagli antibiotici. Abbiamo domato le

malattie cardiache attraverso la cessazione del fumo, una migliore gestione medica dei fattori di rischio come il colesterolo alto e migliori interventi per una condizione che ha chiari punti di intervento e risponde più prontamente ai cambiamenti dello stile di vita.

Il cancro è una storia diversa. Ancora oggi continua a occupare il nostro immaginario collettivo come il re dei terrori: insidioso, capriccioso, implacabile. Chiunque abbia sofferto di cancro, o abbia sofferto a fianco di una persona cara con la malattia – una parte considerevole della popolazione, dato che a più di uno su tre

di noi verrà diagnosticato un tumore nel corso della nostra vita - conosce l'angoscia e l'impotenza che si trascinano dietro la diagnosi.

Nel 2015, uno studio su *Science* sembrava confermare la nostra paura primordiale. Ha affermato che solo un terzo della variazione del rischio di cancro nei tessuti è dovuto ad aggressioni ambientali o predisposizioni genetiche ereditarie. La maggior parte del rischio, hanno concluso i ricercatori, era dovuta alla "sfortuna", mutazioni casuali durante la normale replicazione del DNA.



E sebbene quello studio abbia provocato torrenti di critiche sul fatto che le sue conclusioni basate su studi sui tessuti possano essere attribuite alle popolazioni, è vero che il cancro è il prezzo che paghiamo come organismi composti da trilioni di cellule. La divisione cellulare è un processo imperfetto; come una tastiera

biologica con una lettera mancante, commette errori. Per questo motivo, è improbabile che il cancro possa mai essere debellato.

La realtà del cancro si trova da qualche parte tra l'ideale di salute pubblica della perfetta prevenzione e il deprimente stocastico della sfortuna. La ricerca attuale suggerisce che almeno la metà dei casi di cancro - le stime vanno dal 30 percento fino al 70 percento - potrebbe essere prevenuta applicando ciò che già sappiamo. L'altra metà dei casi di cancro, compresi i tipi sfuggenti e spesso mortali, spesso rilevati troppo tardi per fare la differenza, come i tumori ovarici, del pancreas e del cervello,

potrebbero essere rilevati e potenzialmente persino prevenuti molto prima se la scienza di base e le promettenti tecnologie diagnostiche ricevessero il sostegno governativo sostenuto di cui hanno bisogno.

In parole povere, il cancro deve essere inquadrato non solo come una malattia curabile, ma anche come una malattia prevenibile. "Avremo sempre bisogno di buoni trattamenti", afferma Timothy Rebbeck , il professor Vincent L. Gregory, Jr. di prevenzione del cancro presso la Harvard TH Chan School of Public Health e il Dana-Farber Cancer Institute e direttore del Zhu Family Center

for Prevenzione globale del cancro . “Ma non possiamo trattare la nostra via d'uscita da questo problema. Per intaccare il senso di salute pubblica, dobbiamo prevenire il cancro”.

Un triste riscontro

Nel 2019, secondo l'American Cancer Society, a circa 1.762.450 persone verrà diagnosticato un cancro negli Stati Uniti e circa 606.880 moriranno a causa della malattia. A livello globale, il cancro ha ucciso circa 9,6 milioni di persone nel 2018, più della

malaria, della tubercolosi e dell'HIV messi insieme. In questo secolo, il cancro diventerà non solo la principale causa di morte nel mondo (in 91 nazioni è già la prima o la seconda causa di morte prima dei 70 anni, secondo l'Organizzazione Mondiale della Sanità), ma anche il più grande ostacolo al miglioramento della vita aspettativa in decine di nazioni.

Le ragioni dell'ascesa del cancro sono complesse. Parte della tendenza è demografica: la popolazione umana cresce e invecchia ogni anno, il che significa che più persone sono vulnerabili alla malattia, il che sfrutta il sistema immunitario in declino e il danno

accumulato al DNA che accompagna l'invecchiamento. Ma anche i principali fattori di rischio del cancro stanno cambiando. Mentre il fumo è in calo negli Stati Uniti, ad esempio, è in aumento in Africa e nel Mediterraneo orientale, poiché le aziende del tabacco si espandono in nuovi mercati. E mentre l'uso di sigarette è il fattore di rischio più importante per il cancro in tutto il mondo, le infezioni cancerose, come l'epatite e il virus del papilloma umano (HPV), entrambi prevenibili con i vaccini, rappresentano fino al 25% dei casi di cancro in alcuni casi di paesi a reddito medio.

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Queste sabbie mobili della causalità sono evidenti anche negli Stati Uniti. Negli ultimi 25 anni, mentre i decessi per cancro sono aumentati di numero con l'aumento della popolazione, il tasso di mortalità per cancro è costantemente diminuito. Nel 2016, il tasso di mortalità per cancro tra uomini e donne insieme era sceso del 27% dal picco del 1991. Il motore di questa impressionante

impresa di salute pubblica è stato il calo del fumo, sebbene anche la diagnosi precoce e il miglioramento dei trattamenti abbiano svolto un ruolo. Nel 1965, il 42% degli adulti statunitensi erano fumatori di sigarette; nel 2017 appena il 14 per cento. I tassi di mortalità per cancro al polmone sono diminuiti di pari passo, scendendo del 48% dal 1990 al 2016 tra gli uomini e del 23% dal 2002 al 2016 tra le donne.

Quella vittoria per la salute pubblica è ora in pericolo. Nei prossimi cinque o dieci anni, affermano gli esperti, gli effetti cancerogeni dell'obesità potrebbero effettivamente invertire la tendenza al

ribasso introdotta dal declino del fumo. In effetti, l'obesità potrebbe presto diventare il fattore di rischio numero uno per il cancro negli Stati Uniti e, infine, in tutto il mondo. E data l'apparente irreversibilità dell'obesità, contrastare l'aumento concomitante del cancro sarà estremamente difficile. Negli Stati Uniti, si stima che il 39,5% degli adulti sia obeso e un ulteriore 31,8% in sovrappeso.

Il Centro familiare Zhu per la prevenzione globale del cancro

Nel febbraio 2019, la Harvard TH Chan School of Public Health ha istituito lo Zhu Family Center for Global Cancer Prevention, un centro interdisciplinare innovativo che si concentrerà sull'istruzione e sulla ricerca volte a prevenire il cancro e a migliorare la diagnosi precoce. A differenza della maggior parte della ricerca attuale sulla prevenzione del cancro, che si svolge in discipline isolate che raramente comunicano o uniscono le forze, lo Zhu Family Center incoraggerà le collaborazioni tra i ricercatori che esplorano le cause di base del cancro, coloro che costruiscono tecnologie che possono essere utilizzate per rilevare precocemente il cancro, e quelli formati per attuare tali strategie nelle comunità locali.

