SPECIAL REPORT

Epidemiologic Signatures in Cancer

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For more than a century, the United States has devoted considerable effort to measuring the population-based cancer burden. The effort began with the measurement of disease-specific mortality. The compilation of annual mortality statistics began in 1900, and nationwide coverage was achieved in 1933.[1] The measurement of incidence was understandably more challenging, because it is easier to collect information about death than about diagnosis. The state of Connecticut initiated a population-based cancer registry in 1935,[2] and the National Cancer Institute established a national cancer registry in 1973 — the Surveillance, Epidemiology, and End Results (SEER) Program.[3]

Over the years, another challenge has become apparent: observed cancer burden can be influenced by diagnostic practice.[4] New imaging and other diagnostic methods can allow a cancer diagnosis to be made earlier in the disease course, detect nodal and metastatic involvement not recognized previously (shifting the stage of cancer upward),[5] and even reveal some cancers that would otherwise not become evident clinically — a phenomenon now referred to as overdiagnosis.[6] The incidence of cancers that have a substantial disease reservoir of indolent, subclinical forms is particularly sensitive to the degree of diagnostic scrutiny — the combined effect of the frequency of diagnostic or screening examinations (including the physical examination, imaging, and laboratory testing), the ability of the examinations to detect small irregularities, and the threshold to label these as cancer. These factors can lead to rapid, iatrogenic swings in reported incidence and conspire to make cancer incidence an unreliable measure of true cancer occurrence.

In this article, we make use of 40 years of data to examine patterns of incidence and mortality for various cancers, following the intellectual lineage of Bailar and others.[7-10] We go on to posit what these epidemiologic signatures might reveal about true cancer occurrence, overdiagnosis, and treatment advances. By "true cancer occurrence," we mean the underlying incidence of clinically meaningful cancer (i.e., reported incidence minus overdiagnosis) (see Glossary). We also consider the potential value of a variable that may serve as a marker for changes in true cancer occurrence: the incidence of metastatic disease. We conclude by offering general princi-

Glossary

Mortality: The rate of death from a specific cause (or all causes combined) in a defined population in a given period.

Incidence: Although conventionally defined in terms of disease occurrence, reported incidence is actually the rate of disease diagnosis in a defined population in a given period.

Overdiagnosis: The diagnosis of cancers that would otherwise not become clinically evident — an unintended side effect of increased diagnostic scrutiny.

True cancer occurrence: The underlying incidence of clinically meaningful cancer (i.e., reported incidence minus overdiagnosis).

Clinically meaningful cancer: Cancer that would progress to cause symptoms and require treatment if left untreated and put the patient at risk for premature death.

Metastatic incidence: The rate of cancer that is first diagnosed with metastases in a given period; its pattern over time may be indicative of trends in true cancer occurrence.

ples for interpreting signatures as well as suggestions for additional data that would allow for more robust inferences.

APPROACH

We examined mortality and incidence patterns from 1975 through 2015 for selected cancers in the United States. Mortality data come from the National Vital Statistics System maintained by the National Center for Health Statistics. Incidence data (combining invasive and in situ cancers) come from the original nine SEER registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, and Utah.

For each cancer, we illustrated mortality and incidence trends using a pair of graphics. The first depicts the absolute rates over time, age-adjusted to the U.S. 2000 standard population. The second depicts the relative rates over time, in which the 1975 rate serves as the reference group. To dampen the volatility of less commonly occurring cancers, all incidence data were calculated with the use of a 3-year running average.

We also examined data on the incidence of metastatic disease — a metric that includes only cases in which cancer is first diagnosed when a patient presents with metastases, not those in which early-stage cancer is diagnosed and then progresses to metastatic disease. These data are not recorded for the hematologic cancers and were available only beginning in 1988 for lung and prostate cancer. Thus, for these two cancers, the relative rate of the incidence of metastatic disease uses the 1988 rate as the referent group. To illustrate potential divergent trends in overall incidence and in the incidence of metastatic disease in subsequent years, the relative rate of the incidence of metastatic disease in 1988 was set as equivalent to the relative rate of overall incidence in 1988 (1.14 for lung cancer in men, 1.95 for lung cancer in women, and 1.46 for prostate cancer) instead of 1.0.

