Defining, measuring and preventing the diagnosis of cancer as an emergency: a critical review of current evidence

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Abstract

Many cancer patients are diagnosed through emergency presentations, which are associated with poorer clinical and patient-reported outcomes. Reducing the proportion of cancer patients who are diagnosed as emergencies is desirable, but the optimal means for achieving this aim are uncertain as tumour, patient and healthcare factors are involved, often in combination. We reviewed the literature to inform future policy and research. Most evidence relates to few high-income countries, colorectal and lung cancer, and defines emergency presentations contextually (e.g. whether patients presented to emergency health care services and/or received emergency treatment shortly before their diagnosis). Consistent variations in risk of emergency presentations by patient characteristic and cancer type have been described, but there is limited evidence on whether and how such presentations can be prevented. Evidence about symptoms and healthcare utilisation prior to emergency presentations is sparse.

Interventions aimed at improving earlier diagnosis of cancer will also reduce emergency presentations. These may include:

- Optimising uptake of screening interventions (e.g. colorectal cancer);
- Addressing access or psychosocial barriers to prompt help-seeking for symptoms;
- Enabling point-of-care testing and access to rapid specialist / multi-disciplinary diagnostic assessment and tests.

Additionally, reconfiguring out-of-hours cover by oncology services to optimise the treatment of emergency presenters may improve their outcomes.

Harmonising definitions and data collection methods can help in surveillance and international comparisons. Research on emergency presentations in low/middle income countries, child and young adult patients, and those with rarer cancers should be prioritised.

Introduction

Most cancer patients are diagnosed after symptom onset, and many present to emergency care services, often with life-threatening manifestations of their underlying cancer. [1-5] The diagnosis of cancer as an emergency is associated with poorer clinical and patient-reported outcomes. These include less frequent use of treatment with curative intent, well established associations between emergency presentations, and poorer survival and worse quality of life and patient experience.

Specifically evidence for patients with many common and rarer solid tumours, including colorectal, oesophageal and lung cancer, indicates that emergency presenters are less likely to be treated with curative intent (denoted in 3 out of the 4 studies in available literature with use of respective surgery).[6-9] The association between emergency presentation and less frequent use of treatments with curative intent persists after adjustment for socio-demographic and tumour factors including, critically, stage at diagnosis.[8, 9]

Further, emergency presentation is associated with lower 1-year survival for patients with any of 15 cancers compared with electively diagnosed cases (e.g. 50% vs 82% for colorectal and 12% vs 40% for lung cancer).[5] Associations between emergency presentation and poorer survival are particularly strong in the short-term (e.g. 1-month and 1-year as opposed to 5-year).[6, 8, 10-12] Although stage at diagnosis explains part of this association, emergency presentations are independently associated with lower survival even after adjustment for stage.[13, 14]

Lastly, considering patient-generated outcomes, evidence from a national patient experience report indicates that emergency presenters report worse experience of subsequent cancer care [15].

Consequently, decreasing the proportion of cancer patients who are diagnosed through emergency presentations is desirable. However, complex mechanisms leading to such events, involving tumour, patient and healthcare factors, make progress towards this objective challenging.[16]

Motivated by these considerations, we provide a critical overview of the current evidence about the complex problem of diagnosis of cancer as an emergency. Our objective is to better inform future public health and healthcare interventions and research aimed at reducing the proportion of cancer patients who are diagnosed as emergencies.

After examining relevant conceptual and operational definitions, we consider theoretical frameworks about how emergency diagnoses of cancer could be prevented. We review evidence on prior healthcare utilisation and symptoms among emergency presenters; and the frequency and predictors of emergency presentations, specifically focusing on how socio-demographic inequalities vary for patients with different cancers. Lastly we describe priorities for future policy initiatives and research. We base our analysis on a recent systematic review of the evidence (**Box 1**), additionally drawing on our prior clinical, public health and research experience.

[INSERT BOX 1]

1. Evidence overview

Study Selection

A reviewer (YZ) performed the search and subsequently screened the titles, and where appropriate the abstracts, of 13,972 yielded publications. A second reviewer (GL) independently screened 10% of the initial yield of titles and abstracts. Disagreements between the two raters were discussed and adjudicated. Both reviewers subsequently independently assessed the full texts of 26 studies initially judged as relevant, of which 4 were subsequently excluded (3 were conference abstracts and 1 was not population-based). Two studies had a great degree of overlap in the presented data, and the earlier and less comprehensive paper was excluded.[17] References in relevant articles were hand-searched for additional articles meeting inclusion criteria, leading to the inclusion of 2 additional studies. An additional study and relevant grey literature were added based on prior knowledge of the authors, resulting in the final inclusion of 24 peer-reviewed publications **(Appendix 1)** and 6 online reports.