Il direttore del centro è Timothy Rebbeck, Vincent L. Gregory, Jr. Professore di prevenzione del cancro presso la Harvard Chan School

e Dana-Farber Cancer Institute (DFCI), professore di oncologia medica presso DFCI e direttore associato per l'equità e il coinvolgimento presso il Dana-Farber/Harvard Cancer Center. Rebbeck conduce studi di epidemiologia molecolare sull'eziologia del cancro, i risultati, le disparità di salute e la salute globale. Il suo lavoro ha portato a approfondimenti sulle cause genetiche e ambientali dei tumori al seno, alla prostata, alla pelle, all'endometrio e alle ovaie.

“Speriamo di creare una nuova nicchia nel campo della prevenzione del cancro”, afferma Rebbeck, “trovando aree che non sono interamente tecnologia e non interamente salute pubblica, ma l'interfaccia di questi diversi regni. È qui che pensiamo di poter avere un impatto”.

L'obesità è un fattore di rischio consolidato per almeno 13 tumori. Secondo un rapporto del 2019 su *The Lancet Public Health* , negli Stati Uniti il peso corporeo in eccesso rappresentava fino al 60% di tutti i tumori dell'endometrio, il 36% dei tumori della cistifellea, il 33% dei tumori del rene, il 17% dei tumori del pancreas e l'11% dei tumori. mielomi multipli nel 2014.

Secondo lo studio The Lancet Public Health , l'aumento dell'obesità tra i giovani potrebbe presagire una maggiore ondata di cancro nel prossimo futuro . Negli Stati Uniti, l'incidenza è aumentata significativamente per sei tumori correlati all'obesità nei giovani

adulti, con ogni generazione successivamente più giovane che ha subito un tasso di cancro più elevato rispetto alla generazione precedente. Questi casi di cancro fungono da sentinelle per future malattie nelle persone anziane. Alla luce dell'aumento dei tassi di cancro del colon-retto tra i giovani adulti, una tendenza che suggerisce fattori ambientali, l'anno scorso l'American Cancer Society ha abbassato l'età consigliata per il primo screening del cancro delle persone, da 50 a 45 anni.

Calcolo dei benefici della prevenzione

Due tipi di prevenzione possono ridurre sostanzialmente i decessi per cancro. La prima, e più importante, è la prevenzione primaria: scongiurare una neoplasia attaccandone le cause e promuovendo i fattori che la proteggono. Tasse su sigarette e alcol, vaccinazione contro agenti patogeni cancerogeni come HPV ed epatite B, promozione di un'alimentazione sana e regolare esercizio fisico: sono tutti esempi di prevenzione primaria. La prevenzione primaria funziona quando le condizioni sociali ed economiche, l'ambiente edificato, i sistemi sanitari e sanitari pubblici collaborano per sostenerla.

La prevenzione secondaria controlla il cancro mediante screening per rilevare la malattia nelle sue fasi iniziali e, se necessario, intervenendo precocemente nel corso della progressione della malattia. La prevenzione secondaria ha contribuito a ridurre i tassi di mortalità dei tumori della mammella, del collo dell'utero e del colon-retto, tra gli altri.

Studi epidemiologici a lungo termine hanno chiarito quali tumori sono prevenibili e di quanto, se i fattori di rischio specifici sono stati ridotti. Un rapporto del 2016 su *JAMA Oncology* di Ed Giovannucci della Harvard Chan School , professore di nutrizione

ed epidemiologia, e Minyang Song , assistente professore di epidemiologia clinica e nutrizione, hanno scoperto che il 20-40 percento dei casi di cancro e circa la metà dei decessi per cancro potrebbero essere potenzialmente prevenuto attraverso la modifica dello stile di vita, incluso smettere di fumare , evitare il consumo di alcolici , mantenere un indice di massa corporea compreso tra 18,5 e 27,5 e fare esercizioad intensità moderata per almeno 150 minuti o ad intensità vigorosa per almeno 75 minuti ogni settimana. (Un ulteriore vantaggio è che la promozione dei fattori di rischio protettivi del cancro potrebbe anche prevenire

altre malattie comuni non trasmissibili, come il diabete di tipo 2, le malattie cardiache, la demenza e la depressione.)

A 2018 study in *Science*—co-authored by Song, Giovannucci, and Harvard Chan's Walter Willett, professor of epidemiology and nutrition—made an even more emphatic case for prevention. It noted that for cancers in which most of the driving genetic mutations are caused by the environment—such as lung cancers, melanomas, and cervical cancers—85 to 100 percent of new cases could be eliminated through smoking cessation, avoidance of

ultraviolet radiation exposures, and vaccination against HPV, respectively.

"With such further research, we envision that cancer death rates could be reduced by 70 percent around the world, even without the development of any new therapies," the authors concluded. "Such a reduction, similar to that for heart disease over the past six decades, will only come about if research priorities are changed." Specifically, the authors argue for more support of molecular, behavioral, and policy research on prevention.

Even individuals at high inherited genetic risk for cancer can benefit from lifestyle change, adds Peter Kraft, professor of epidemiology at the Harvard Chan School. In 2016, Kraft published a paper in *JAMA Oncology* showing that U.S. women who were in the highest decile of breast cancer risk because of factors they could not alter—mostly genetics but also family history, height, and menstrual and/or reproductive history—actually benefited the most from a healthy lifestyle. In fact, the women who had the highest nonmodifiable risk but also kept their weight down, did not drink or smoke, and did not use menopausal

hormone therapy had about the same breast cancer risk as an average woman in the general population.

"Although our day jobs are studying the genetics of cancer, genetics is not destiny, by any means," says Kraft. "This is something we've seen consistently across many cancers—and many diseases generally. Even if you're high-risk based on your genetics, there's still plenty that you can do to reduce your risk. In fact, high-risk individuals are the people who seem to reap the biggest benefit from adopting healthy lifestyles."

Cancer Clues across Two Dimensions

Should anyone still doubt that many cancers are preventable, the inarguable proof is how the disease plays out over time and space. Cancer rates and types can starkly change within a country and starkly vary between countries. These variations are not genetic—a small minority of cancers are directly attributable to known, death-dealing DNA mutations. Rather, they reflect external—and, in principle, modifiable—risk factors.