DESIRABLE SIGNATURES

Figure 1 includes signatures readily understandable to clinicians. Figure 1A illustrates signatures that reflect well on the value of medical care. Stable incidence signals stable true cancer occurrence; thus, the associated declining mortality provides a clear signal of improvements in cancer treatment. The top graphs show the age-adjusted absolute frequencies of incidence and mortality, whereas the bottom graphs show their relative frequencies to the base year of 1975.

In Hodgkin's lymphoma, the gradual decline in mortality — juxtaposed with generally stable incidence — reflects a steady improvement in treatment across time.[11] In chronic myeloid leukemia (CML), the mortality decline is much more precipitous, occurring in a narrow window spanning the new millennium. This rapid decline coincides with the introduction of imatinib and confirms that the agent was indeed a genuine breakthrough that was implemented rapidly into practice.[12]

Figure 1B illustrates signatures consistent with a rise and fall in true cancer occurrence and highlights the value of efforts to identify causal factors and eliminate them. Here, we focus on the cancer responsible for the most deaths in the United States (lung cancer, which caused more deaths than the next three cancers combined in 2018[13]) and examine the effect of the rise and fall of its most potent risk factor (cigarette smoking).

In 1950, case–control studies by Wynder and Graham in the United States[14] and by Doll and Hill in England[15] identified cigarette smoking as being strongly related to lung cancer. Six years later, data from a prospective cohort assembled by Doll and Hill showed that heavily smoking British physicians were 20 times more likely to die from lung cancer than were their nonsmoking colleagues.[16] In 1964, U.S. Surgeon General Luther Terry confirmed that there was no doubt that cigarette smoking caused lung cancer.[17] The prevalence of ever smoking peaked during the 1950s among men; however, the peak was delayed until the 1970s among women (ironically, one of the effects of the women's movement during the late 1960s was the greater acceptability of smoking — something cigarette advertising quickly capitalized on).[18,19] Because of the different timing of exposure, we consider men and women separately.

What is most striking about these signatures is that incidence and mortality move together. For both sexes, the rise and fall of cigarette smoking is followed (approximately three decades

