A Proposal to Improve the Early Diagnosis of Symptomatic Cancers in the United States

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ABSTRACT

Many people are diagnosed with cancer after presenting with signs and symptoms of their disease to a healthcare provider. Research from developed countries suggests that, in addition to indicating later-stage disease, symptoms can also indicate earlier-stage disease, leading to investment in research and quality improvement efforts in the early detection of symptomatic cancers. This approach, labeled early diagnosis of symptomatic cancers, focuses on identifying cancer at the earliest possible stage in patients with potential signs and symptoms of cancer, and subsequently diagnosing and treating the cancer without delay. In the United States, early detection has focused on cancer screening, with relatively less research focused on early diagnosis of symptomatic cancers. In this commentary, we propose that research focused on early diagnosis of symptomatic cancers provides an important opportunity to achieve more earlier-stage cancer diagnoses in the United States. We highlight the potential of these efforts to improve cancer outcomes, and outline a research agenda to improve early diagnosis of symptomatic cancers in the United States focused on defining and describing pathways to cancer diagnosis, identifying signs and symptoms that can be used to promote early cancer detection, and developing interventions to improve early diagnosis of symptomatic cancers.

Introduction

Most cancers are diagnosed after patients present with signs or symptoms to a healthcare provider. In addition to indicating later-stage disease, signs and symptoms can indicate early-stage cancer (1), and earlier stage at diagnosis is associated with better survival for many cancers (2). Several developed countries, particularly those in the International Cancer Benchmarking Partnership (the United Kingdom, Denmark, Sweden, Canada, and Australia), have identified the importance and potential impact of efforts to achieve earlier-stage diagnosis for these symptomatic cancers (3, 4). However, early detection in the United States currently emphasizes cancer screening, which focuses on identifying precancerous lesions and preclinical cancer in asymptomatic adults, and relatively little research has focused on improving early detection of symptomatic cancers. In this commentary, we describe this additional early detection approach: early diagnosis of symptomatic cancers, which focuses on identifying cancer at the earliest possible stage in patients with potential signs and symptoms of cancer, and subsequently diagnosing and treating the cancer without delay (2). We highlight the potential of early diagnosis of symptomatic cancers to improve cancer outcomes, and outline key research questions aiming to improve early diagnosis of symptomatic cancers in the United States.

Most Cancers in the US Are Diagnosed Following Symptomatic Presentation

Screening clearly cannot be the pathway to diagnosis for all cancer cases. The majority of cancers do not have recommended screening tests: only colorectal, lung, breast, and cervical have A or B ratings from the United States Preventive Services Task Force (USPSTF; ref. 5). Even among these cancers, screening uptake is far from complete. Guideline concordance was 67%, 73%, and 81% for colorectal, breast, and cervical cancer screening in 2018, respectively, and only 6% for lung cancer screening in 2015 (6). Furthermore, screening tests do not perform perfectly, interval cancers occur, and recommendations for screening based on risk factors (e.g., age, smoking history) and intervals mean that only some higher-risk individuals are screened. Although the exact number of screen-detected cancers in the United States is unknown, predicted cancer incidence can be used to estimate the proportion of screen-detected cancers. In 2020, a total of 1,806,590 new cancer cases will be diagnosed in the United States (7). If we assume the best-case scenario, that screen-detectable cancers are exclusively diagnosed by screening, 37% of cancers diagnosed in 2020 would be screen detected, leaving 63% to be diagnosed via other pathways (**Table 1**). Accounting for incomplete screening uptake, the proportion of potentially

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Table 1. Estimated new cancer cases in 2020 that could be screen detected.