For example, lung cancer eclipsed all other cancers during most of the 20th century in the United States because per capita cigarette consumption shot up from 54 cigarettes a year in 1900 to 4,345 cigarettes in 1963, then fell to 2,261 in 1998. The initial upward trend was powered by corporate profiteering. The downward slope was powered by the landmark 1964 U.S. Surgeon General’s report on smoking and health, which firmly linked smoking and lung cancer and led to public education, indoor smoking bans, and higher tobacco taxes. Another instance of a breathtaking prevention success within a country took place in the 1980s and 1990s in Taiwan, which saw an 80 percent decline in liver cancer

rates in birth cohorts that received hepatitis B vaccination early in life. (The most common causes of liver cancer are infection with the hepatitis B virus in Africa and East Asia, and the hepatitis C virus in the U.S. and Europe.) And Australia recently reported it is on course to completely eliminate cervical cancer in the coming decades through vaccinations.

The spatial dimension of cancer is equally revealing. When racial or ethnic groups migrate from one part of the world to another, their cancer risks quickly take on the local patterns. Between 1975 and 2003, for example, numerous studies looked at cancer

incidence in U.S. Caucasians, immigrant groups, and matched controls. Among the populations studied were first- and second-generation Japanese immigrants, Asian American women, Vietnamese Americans, and Hmong refugees from Vietnam, Laos, and Thailand. Drawing on data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program, the studies found that the kinds of cancers that were newly diagnosed among first-generation immigrants in the U.S. were nearly identical to the kinds in their native countries. But over subsequent generations, their cancer patterns became distinctly American. This was especially true for cancers related to

hormones, such as breast, prostate, and ovarian cancers, and to cancers attributable to Westernized diets, such as colorectal malignancies.

Understanding Cancer’s Genesis

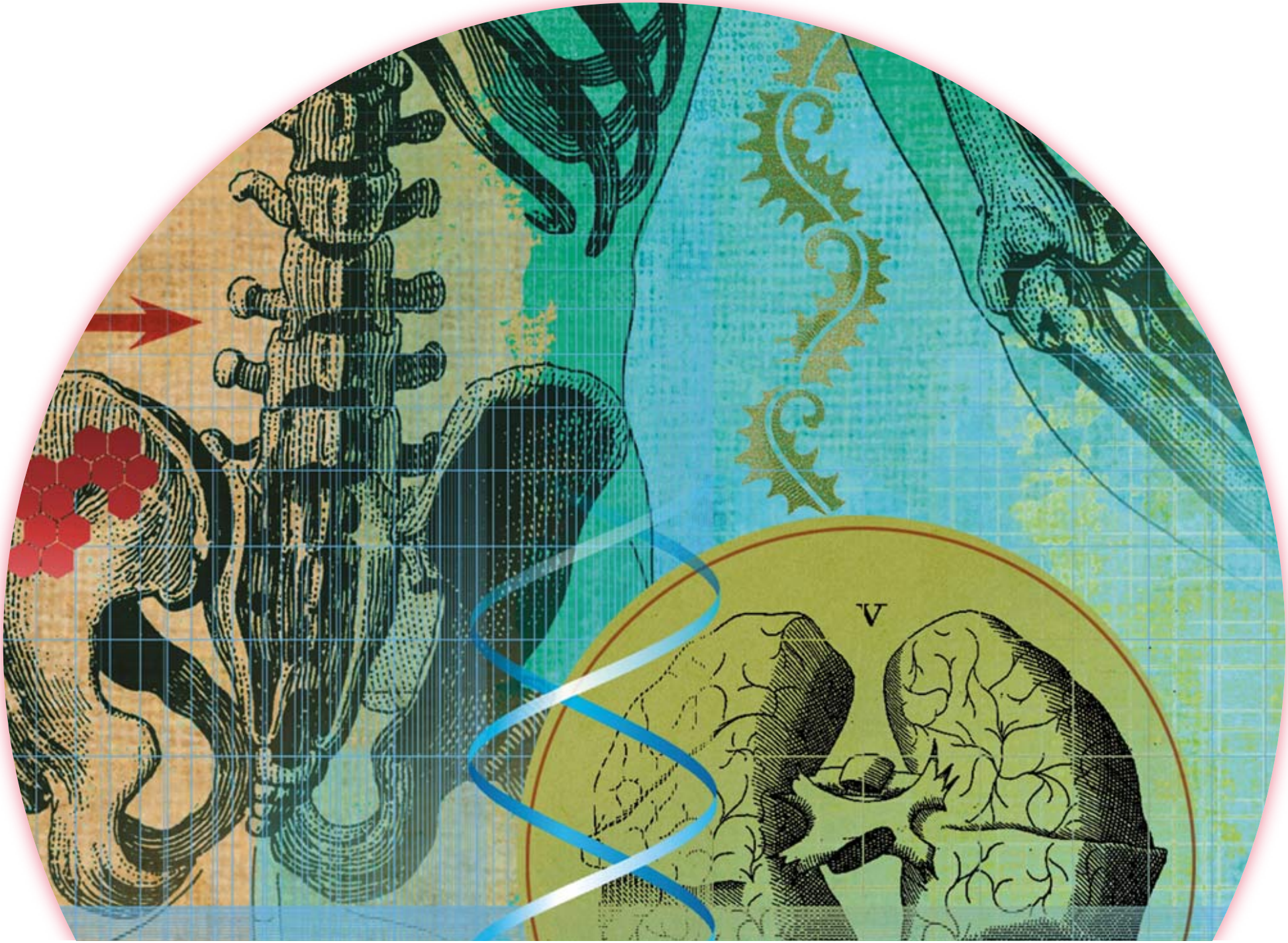
Given the fact that many cancers can be averted, what would it take to make the dream of prevention a reality?

First, scientists say, we must understand the earliest biological events that give rise to the birth of a cancer cell. While genomic analyses have provided a good molecular description of cancer, researchers still don’t understand how and when cells start to go rogue.

“Cancer initiation is much less well understood than the biology of cancer cells themselves,” says Brendan Manning, professor of genetics and complex diseases at the Harvard Chan School. “Cancer cells are doing things that normal cells do, only in an uncontrolled manner. So, how is cancer initiated? What are the

brakes on early cancer? What are the challenges that the cancer cell faces in becoming a cancer cell? How does the cancer cell remove enough of those brakes so that it will become malignant?" Answering those questions will also shed light on the mechanisms by which apparent cancer risk factors, such as aging or obesity or chronic inflammation, trigger uncontrolled cell growth and progression to cancer, says Manning.