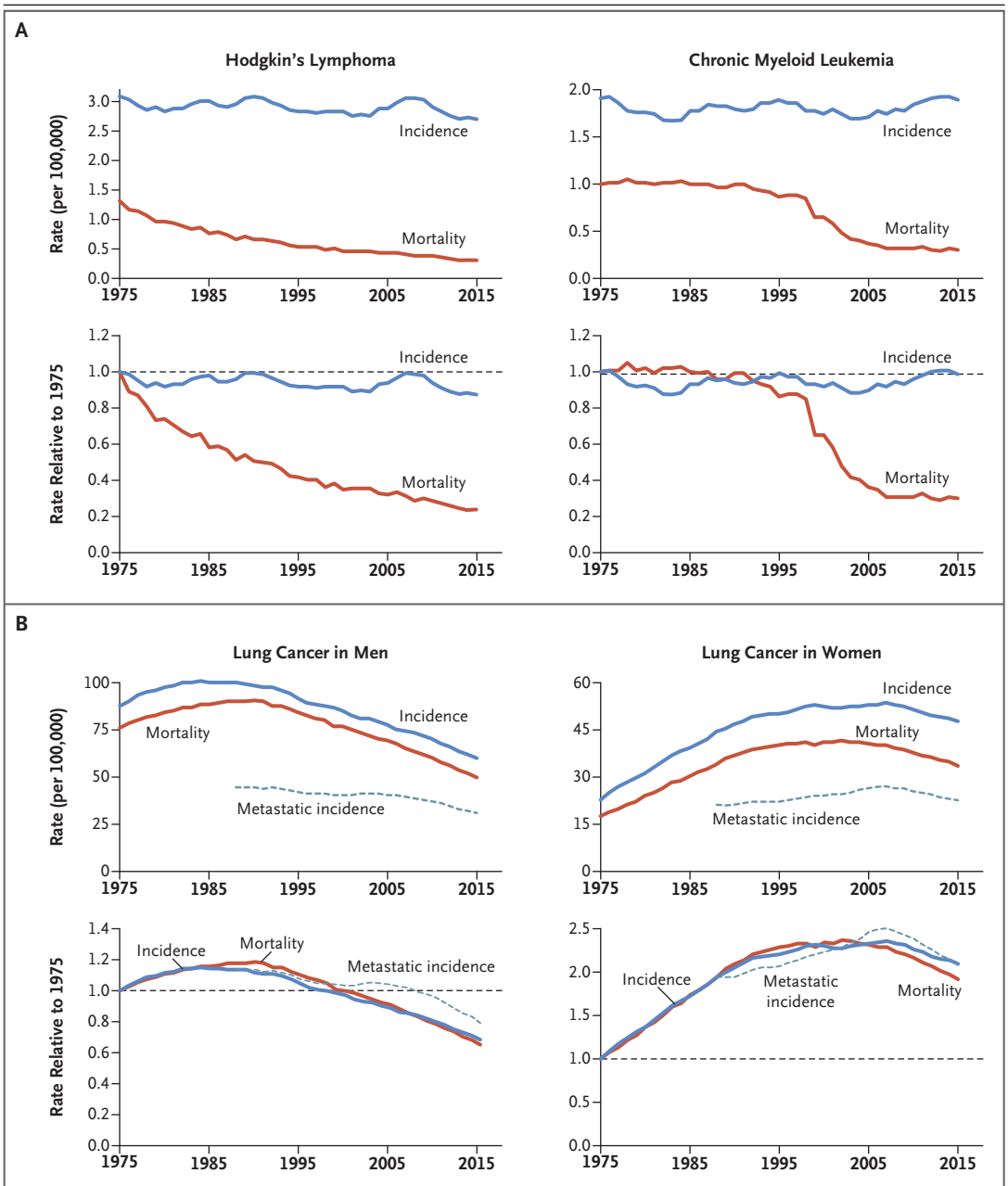

Figure 1. Readily Understandable Signatures.

Panel A shows improvements in treatment with stable true cancer occurrence. Panel B shows the rise and fall in true cancer occurrence. Mortality is disease-specific — that is, the rate of death attributed to the specified cancer. "Metastatic incidence" denotes the incidence of metastatic disease.

later) by a rise and fall in the occurrence of lung cancer.

Figure 1B also includes the incidence of metastatic disease: the rate at which persons receive a first diagnosis of cancer when they present with distant metastases. Although this metric closely tracks incidence and mortality, its relative rate is slightly elevated in more recent years. This probably reflects upstaging, in which more intensive diagnostic evaluation and increasingly sensitive tests are able to detect tiny metastases not identified in earlier years — in this case,