Cancer site	All cancers *n* (%)	Based on screening rates[a] *n* (%)
All cancer sites	1,806,590 (100)	1,806,590 (100)
Screen-detectable cancers	667,050 (36.9)	324,800 (18.0)
Breast	276,480 (15.3)	201,277 (11.1)
Lung and bronchus	228,820 (12.7)	13,500 (0.7)
Colorectal	147,950 (8.2)	98,831 (5.5)
Cervical	13,800 (0.8)	11,192 (0.6)
Cancers without recommended or available screening tests	1,139,540 (63.1)	1,481,790 (82.0)

Note: Data are based on 2020 estimated incidence from the American Cancer Society (7). Both colorectal and cervical cancer screening, depending on test modality, can prevent cancer through identification and treatment of precancerous lesions (e.g., colonoscopy). The proportions of cancers prevented are not included in these estimates.

[a]To estimate the number of screen-detected cancers based on screening uptake rates, we multiplied cases for each cancer by the screening uptake proportions reported in the Cancer Trends Progress Report (6): 72.8% of women had a mammogram in the past 2 years, 5.9% of adults at risk for lung cancer due to smoking had a low-dose CT in the previous year, 66.8% of adults received guideline-concordant colorectal cancer screening, and 81.1% of women had recent cervical cancer screening. Given the lack of age-specific information in the estimated 2020 incidence, we could not restrict screen-detectable cancers to only those eligible for screening based on guidelines; however, such a restriction would decrease the proportion of screen-detected cancers.

screen-detected cancers falls to 18%, with 82% of all cancers being detected in non-screening pathways, further illustrating that the majority of cancers are not screen detected.

Symptomatic presentation, occurring when a person with signs (e.g., weight loss, anemia) or symptoms (e.g., fatigue, pain) of cancer presents to a healthcare provider, is the most common route to cancer diagnosis. Empirical evidence examining routes to cancer diagnosis in the United States is limited in part due to the lack of prediagnostic information collected in cancer registries, and has therefore tended to come from individual healthcare systems. Robust evidence from other developed countries provides a clearer picture that symptom-detected cancers far outnumber screen-detected cancers. England has conducted perhaps the most comprehensive examinations of pathways, using Routes to Diagnosis based on administrative and cancer registry data (8), and the National Cancer Diagnosis Audit, consisting of a population-based sample of cancer patients from primary care practices (9). Results from these data sources showed that 5% to 7% of all cancers were detected by the national screening programs, while 63% to 72% were diagnosed in primary care settings. The International Cancer Benchmarking Partnership (ICBP), consisting of eight countries (Wales, England, Scotland, Northern Ireland, Denmark, Canada, Sweden, Australia), has also characterized routes to diagnosis across several cancers (10). For example, findings for routes to colorectal cancer diagnosis showed that 16% of cancers were screen detected, while 82% were diagnosed after symptomatic presentation, with 73% of symptomatic cancers detected following a primary care visit (11). Thus, even in systems with organized screening programs and good access to care, the majority of cancers are symptom detected, and many initial encounters occur in primary care, suggesting a key setting to focus efforts for the early diagnosis of symptomatic cancers. In turn, while increasing and optimizing screening continues to be important for early detection, additional opportunities to detect earlier-stage cancers exist in identifying symptomatic patients.

Efforts to Improve the Early Diagnosis of Symptomatic Cancers Could Help to Improve Cancer Outcomes

Signs and symptoms are the best (if not the only) potential indications of cancer in the absence of screen detection, and there is a growing body of evidence that these signs and symptoms can be used to identify earlier-stage disease in primary care (1, 12). For example, a recent study examined associations between 20 common presenting symptoms and stage of diagnosis in a population-based cohort of 7,997 cancer patients from the National Cancer Diagnosis Audit (NCDA) in England (1). While some symptoms (e.g., neck lump) were associated with greater odds of stage IV (advanced) disease, several symptoms (e.g., breast lump, postmenopausal bleeding, rectal bleeding) were consistently associated with lower odds of advanced stage at diagnosis. Furthermore, results showed that for 13 of 20 symptoms, more than half of patients were diagnosed at a nonadvanced stage, and for 19 of 20 symptoms (all except neck lump), more than one-third of patients were diagnosed at a non-advanced stage. Taken together, the findings suggest that commonly presenting signs and symptoms of cancer can indicate earlier-stage cancers and could therefore be used to promote early diagnosis of symptomatic cancers.