Manning's lab explores how the body's cells and tissues sense nutrient shifts in their local environment and adapt accordingly. "The cells in our body have the ability to acclimate to changes in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nutrient availability, and this is achieved through special lines of communication—referred to as nutrient sensing pathways—that serve to tune cell metabolism to match these changes,” he says. “Understanding these fundamental mechanisms has provided us with key insights into how nutrient sensing becomes corrupted in

human cancers, which universally exhibit alterations in cellular metabolism that underlie uncontrolled growth."

Another biological unknown is the role of the microbiome—the trillions of microbes in and on our bodies—in human cancer. "These living organisms can at times be found right at the site of the cancer," says Wendy Garrett, professor of immunology and infectious diseases at the Harvard Chan School. "We are beginning to see very provocative associations between the microbiome and cancer, and interesting molecular mechanisms—which are emerging from experiments with cells and in tissue

cultures and preclinical mouse models—may explain these associations.”

One intriguing culprit on which Garrett and her colleagues are focusing is *Fusobacterium nucleatum*, normally a microbial denizen of the mouth. Garrett’s lab and others have shown that the bacterium is abundant in colon tumors. She wants to find out why, whether such bacteria are important early signals for carcinogenesis, and if any interventions—such as changing one’s everyday behaviors and exposures, including diet and tobacco use

—map onto the microbiome and could potentially halt the disease process.

The microbiome is proving to be a vast and inviting landscape in cancer biology. In humans, gum disease caused by bacterial infections has been connected to higher risk of pancreatic cancer. In mice, lung tumors appear to alter nearby bacterial populations to help the tumors thrive—and antibiotics appear to shrink the tumors. Experiments in mice have even linked a disrupted gut microbiome to greater risk of invasive breast cancer.

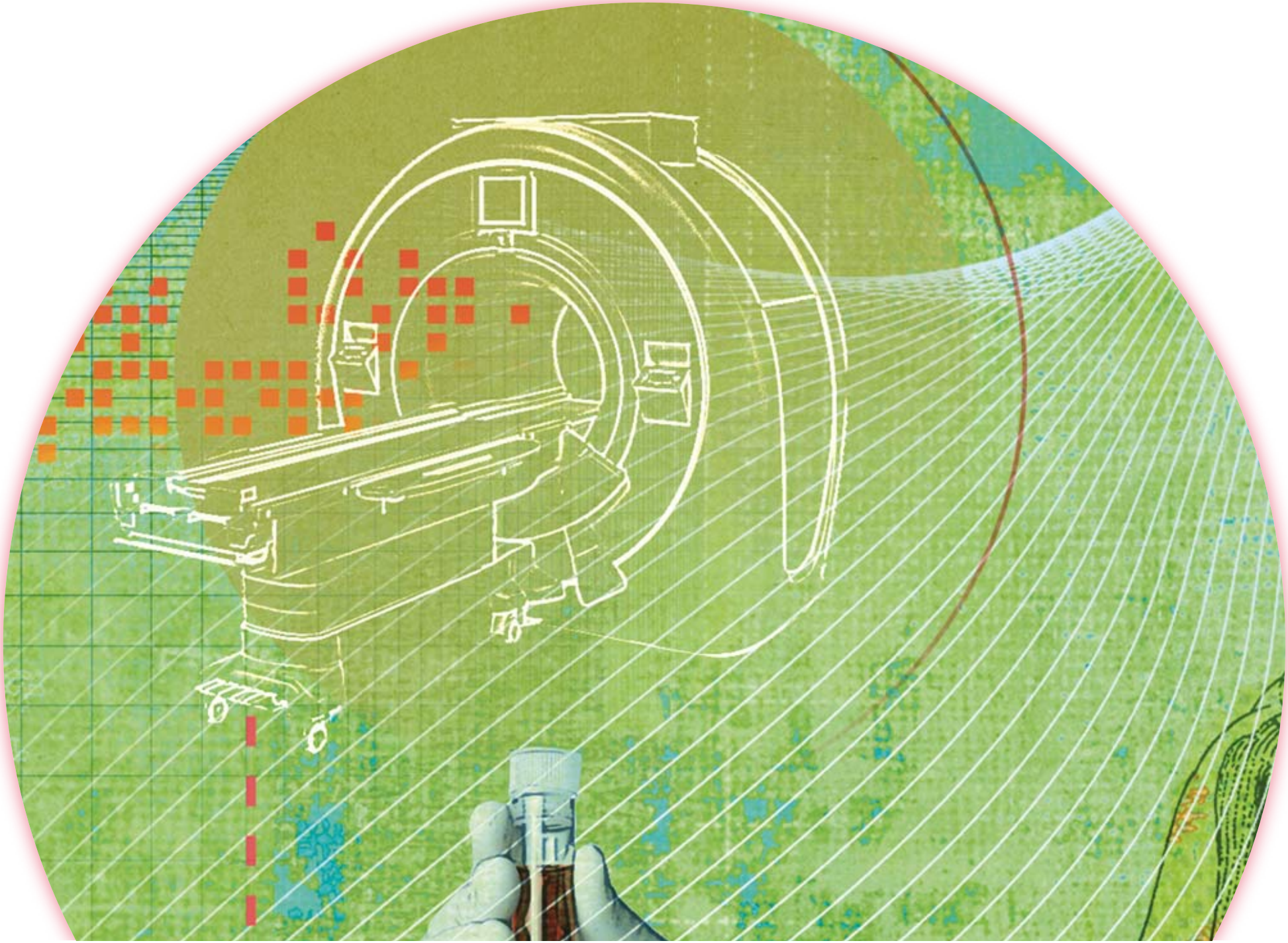
"It's possible that the cancers for which we currently don't fully understand risk factors—such as pancreatic and ovarian cancer—might be tied to infections and therefore be preventable," says Giovannucci. "Forty years ago, we didn't know what caused stomach cancer. Now we know: the bacterium *Helicobacter pylori*." *H. pylori* is treatable with antibiotics, and stomach cancer rates have dropped considerably as a result.