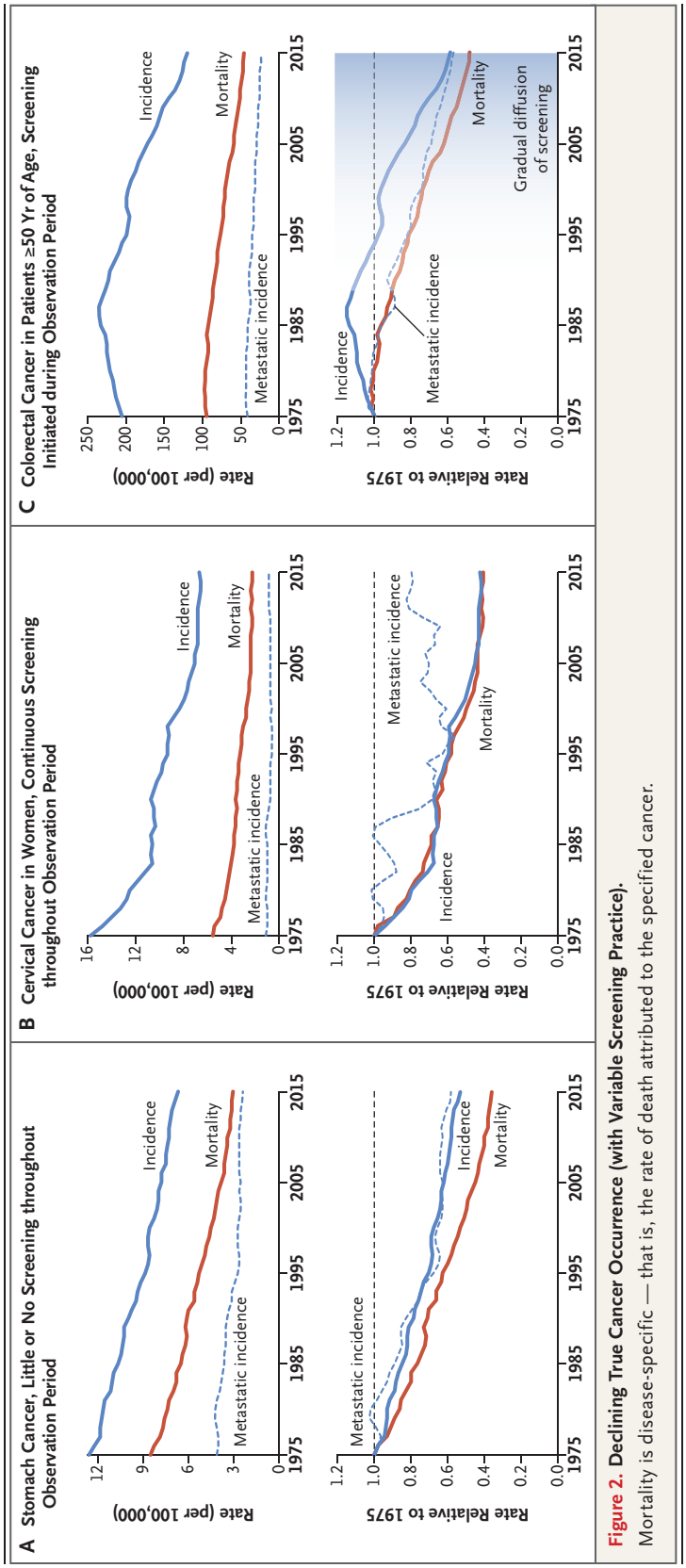

Figure 2. Declining True Cancer Occurrence (with Variable Screening Practice).
Mortality is disease-specific — that is, the rate of death attributed to the specified cancer.

because of the growing use of positron-emission tomography combined with computed tomography.[20,21]

Figure 2 illustrates signatures that are arguably the most desirable for society in general, because they suggest that stomach, cervical, and colorectal cancer are now simply less common than they were in 1975. The finding of incidence and mortality declining at approximately the same rate is consistent with declining true cancer occurrence.

These signatures also reflect the full range of possible screening practices: from little or no screening in stomach cancer to continuous screening in cervical cancer, as well as an intermediate screening condition in colorectal cancer. Thus, although the signatures are similar, the underlying explanations for the decline may differ. In stomach cancer, it is typically explained by a decline in a powerful risk factor (*Helicobacter pylori*) perhaps related to increasing use of food preservatives, the dissemination of refrigeration, or both.[22] In cervical cancer, the decline is typically explained by effective screening — the detection and successful treatment of precancerous lesions.[23]

Because screening was initiated during the period of observation, there is an opportunity to see its effect in the colorectal-cancer signature (restricted to the commonly recommended target population for screening: patients ≥50 years of age). There is no evidence of cancer overdiagnosis; in fact, incidence began to steadily decline before widespread screening. Furthermore, the incidence of metastatic disease and mortality declined steadily throughout the period. Because these trends predate screening (and because the effect of early cancer detection and removal of precancerous lesions is necessarily delayed), this signature reflects some decline in true cancer occurrence in this age group that is unrelated to screening.[24]

UNDESIRABLE SIGNATURES

As exemplified in the female lung-cancer signature before 2000, a concordant rise in incidence and mortality is clearly undesirable. Figure 3 illustrates signatures that are instead discordant: the reported incidence is rising, yet mortality is stable. Stable mortality should be viewed as a marker for stable true cancer occurrence. Although

