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Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence

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Abstract

Early diagnosis is an important aspect of contemporary cancer prevention and control strategies, as the majority of patients are diagnosed following symptomatic presentation. The nature of presenting symptoms can critically influence the length of the diagnostic intervals from symptom onset to presentation (the patient interval), and from first presentation to specialist referral (the primary care interval). Understanding which symptoms are associated with longer diagnostic intervals to help the targeting of early diagnosis initiatives is an area of emerging research. In this Review, we consider the methodological challenges in studying the presenting symptoms and intervals to diagnosis of cancer patients, and summarize current evidence on presenting symptoms associated with a range of common and rarer cancer sites. We propose a taxonomy of cancer sites considering their symptom signature and the predictive value of common presenting symptoms. Finally, we consider evidence on associations between symptomatic presentations and intervals to diagnosis before discussing implications for the design, implementation, and evaluation of public health or health system interventions to achieve the earlier detection of cancer.

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Introduction

Diagnosing cancer earlier is a critical aim of contemporary cancer control policies. Screening interventions can achieve asymptomatic detection but are currently only available for a limited number of cancer sites, and their effectiveness is further constrained by limited sensitivity and both suboptimal and unequal uptake. This means that the majority of cancer patients continue to be diagnosed following symptomatic presentation, for whom timely diagnosis is associated with better clinical and patient-reported outcomes [1–5]. Diagnosing cancer at an earlier stage is also likely to be cost-effective given the increasing costs of novel drug therapies for advanced stage disease [6]. These considerations highlight the need for efforts aimed at shortening intervals to diagnosis in patients who present with symptoms.

Substantial variation in measures of diagnostic timeliness exists between patients with different cancers [7–10]. Much of this variation has been attributed to the differing nature, frequency, and combinations of presenting symptoms (the 'symptom signature') of each cancer site (as defined in Box 1), though empirical evidence supporting this explanation is sparse. Presenting symptoms can influence the time from symptom onset to first presentation (the patient interval) and the time from first presentation to subsequent referral to specialist care (the primary care interval) [11]. Studying how different symptoms are associated with the length of these two intervals is therefore a priority for early diagnosis research.

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Box 1
Defining symptom signature and diagnostic difficulty

In this Review, we make frequent use of two terms: **symptom signature** and **diagnostic difficulty**.

Symptom signature denotes the nature and relative frequency of symptoms (or symptom combinations) reported at presentation by patients later diagnosed with a particular cancer [13,14]. We describe symptom signatures as being 'narrow' when most patients present with a particular symptom (as is the case for breast lump in the context of breast cancer) or 'broad' when patients present with a larger range of symptoms (as is the case for colorectal cancer).

The term **diagnostic difficulty** (of a given cancer site) has previously been used to characterize cancer sites as "harder-to-suspect" (e.g. multiple myeloma, pancreatic cancer) or "easier-to-suspect" (e.g. breast cancer, melanoma) based on the profile of presenting symptoms [13]. It represents the perceived predictive value for cancer of the presenting symptoms of the 'average' patient.

We discuss methodological challenges in capturing data on symptoms at presentation and intervals to diagnosis and subsequently examine the symptom signatures of cancer sites and how this relates to diagnostic difficulty (Box 1). Diagnostic difficulty is related to the positive predictive value (PPV) of a symptom for a given disease, which is the proportion of all patients with the same symptom who will be found to have the disease. While PPV is a continuous measure, explicit threshold categories for investigation or other assessment can be considered, though until recently there have been no such applications in policy. Since 2015, the English National Institute for Health and Care Excellence (NICE) has mandated referral for specialist assessment for patients presenting in primary care with symptoms associated with a PPV for cancer that exceeds 3% [12]. This provides a practical reference point for judging the clinical significance of a symptom in the context of cancer diagnosis and has informed our interpretation throughout this Review.

Finally, we summarize available evidence on the association between symptomatic presentations and diagnostic intervals and discuss how this evidence could inform the design of early diagnosis interventions.

How Can Presenting Symptoms and Intervals Before Diagnosis be Measured?

Capturing information on symptoms is challenging, as the majority cannot be objectively observed and their appraisal by individuals is influenced by sociocultural factors such as level of education and health literacy (including awareness of likely cancer symptoms), cancer fear, or fatalism [14,15]. When more than one symptom is experienced, the combination of symptoms could also influence appraisal and help-seeking. Additionally, several symptoms may have conflicting or overlapping meanings in lay and professional language, and this is reflected in heterogeneous terminology in published literature. For example, abdominal bloating (uncomfortable sensation of fullness) and distension (visible increase in abdominal girth) have been used interchangeably [16,17], while 'change in bowel habit' is often used by clinicians to denote a clinical suspicion of colorectal cancer beyond the presence of constipation or diarrhea alone [18]. Further, heterogeneity exists within certain nonspecific symptoms: 'abdominal pain,' for example, encompasses a range of presentations that vary greatly in nature, intensity, duration, and temporal evolution.

Box 2
Approaches to measuring presenting symptoms in cancer patient populations

Self-reported symptom information.

Information on presenting symptoms can be directly elicited from patients through semistructured interviews [26–31] or questionnaires [32,33]. Such methods can elicit valuable first-hand insights into the symptomatic and diagnostic experience.

Patients may be prompted to identify their presenting symptoms from a predefined list (symptom recognition) or to describe them without any prompting (symptom recall), which can affect the degree of recall inaccuracies or bias. Prompting patients to consider their symptom status in respect of calendar 'landmark' dates (such as public holidays or events and dates of personal significance) may be helpful [34]. Studies can also be distinguished by whether the information is collected before or after the diagnosis. Collecting data about presenting symptoms after diagnosis is more convenient due to easier identification of cases but it can lead to both recall and survivorship bias. The latter results in underrepresentation of cancer patients with poor prognosis, whose presenting symptoms could be different to those of the studied patients [35]. In comparison, collecting information prospectively (before a diagnosis of cancer is made) has the advantage of minimizing such potential biases [36–38].

Records-based symptom information.

Alternatively, information on presenting symptoms can be recorded during healthcare encounters (e.g., with a primary care physician) and captured as part of the patients' health records [39–41]. Both coded and free-text information may be extracted [42–45].

In principle, studies collecting symptom information from patient records are less prone to the risk of selection and recall bias, as information on presenting symptoms is collected prospectively and prior to diagnosis for all patients. However, such methods critically rely on the symptoms both being elicited during the consultation and being accurately recorded; in many instances, these assumptions may not be met [46,47]. Additionally, psychosocial barriers (such as embarrassment [47–49]) and perceived or actual time pressures during the consultation [50] may prevent complete disclosure of certain symptoms to the doctor. Coded information can also be less sensitive to qualitative distinctions in symptom experience such as temporal evolution, particularly if multiple symptoms are recorded.