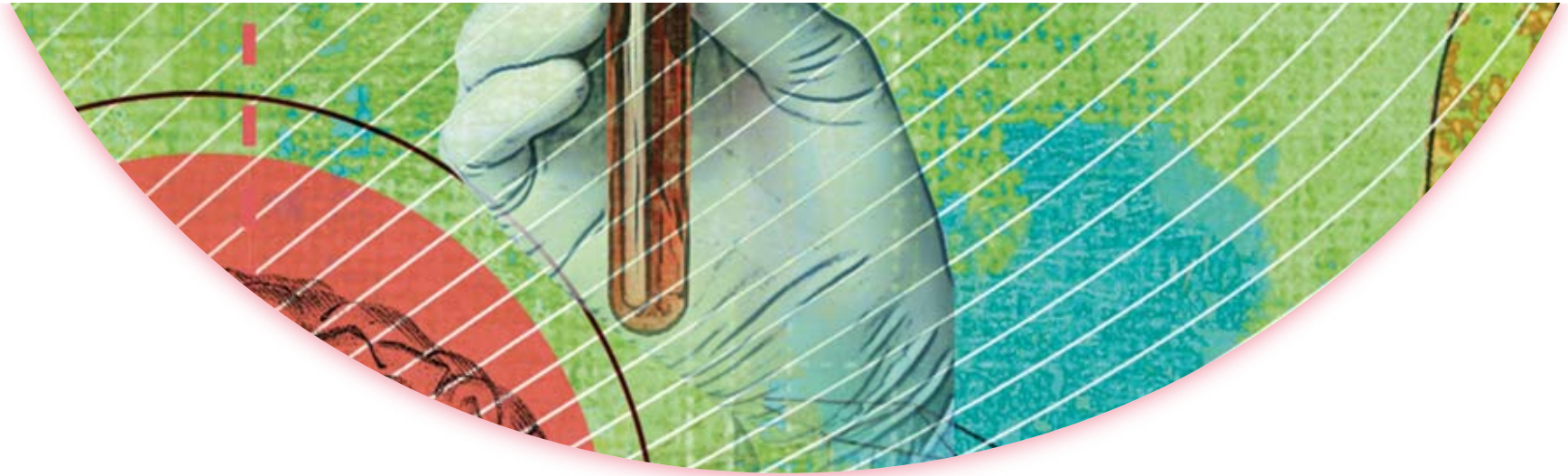
Prevention via Detection

With many tumors, there is a lag time of 20 years or more between the development of the first cancer cell and the onset of end-stage metastatic disease. Knowing each cancer's basic biology could lead to a host of new technologies that register early biomarkers of the disease, potentially opening up new ways to head off malignancy before it spreads. That prospect would be transformative for the implacable cancers that don't cause symptoms until they have reached their late and often incurable stages.

Among these promising biomarkers are proteins that signal early tumors, DNA or RNA, small molecules, circulating tumor cells, immune cells, and other infinitesimal biological entities. Scientists are also fashioning synthetically engineered biomarkers that harness the body's own biology to spin off early signals of disease. "It's a matter of screening technology getting refined enough so that you can find two suspicious molecules in four liters of blood which suggest you are at risk for or have already developed cancer," says Rebbeck.

Sangeeta Bhatia, a biomedical researcher and early-detection pioneer, and the John J. and Dorothy Wilson Professor of Engineering at the Massachusetts Institute of Technology, injects nanoparticles into the bloodstream that respond to cancer-associated enzymes. When the particles find the enzyme for which they are designed, a chemical reaction produces "reporters": synthetic chemicals eliminated in the urine that can tip off researchers to a nascent malignancy. Her lab is searching for highly specific biomarkers for often-elusive tumors of the ovary and lung and in colon metastasis. Clinical trials for the technology will begin later this year.





“Ultimately, we’d like to be in a place where you could do a urine test on a paper strip for a defined set of cancers,” Bhatia says. Other scientists envision, in the more distant future, continuous monitoring of cancer risk through smart toilets, wearables such as diagnostic imaging bras, and other passive and noninvasive technologies.

In clinical medicine, the value of screening tests is gauged by their sensitivity and specificity. Sensitivity measures a test’s ability to identify people who have the condition that is being tested for; a highly sensitive test will not generate false-negative results. Specificity measures a test’s ability to identify people who do not have the condition that is being tested for; a highly specific test will not generate false-positive results.

All the futuristic approaches described above require knowing that a technology’s molecular quarry is made by a certain kind of cancer cell and only that cancer cell—that is, the screening test

must be highly specific. Since many tiny malignancies never go on to become metastatic disease—because the immune system reins in such cells—the ideal biomarker would not only tip off doctors to the presence of a cancer or precancer but also predict whether the suspect cells are aggressive or slow-growing. "[O]ne can imagine a day when healthy individuals are routinely tested for these biomarkers to detect early cancers, along with lipid concentrations to detect early cardiac disease, at periodic visits to their physicians," the Harvard Chan School scientists wrote in *Science* in 2018.

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Before liquid biopsies, “smart tattoos” that light up in the presence of cancer cells, small ingestibles that monitor the gastrointestinal tract, and other early-detection tests that sample blood, urine, saliva, or the breath can ever become part of the annual physical, they will have to be honed to the point of 99.9

percent accuracy or higher, similar to the accuracy of the early-pregnancy urine tests available at any drugstore. That is, they must be both highly sensitive and highly specific. This high degree of accuracy prevents false negative or false positive results when the test is used in large numbers of people.

Such tests could also help doctors decide whom to monitor more closely for cancer. "Advances in biomarker testing could help us better risk-stratify the population," says Jane Kim, professor of health decision science at the Harvard Chan School. "The whole point of screening is to pull out the people who are at lowest risk

and focus your attention on those at highest risk. Today, with cervical and even colorectal cancer, there is a prevention mechanism: You remove precancerous lesions before they develop into cancer. But with breast cancer, you need early detection, because there are no really strong prevention mechanisms. Risk-stratifying patients would help efficiently identify high-risk patients through prevention and early detection."

Validating today's candidate biomarkers will partly depend on long-term cohort studies—such as the Nurses' Health Study—

that have followed healthy volunteers over decades, collected biological material from these volunteers, and tracked the natural course of diseases as the participants aged. To speed the clinical validation of such early diagnostic tests, researchers will first try them out on people at high genetic risk for various cancers, for whom the tests have a higher likelihood of detecting an abnormality and making an impact.

“Combining basic science and cohort studies would also facilitate the discovery and validation of new biomarkers,” says Manning. “If you’re banking molecular information from blood and tissue,

and the data changes over time, you can look back retrospectively at thousands of patient outcomes and see if the changes predicted an outcome or might be related to that outcome. Basic science holds the key to determining how that identified biomarker links back to the disease state and whether it is contributing to the disease's onset—perhaps as a risk factor—or is a consequence of the disease."