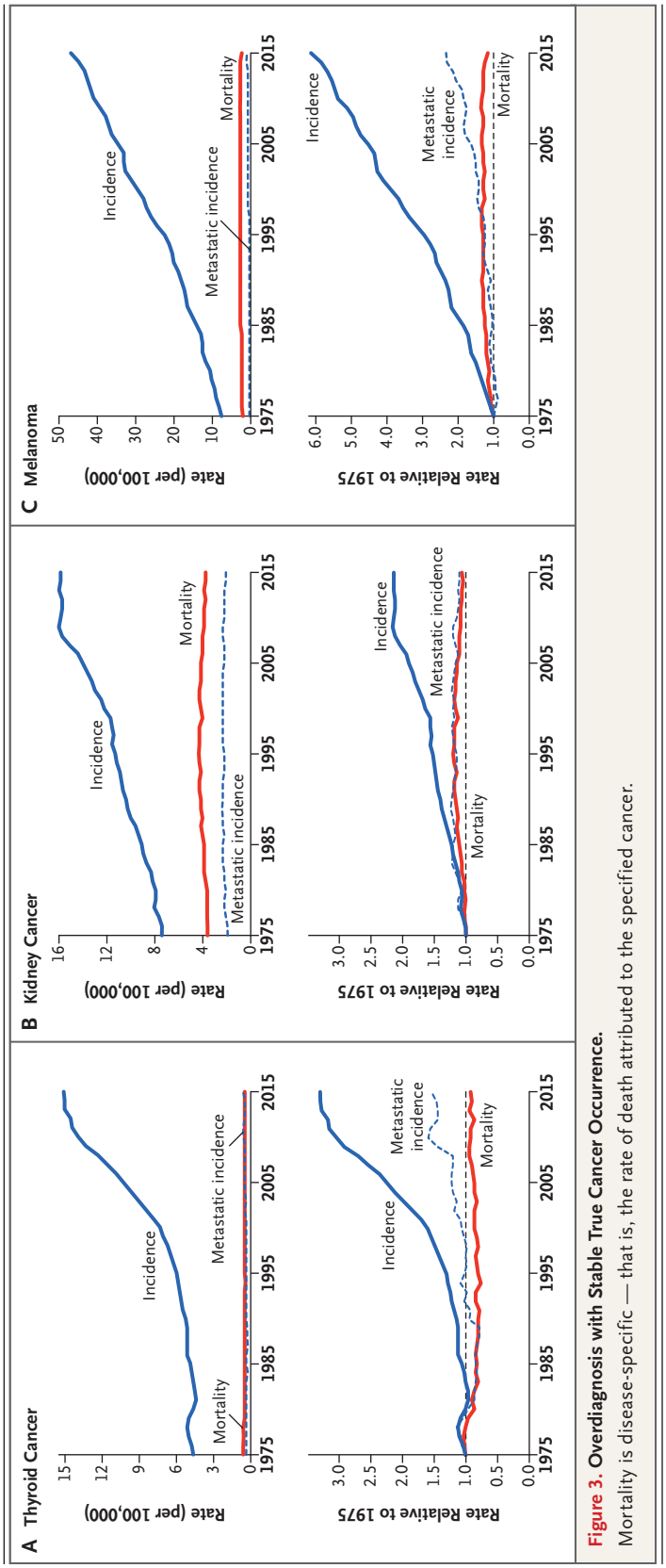

Figure 3. Overdiagnosis with Stable True Cancer Occurrence.
Mortality is disease-specific — that is, the rate of death attributed to the specified cancer.

it is possible that stable mortality could result from a combination of increasing true cancer occurrence and improvement in treatment, such a perfect annual counterbalancing of opposing forces would be a remarkable coincidence.

Thus, the signatures for thyroid cancer, kidney cancer, and melanoma suggest the detection of cancers not destined to cause death: overdiagnosis. Although it is difficult to know which persons are subject to overdiagnosis, overdiagnosis is easily appreciated at a population scale. These signatures are undesirable because they imply that more people are being told they have cancer — and more are being treated for cancer — while true cancer occurrence remains stable.

The additional finding of stable incidence of metastatic disease further supports stable cancer occurrence. Although the small increases in the incidence of metastatic thyroid cancer and melanoma observed in more recent years could represent the onset of increasing cancer occurrence, they more likely reflect upstaging.