Crucially, there is also evidence that reducing the time to diagnosis for symptomatic cancers improves clinical outcomes. Representing the most complete synthesis of this evidence, a 2015 systematic review examining associations between time to diagnosis and clinical outcomes for symptomatic cancers of any type in 209 studies concluded that shorter times to diagnosis for some symptomatic cancers improved survival, earlier-stage diagnoses, and quality of life (13). The strongest evidence existed for breast, colorectal, head and neck, testicular, and melanoma, highlighting that the benefit of expedited diagnosis varies widely across cancers, given variability in

whether symptoms present early in cancer progression and the specificity of the presenting symptoms for a particular cancer (12). Although improving clinical outcomes is critical to justify efforts to improve the early diagnosis of symptomatic cancers, additional benefits of these efforts include improving care quality through achieving more timely diagnoses (14) and reducing treatment costs through identifying earlier-stage disease (2).

A Research Agenda to Improve Early Diagnosis of Symptomatic Cancers in the United States

On the basis of a juxtaposition of these potential benefits, and the incomplete knowledge we currently have about many aspects of symptomatic cancer diagnosis in the United States, we propose three questions to guide research on early diagnosis of symptomatic cancers.

What are the care pathways, including prediagnostic care, for symptomatic cancers?

Describing care pathways for symptomatic cancers, including care occurring before diagnosis, can help guide efforts to improve care quality, and subsequently cancer outcomes, by identifying missed opportunities to achieve early diagnosis of symptomatic cancers and potential targets for intervention. Countries in the ICBP, particularly the United Kingdom with Routes to Diagnosis and the NCDA (8, 9), have prioritized examination and international comparison of prediagnostic care pathways (4, 10). U.S. population data that includes prediagnostic cancer care information is similarly available in individual healthcare systems and can be used to examine pathways within and across systems. A key challenge of this work, however, is creating consistent definitions and measures of prediagnostic events and pathways for different systems and cancers. The international early diagnosis research community has generated conceptual frameworks and standards to help guide this research. In particular, the Aarhus statement, created by a multidisciplinary international group of early diagnosis experts, provides definitions for key time points (e.g., date of first presentation) and intervals in diagnostic pathways, as well as guidance on measurement of these pathways (4). The Aarhus statement was used to operationalize pathways in the ICBP's Module 4, which involved rigorous survey development to facilitate cross-country comparisons of diagnostic routes and intervals for breast, lung, colorectal, and ovarian cancers (10). Although the United States is not part of the ICBP, these models can be adapted for use in U.S. healthcare systems, allowing for international comparison of care pathways for symptomatic cancers and a greater understanding of how strategies to promote early diagnosis of symptomatic cancers from other developed countries (e.g., public awareness campaigns in England, diagnostic centers for those with nonspecific symptoms in Denmark; ref. 15) may be applied in the United States.

Which clinical signs and symptoms can be used to identify patients at higher risk for specific cancers?

Identifying signs and symptoms that can be used to distinguish patients at higher risk for specific cancers from those with lower risk is crucial to ensure timely diagnosis and appropriate healthcare resource allocation for higher-risk cases. Emerging research from the United Kingdom has begun to unpack which presenting signs and symptoms may be useful in predicting higher cancer risk in primary care (12) and, using national data sources such as the NCDA and Clinical Practice Research Datalink, the nonspecific signs and symptoms that may indicate earlier-stage disease, such as abdominal symptoms (16) and raised platelet counts (17). Further understanding is needed about which symptoms (and symptom combinations), beyond "red flag" warning signs, may be useful in developing predictive risk models, and which data sources are well-suited to examine these associations and complete care pathways in different healthcare delivery systems in the United States.

How can we improve the pathways to diagnosis for symptomatic patients?

In addition to better describing pathways to diagnosis and identifying symptomatic patients at higher risk of cancer, strategies to improve early diagnosis of symptomatic cancers, occurring at different points in the pathway, need to be developed and evaluated. We provide three fruitful areas of investigation.