But being able to find an early cancer or predict its progression is not enough. "The key thing is that you have an intervention and that it's actionable," says Rebbeck. Such interventions might

include surgery, cancer vaccines, anti-inflammatory drugs, a standard chemoprevention treatment, tinkering with the body's microbiome, or even lifestyle change. "If you detect an early cancer biomarker but cannot act on it, then it may just produce anxiety," he says. "There is a quote from Sophocles that we sometimes use: 'Knowledge is but sorrow when wisdom profits not.'"

From Science to Action

Just as crucial will be translating new scientific insights into public health practice—a field known as implementation science. "Public health impact is efficacy times reach," says Karen Emmons, professor of social and behavioral sciences at the Harvard Chan School. "We often develop interventions without thinking about the end users and what could get in the way of true impact, so shame on us as a field. As a scientific community, we think, rather arrogantly, 'Well, we've shown that colorectal cancer screening is important—why don't community health centers just make sure that everybody has colorectal cancer screening? It's clear that vaccines are important—why aren't all

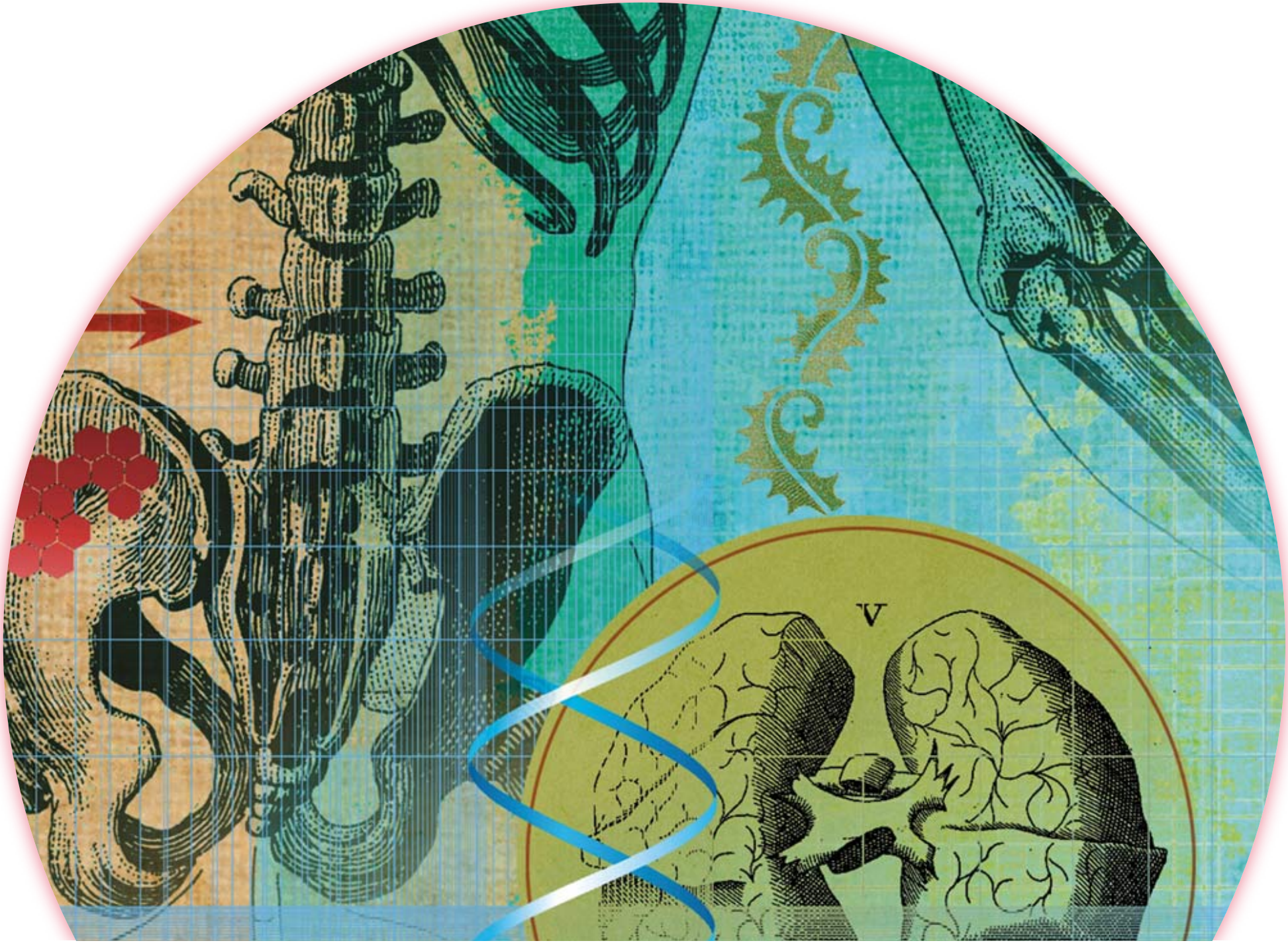
kids getting HPV vaccine?' But the real question is: How do you structure systems to make those goals possible?"

Today's cancer prevention and detection efforts regularly fall short in their impact. Although HPV vaccination administered in preadolescence, before a teen becomes sexually active, theoretically prevents some 90 percent of cervical cancers, the U.S. vaccination rate among adolescents is low. In 2017, only 42 percent of girls and 31 percent of boys received the two recommended doses before their 13th birthday. Similarly, in 2015, only 50 percent of women ages 40 years and older reported

having a mammogram within the previous year, and only 64 percent within the previous two years.

Even the most well-established intervention against the most formidable cancer threat in the U.S.—lung cancer—is only fitfully used. "For some time after we started doing lung cancer screening for smokers, we didn't also do smoking cessation with them," says Emmons. "Even today, we still do it inconsistently. Now how stupid is that?"

Alan Geller, senior lecturer on social and behavioral sciences at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the Harvard Chan School, has seen up close how the failure to translate science into action and policy leads to health disparities. “All of my work now is trying to ask the big question of who unnecessarily dies from preventable diseases,” he says. “Smoking rates are at best stabilizing among low-income people in the U.S. —but they’re stabilizing at 30 to 33 percent of the adult

population. Among the well-to-do, smoking rates have for years been well below 10 percent. It's not a racial disparity—it's an income disparity, because the smoking rate among whites and African Americans is exactly the same. So we should target low-income people. Public health needs to go where high-risk people are."