SIGNATURES WITH MIXED SIGNALS

Figure 4 illustrates the more complex epidemiologic signatures of breast and prostate cancer (restricted to women and men, respectively, ≥40 years of age) that present mixed effects: rising incidence and falling mortality. Coincident with the introduction of widespread screening mammography, breast-cancer incidence increased rapidly and has apparently settled at a new, higher baseline. This could represent either a substantial (and focal) increase in true cancer occurrence or overdiagnosis associated with the introduction of widespread screening. The relatively stable incidence of metastatic disease, however, favors the latter explanation. The decline in mortality observed starting in the 1990s could reflect either improved treatment or screening or some combination of the two.[25] Other data suggest that improved treatment is the primary explanation.[26-30]

Coincident with the introduction of widespread prostate-specific antigen (PSA) screening, prostate-cancer incidence increased dramatically — yet has subsequently declined nearly to its 1975 baseline. This remarkable volatility cannot be explained by changes in true cancer occurrence. Instead, it highlights how sensitive prostate cancer is to diagnostic scrutiny — in this

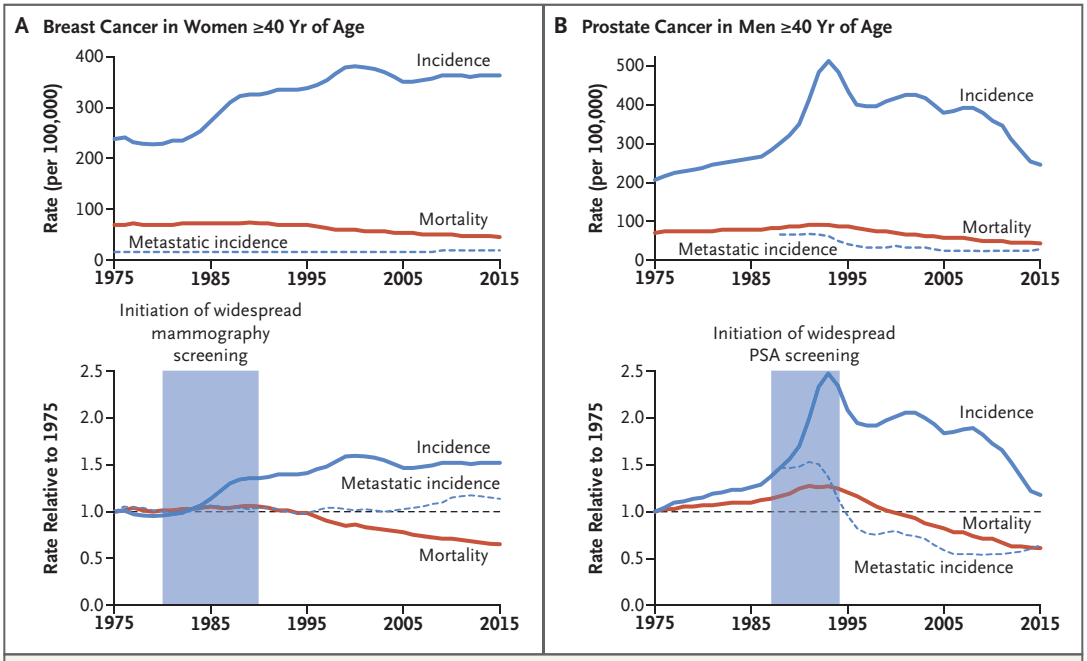

Figure 4. Breast and Prostate Cancer.

Mortality is disease-specific — that is, the rate of death attributed to the specified cancer. PSA denotes prostate-specific antigen.