Increased patient awareness of potential cancer symptoms

Improving patient awareness of cancer symptoms can prompt individuals to seek medical help for possible cancer symptoms, potentially leading to more timely diagnosis (18). Although improving access to healthcare is important to reducing cancer disparities, decreasing delays in help-seeking for potential symptoms may represent an additional opportunity to reduce disparities (19). Population-based studies from England and, more recently, the United States have shown that disadvantaged populations, particularly those with low socioeconomic status, have lower cancer symptom awareness (20, 21), and that lower symptom awareness is associated with delayed help-seeking for symptoms (22, 23). Research from England has also shown that public awareness campaigns for lung and colorectal cancers increased symptom awareness (24), and that an education campaign about potential signs of lung cancer resulted in a stage shift (25). Interventions to improve cancer symptom awareness in socioeconomically deprived areas of the United Kingdom are currently underway (26), with the aim of improving awareness and encouraging early help-seeking behavior in disadvantaged populations to ultimately reduce disparities in distal cancer outcomes. Given the potential of this work to improve early diagnosis of symptomatic cancers and reduce disparities, more research is needed to assess associations between cancer symptom awareness and patterns of help-seeking in populations with less

awareness and how increased awareness affects subsequent cancer outcomes.

Use of information in electronic health records to identify high-risk symptomatic patients

Diagnostic errors in cancer harm patients (14) and are common reasons for ambulatory malpractice claims in the United States (27). Stemming from efforts to reduce diagnostic errors and identify missed opportunities in cancer diagnosis, research on the use of triggers in EHRs to identify symptomatic patients in need of diagnostic follow-up has shown that triggers can be used to reduce time to diagnostic evaluation for cancer (28, 29). For example, Murphy and colleagues (29) showed that an EHR trigger-based intervention in two U.S. primary care settings reduced time to diagnostic evaluation for patients with colorectal and prostate cancers. More research is needed to develop EHR triggers that have sufficient sensitivity and specificity for cancer based on combinations of clinical features, vital signs, and commonly collected laboratory tests. Having identified triggers, demonstrating their impact on stage at diagnosis and cancer outcomes will be imperative before broader implementation aimed at achieving more early-stage diagnoses.

More cancer-specific and more useful point-of-care diagnostic tests for primary care providers

Developing, evaluating, and implementing tests for early cancer detection in first-contact settings is an area for improvement, and could be especially helpful in promoting early diagnosis of symptomatic cancers in populations where diagnostic testing is difficult to access, as may be the case for rural and other underserved populations. As part of this burgeoning interest, the CanTest Collaborative, consisting of international primary care cancer researchers, has developed a framework to guide and stimulate research on the development, evaluation, and implementation of point-of-care tests to support primary care providers in their ability to effectively and efficiently make determinations about cancer (30). In conjunction with improving point-of-care tests, there is a need for continued medical education to ensure that healthcare providers have the requisite knowledge and skills to identify and evaluate symptomatic patients with potential cancer (15). Because symptoms are common, but cancer diagnoses are rare, identifying and assessing new technologies aimed at point-of-care testing, along with a focus on healthcare provider education and decision support, could be especially valuable in more accurately triaging high-risk patients.

Conclusion

Lack of research on early diagnosis of symptomatic cancers is a missed opportunity to improve cancer outcomes. These efforts should be added to the rich body of research focused on cancer screening and biomarker discovery. The proposed research agenda aims to direct these efforts and suggests that the tools and common language needed for this work already exist, but need to be adapted for use in the United States. The notion that most cancers present symptomatically is not new but has been somewhat overlooked in the United States. Until we have equitable access to high-quality cancer treatments and better accuracy and uptake in screening, we have an imperative to examine how symptomatic cancers are diagnosed, who unduly bears the burden of diagnostic delays in these cancers, and what interventions might help increase timely diagnosis of symptomatic cancers in the United States.

Disclosure of Potential Conflicts of Interest

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Disclaimer

The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the United States Government.

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