Geller adds that with smoking, four strategies could substantially reduce cancer deaths. "First would be to work really hard in the U.S. South, where smoking rates are double those in the North. Second would be working among people with mental health

issues, because 41 percent of all smokers have diagnosed mental health conditions. Third would be figuring out how we could intervene with people who have GEDs [general education diplomas, also known as high school equivalency certificates]; 14 million people in the United States have one, and as a group their smoking rates are 40 percent. And fourth would be working with people in public housing—figuring out how their doctors and housing providers can give them access to nicotine replacement therapy, which is extraordinarily inexpensive, and how they can use community health workers and patient navigators. Those are

all beautiful, low-cost, public health models for smoking cessation and lung cancer prevention."

"When you look at cancers that are preventable, as soon as something comes online to screen or prevent, you start to get pretty sharp disparities by race, ethnicity, and income."

—Karen Emmons, professor of social and behavioral sciences

It’s almost a public health truism that when breakthrough medical advances hit the market, they disproportionately benefit people of means and thus widen health disparities. This divide is brutally apparent with cancer. From 2012 to 2016, for example, death rates in the poorest U.S. counties were two times higher for cervical cancer and 40 percent higher for male lung and liver cancers compared with rates in the richest counties. Poverty is also linked with lower rates of routine cancer screening, later stage at diagnosis, and a lower likelihood of receiving the best treatment.

"There are still parts of this nation where the rates of cervical cancer mirror those in developing countries—not developed countries," notes Susan Curry, distinguished professor of health management and policy and dean emerita of the College of Public Health at the University of Iowa, and immediate past chair of the U.S. Preventive Services Task Force. "Are there barriers to screening within the population eligible to be screened? Are there barriers in terms of the organization and availability of screening? Are there barriers in terms of, you can get screened, but if you don't have the means to follow up on a positive test or don't understand what that is, then screening is for naught? We can

pinpoint some pretty disturbing disparities. But how much are we investing in the intervention science that we need to close those gaps?"

These divergences are writ larger on the global stage. Earlier this year, *The Lancet Global Health* published a damningly titled article: "Cervical cancer: lessons learned from neglected tropical diseases." The malignancy claims 310,000 lives annually around the globe, making it the fourth-most-common cancer killer of women. "[C]ervical cancer is not a disease of the past—it is a disease of the poor," the authors state. They go on to list the

hurdles that cervical cancer—which could virtually be eliminated from the planet with vaccination and screening—shares with neglected tropical diseases: Both accompany poverty; strike populations mostly overlooked by policymakers; are associated with stigma and discrimination; strongly affect female morbidity and mortality; tend to be neglected in clinical research and technological development; and can be controlled, prevented, and conceivably eliminated through currently available solutions that are cheap and effective.

It's worth noting that in Africa, more people die from cancer than from malaria. And while overall cancer death rates have been rising in Africa—and will double in the next 20 years—malaria death rates are dropping because of concerted efforts to prevent and treat the infection.

A 2009 study in the journal *Cancer Epidemiology, Biomarkers & Prevention* underscored the fact that the newest and best cancer preventions disproportionately benefit people of means. The study found that the more knowledge, technology, and effective medical interventions there are for a given disease—that is, the

more amenable a disease is to early detection and cure—the wider its disparities, because people who have knowledge, income, and useful social relations stand a better chance of surviving. By contrast, with diseases where effective medical interventions are absent or negligible, such as ovarian or pancreatic cancers, social and economic resources are of limited use, and survival differences between the most and least socially advantaged people are minimal.

“When you look at cancers that are preventable, as soon as something comes online to screen or prevent, you start to get

pretty sharp disparities by race, ethnicity, and income," says Emmons. "Colon cancer is a great example. Before sigmoidoscopy and colonoscopy screening came on board, there were actually slightly higher rates of colon cancer in whites than there were in blacks. Literally within three years after these screening tools were introduced, colon cancer rates among whites fell dramatically, but the rates in blacks did not. You see this over and over again."

Such health inequities represent lives lost to cancer. When Emmons looks at new technologies, she asks: "What is the user

perspective? How will the new technology interface with places where lower-income populations get their care? What does the technology mean for population health management, as opposed to managing the health of an individual? If you don't pay attention to how these technologies are utilized across racial and economic lines, you wind up with persistent disparities that we shouldn't tolerate."

The Prevention Mindset

In the 1970s, a *New Yorker* cartoon depicted two stereotypical (for that era) male scientists standing before a blackboard scrawled with complicated equations. In the middle of these obscure scribbles is the phrase: "THEN A MIRACLE OCCURS...."

So it goes with cancer. "A cure for cancer" is our cultural synonym for a miracle. But as Curry points out, "We're still waiting for that miracle." When cancer treatments work, as they increasingly do, they seem indeed miraculous. But often, they come too late. The real miracle would be to prevent cancer from ever striking.

"Prevention is very hard," Rebbeck concedes. "People want to think about cure. They say we need to cure cancer—and if someone has cancer, you absolutely want to cure it. But what's not gotten into the public mindset is that we need to prevent cancer so that nobody needs to be cured."

"For decades, success in cancer control has been 'just around the corner,'" wrote Tom Frieden, the then-commissioner of the New York City Department of Health and Mental Hygiene, in 2008 in *The Oncologist*. Frieden, who went on to lead the U.S. Centers for Disease Control and Prevention (CDC), added, "Yet, to wage a true

war on cancer, we must expand our approach to give preventive interventions at least as much focus as medical treatment." Pointedly, he added that such a goal would require correcting the imbalance between "money invested in cancer treatment and money invested in cancer prevention."

In the next five to 10 years, the cancer-causing effects of obesity could reverse the downward trend ushered in by the decline in smoking.

Currently, those two streams of funding are wildly unequal. In fiscal year 2018, the last year for which data is available, only 5.7 percent of the National Cancer Institute (NCI) budget was allotted to cancer prevention and control. Today, even the money for treatment research and other programs may be whittled back. The proposed fiscal year 2020 budget for the NCI is $5.2 billion—nearly $900 million less than the enacted 2019 budget. At the CDC, the proposed budget for cancer prevention and control was trimmed by more than $34 million—a 9 percent cut from last year. Globally, cancer prevention research is allotted an estimated 2 to 9 percent of global cancer research funding.