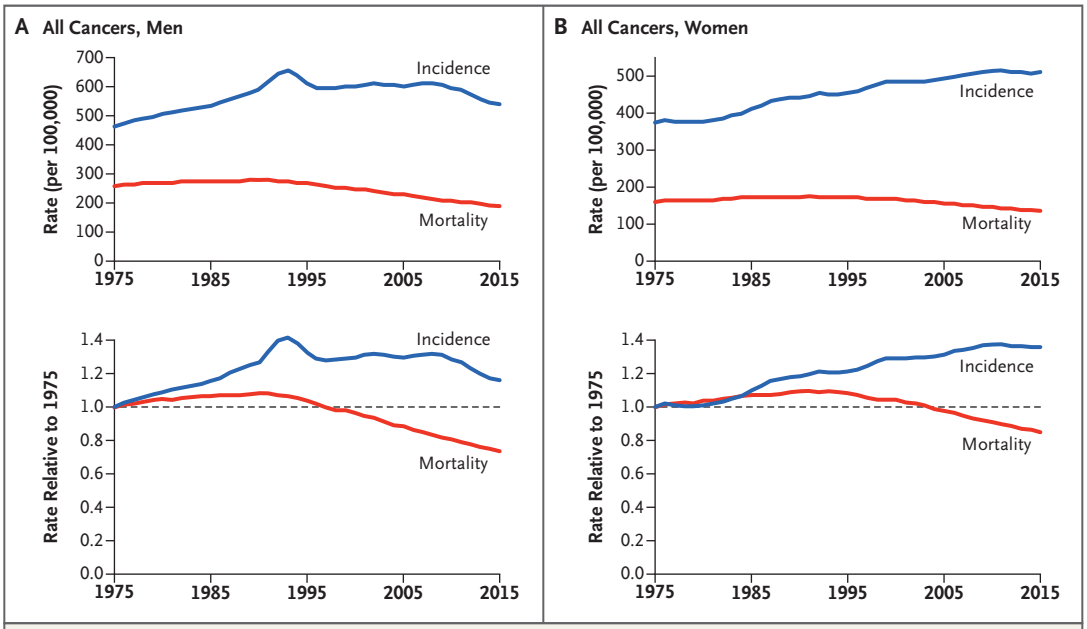

Figure 5. All Cancers Combined.

Data are for male persons (Panel A) and female persons (Panel B) of all ages, but only 1% of cancers in both sexes occur in persons younger than 20 years of age. Mortality refers to the rate of death attributed to all cancers combined.

case, the breadth and frequency of PSA testing and the PSA threshold that leads to a biopsy.[31,32] The incidence of metastatic disease fell markedly after the introduction of screening, which suggests that screening does advance the time of diagnosis for prostate cancers destined to become metastatic. It is important to reiterate, however, that the incidence of metastatic disease includes only cases in which cancer is first diagnosed when a patient presents with metastases (not those in which early-stage cancer is diagnosed and then progresses to metastatic disease). Early diagnosis and treatment of cancers that are destined to manifest as metastases does not necessarily mean they will not ultimately go on to metastasize or cause death.[33] Thus, the decline in mortality that is observed starting in the 1990s could reflect either improved treatment or screening or some combination of the two.

We would be remiss not to consider incidence and mortality for all cancers combined, as Bailar did in 1986 and 1997.[7,8] Our findings are shown in Figure 5. In men, the volatile pattern of overall incidence is clearly driven by prostate cancer, which highlights how common the diagnosis became. The falling incidence in lung and colorectal cancer was canceled out by the rising incidence of melanoma and kidney cancer (a decrease of 59 per 100,000 vs. an increase of 66 per 100,000 between 1975 and 2015).

Among women, rising overall cancer incidence during the 1980s predominantly reflects the rising incidence of lung and breast cancer. The continued rise since the mid-1990s — despite the falling incidence in colorectal, ovarian, cervical, and, more recently, lung cancer — reflects the rising incidence of melanoma, kidney cancer, and thyroid cancer (which is now three times as likely to be diagnosed in women as in men, despite the fact that thyroid-cancer mortality is the same among women and men[34,35]).

Among both sexes, overall cancer mortality has been falling since 1990. Among women, this is largely driven by falling mortality from breast cancer, colorectal cancer, and, more recently, lung cancer. The more pronounced decline among men reflects the more long-standing decline in lung-cancer mortality combined with declines in mortality from prostate cancer and colorectal cancer.

GENERAL PRINCIPLES

The primary goals of this article are to enable general medical readers to interpret trends in the basic measures of population-based cancer burden and to provide insight into true cancer occurrence, overdiagnosis, and treatment advances. In particular, we encourage readers not to interpret cancer-incidence trends in isolation — rather, interpret them in concert with trends in cancer mortality, supplemented by trends in the incidence of metastatic disease, when available.