"The biggest unknown in cancer prevention is how to sustain proven, effective, and lifesaving preventive efforts over the long run," says Howard Koh, the Harvey V. Fineberg Professor of the Practice of Public Health Leadership at the Harvard Chan School and the Harvard Kennedy School; former assistant secretary for health for the U.S. Department of Health and Human Services; and former commissioner of public health for the Commonwealth of Massachusetts. "Prevention should be integral, not optional. But in government, prevention budgets are always the first items to be cut and the last to be restored."

Some researchers go so far as to argue that government research funding should be shifted somewhat from treatment to prevention—because solving the front end of the problem will save countless more lives. Others disagree, arguing that cancer will never go away completely and that, even today, we only know how to prevent about half of cancer cases. “You can take the pie and divide it differently or increase the pie,” says Curry. She would like to see more support for front-line public health. “Clearly, we need more dissemination science. There’s a huge gap between what we know and what we do.”

Manning insists that bench science is just as important in prevention. "In most cases, the biggest breakthroughs in biomedical research, including cancer biology, are made using reductionist approaches in which you're isolating one aspect of the broader biology," he says. "Stripping a biological problem down to its essence is key. We need to keep funding research that allows us to understand with detail and accuracy the aspects of biology that are important for cancer initiation. But right now, there is an overemphasis at the NIH [National Institutes of Health] and at NCI on supporting research that purports to be directly translatable or is seemingly translatable to treatment for

an existing cancer, rather than on understanding how cancer begins."

Shoe-leather population research and high-tech bench science: Both will be needed to stop cancer's unabated rise.

Shaping Public Opinion

Desperate entreaties for increased support of cancer prevention are nothing new. In 1929, James Ewing, the director of cancer

research at Memorial Hospital in New York City, wrote in *Public Health Reports*: "It is only within the last few years that cancer has been considered a public health problem. I suppose that the old attitude was due to the fact that cancer is not an infectious disease; also largely because of the popular notion that it is not preventable; and probably also, to a large extent, to the feeling, fairly well grounded, that the disease is incurable." Ewing hoped for a change in public attitudes. "[C]ancer is a public health problem of the first importance, because many of the forms of cancer are preventable, and if the public were thoroughly

informed, a definite reduction in the incidence of cancer might follow."

Ninety years later, most people still do not grasp that point. Nor do they see that with robust research, the incidence of today's more elusive and frightening cancers could also fall. In the 2017 American Institute for Cancer Research's Cancer Risk Awareness Survey, for example, fewer than half of Americans recognized that alcohol, processed meat, high amounts of red meat, low amounts of fruits and vegetables, and not enough physical activity all have clear links to cancer development. And

contradicting scientific evidence, they tended to blame cancer on factors they couldn’t control rather than on those they could. Nuclear power ranked eighth as a perceived cause of cancer, for example, and food additives ninth. Obesity—which may soon become the top modifiable risk factor for cancer—ranked 16th.

As Frieden explained in 2008 in *The Oncologist*, cancer-causing agents “are not primarily trace chemicals found in food, water, or air, but instead are the major constituents of what humans consume voluntarily. These agents are best viewed as toxins, and public policies can substantially reduce our exposure to them.”

A Moon Shot for Prevention

In 1969, the Citizens Committee for the Conquest of Cancer, inspired by the success that year of the Apollo 11 space mission and propelled by the indomitable philanthropist Mary Lasker, conceived of a "moon shot" for cancer. That December, the group ran a full-page ad in *The Washington Post* and *The New York Times*: "Mr. Nixon: You can cure cancer." At the time, a cure was perceived to be imminent.

President Richard Nixon's grandiloquent response in his 1971

State of the Union address: “The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.”

But the War on Cancer, as the moon shot was called, didn’t reach its goal. Partly, that was because “cure” was an erroneous target. Cancer is not one disease, but more than 200. “We talk about a ‘cure’ for cancer, but no one would ever use the term ‘cure’ for infectious disease—they would talk about a cure for AIDS or TB or malaria,” says the Harvard Chan School’s Giovannucci. “You have to think about these diseases one by one.” More fundamentally, the War on Cancer failed because it spent far too little on cancer prevention and cancer prevention research.

There are many reasons why prevention research is unenticing. Most societies are reactive, not proactive. The final phases of research on treatment are simpler than research on prevention. Curing a patient with advanced disease is more dramatic than preventing disease in a healthy person. And perhaps most conspicuously, treatments earn far higher profits than do new diagnostics or prevention measures.

Yet every great public health success has overcome those entrenched obstacles. “The way I message this to lawmakers is that our well-being is a gift; we can’t take good health for

granted, and prevention is a powerful way to protect that gift. When prevention works, you can enjoy the miracle of a perfectly normal, healthy day," says Koh. "When I interact with lawmakers, I often ask about whether they have experienced the pain of losing a loved one when it could have been prevented. That usually humanizes the conversation and gives it relevance and immediacy."

A cure for cancer is our culture's threadbare metaphor for a miracle. But a cancer prevented is even better than a cancer cured.

When cancer becomes our leading cause of death—as it soon will—cancer prevention will become our leading cause of life.

Madeline Drexler is editor of Harvard Public Health.

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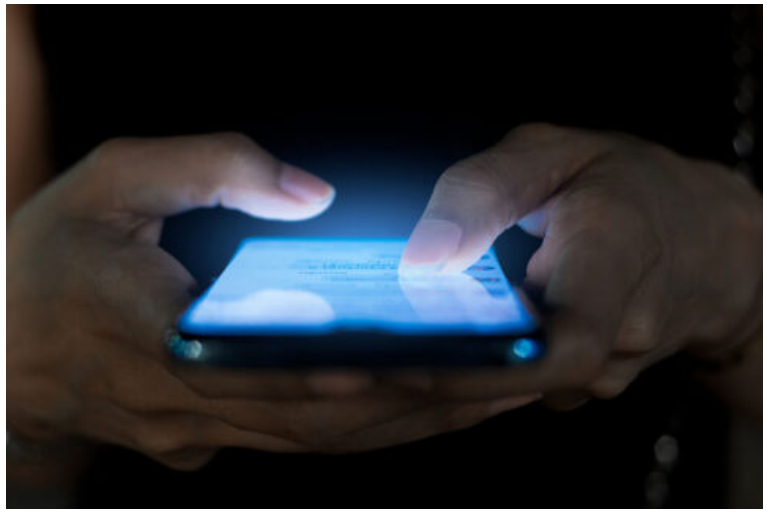

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