There is little ambiguity when incidence is stable. A signature with both stable incidence and stable mortality (not shown), as is roughly the case for pancreatic and bladder cancer, signals little change in cancer occurrence and little change in the effectiveness of treatment. A signature with stable incidence and falling mortality, in contrast, provides a strong signal of improved treatment.

Changing incidence must be interpreted more cautiously. When mirrored by mortality — that is, incidence and mortality move in tandem — changes in reported incidence should be viewed as changes in the underlying incidence of clinically meaningful cancer (as exemplified in the lung-cancer signatures). A sustained increase in incidence coupled with stable mortality, however, suggests something fundamentally different: overdiagnosis superimposed on stable true cancer occurrence.

More complex signatures are more challenging and may be the result of multiple effects. Increasing incidence and falling mortality could be the result of increased true cancer occurrence and improved treatment or, instead, overdiagnosis (i.e., stable occurrence) and improved treatment. Here, the incidence of metastatic disease may serve as an indicator of the change in true cancer occurrence.

Finally, rapid changes — those occurring within several years — are best explained as the effect of medical practice. Thus, the rapid decline in mortality from CML around 2000 and the rapid increase in breast-cancer incidence in the 1980s reflect two dramatic changes in medical practice attributable to distinct driving forces: a genuine breakthrough in the treatment of CML

and the widespread dissemination of mammographic screening.

In contrast, changing environmental exposures would typically exert their effect more slowly. Consider the example of the widespread exposure to one of the most powerful established human carcinogens: tobacco smoke. The lung-cancer epidemic took decades to emerge and then additional decades to partially recede as smoking habits changed. The effects of changes in germline inheritance (genetic drift) are slower still, requiring generations to emerge.

VIRTUE OF SIMPLICITY

Admittedly, our epidemiologic-signatures approach involves the simple interpretation of crude national trends in two or three variables. By far the most important is cancer mortality, which remains the single best measure of progress against cancer.[36] Reported cancer incidence, on the other hand, should not be viewed as a reliable measure of true cancer occurrence. Instead, it must be interpreted in conjunction with mortality (and possibly the incidence of metastatic disease) and knowledge about changing diagnostic practice.

Efforts to add precision with complex statistical models typically involve multiple input variables, which may emanate from select groups of patients not representative of the population. Unstated assumptions (e.g., that reported incidence equals true cancer occurrence) can inadvertently introduce serious errors.[37] Yet the validity of the input data and the effect of assumptions are opaque to peer reviewers and clinicians (the "black box" problem), which makes it difficult to apportion model outputs to changes in exposure, treatment advances, or diagnostic shifts with confidence.

NEED FOR ENHANCED DATA

The acquisition of population-based data on cancer burden is a fundamental attribute of a well-functioning health care system. So too is routine monitoring of these data to identify both environmental and system effects. We believe these efforts warrant not only continued support but also creative thinking by cancer and death registries about how to better capture system-level effects.

Critically, the ascertainment of incident cancer cases should be accompanied by data on the mode of cancer detection. Three broad categories could capture the driving force that led to the cancer diagnosis: patient symptoms and signs (clinically detected), the systematic search for early cancer (screening-detected), or a chance finding (incidentally detected). Distinguishing among these three categories would further explain the origins of changes in reported incidence. More relevant to physicians and patients, data on the mode of detection also provide important prognostic information.

Two additional pieces of information on cancer deaths would also be useful. First is the extent of disease at death: tumor size and stage — particularly data on whether metastases were present. Second is data about the potential role of treatment — specifically, whether the death could have been related to treatment.

CONCLUSIONS

Epidemiologic signatures that illustrate trends in population-based data on cancer burden provide insight into true cancer occurrence, overdiagnosis, and treatment advances. They are important indicators of the potential contribution of environmental exposures, primary preventive interventions, new treatments, and changing diagnostic and screening practices. Falling mortality means that there has been real progress against cancer in the past 40 years — largely reflecting improved treatment and the decline of a uniquely powerful causal factor: cigarette smoking. The lack of an accompanying fall in incidence is an unfortunate side effect of early cancer-detection efforts.

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