The peer-reviewed publications relate to patient populations from 6 countries, namely England (17), Scotland (1), USA (2), Sweden (2), Canada (1), and France (1). Online reports relate to evidence from England, including reports based on the Routes to Diagnosis project, a clinical audit report, and a multi-center European study on emergency presentation of lung cancer.[7, 18-22] In total, evidence relates to 35 cancer sites in peer-reviewed papers, and a few additional (rarer) cancer sites are also covered by online reports.[23, 24] However, most of the evidence relates to only two cancers: colorectal – commonly treated as a single site, and lung cancer. Most of the evidence (e.g. 16/24 publications and most online reports) has been published since 2012, indicating a growing interest in this field.

2. Data sources and definitions

Data sources: Most evidence arises from large administrative or electronic patient record datasets (e.g. 'Routes to Diagnosis' data in England, or SEER-Medicare data in the United States). In fewer studies data were collected through direct inspection of patient records by clinicians or trained researchers. [25-28] A third category includes publications arising from clinical audit initiatives (a quality improvement activity based on the inspection of medical records). [2, 6, 8, 10]

Definitions: There is a substantial degree of heterogeneity in how the diagnosis of cancer as an emergency is defined in different studies. In general, operational definitions employ either *contextual* criteria [i.e. whether the patient's cancer diagnosis followed a presentation to emergency healthcare services (e.g. Accidents and Emergency department)] and/or *clinical* information criteria [i.e. whether urgent (surgical) treatment was used, or whether certain symptoms were present] (**Figure 1**). Studies using clinical information criteria relate to colorectal cancer only. In two studies emergency diagnosis status was defined based on information generated by clinical staff.[10, 29] Definitional and methodological differences are likely to account for different point estimates of the frequency of emergency presentations reported previously. [30]

[INSERT FIGURE 1]

3. Can emergency presentations be prevented?

We found no empirical evidence directly assessing whether emergency presentations were preventable, with three exceptions: First, a clinical audit initiative in England, which judged the potential for preventing emergency presentations by exploring whether emergency presenters had previously consulted with 'red flag' symptoms mandating urgent referral for suspected cancer. They found that 23% of emergency presenters did in retrospect meet the referral criteria.[20] Second, a qualitative analysis of a small case-series of English emergency presenters, described potential breakdowns in the diagnostic process, and the need for better communication of diagnostic uncertainty to encourage symptom re-appraisal and help-seeking.[31] The third relates to a qualitative synthesis of a large series of significant event analysis in England, which showed that the complexity of tumour/ biological factors may deem some emergency presentations unavoidable. However, it has also been suggested that some patient factors and health system initiatives may reduce a proportion of avoidable cases. [32] All these three sources relate to clinical audit initiatives to reduce emergency presentations; it is likely that a much greater number of such local initiatives have examined preventability but most such evidence remains unpublished.[33] The dearth of published evidence on the potential to prevent emergency presentations in cancer patients is striking, considered against the mature literature on judging the preventability of general emergency hospital admissions (or emergency department use) or readmissions.[34, 35]

These findings indicate the need for studies examining the potential for avoiding emergency presentations in the future. Here we propose a framework on which future research can be based, incorporating the influence of tumour (disease), patient and healthcare factors, [16] and a diagnostic timeliness dimension incorporating aspects of the "Pathways to Treatment" model by Walter *et al* (**Figure 2**). [36] In Figure 2 and subsequent text, the term "potentially avoidable" refers to the emergency presentation event, while the modifiable factors relate to the predictors such events.

[INSERT FIGURE 2]

4. Trends, frequency and variation in EP by tumour factors

Time trends

Evidence based on the Routes to Diagnosis dataset suggests substantial reductions in the overall frequency of EP for all cancers over time in England.[1, 5, 37] Specifically, a reduction from 24% to 20% was noted for patients with any cancer between 2006 and 2013. [19] Reductions were greater for malignancies associated with high baseline proportion of emergency diagnosis, such as lung cancer (from 39% in 2006 to 34% in 2013). [19] In contrast, no discernible changes were observed for 'easy-to-suspect' cancers which are associated with very low baseline (<5%) proportion of emergency presenters (such as breast cancer and melanoma).[19]

When regarding trends over time in the proportions of cancer patients diagnosed as an emergency, it is useful to consider the factors to which notable/strong trends in short periods of time can be attributed to – in general, temporal changes in short period of time are unlikely to reflect changes in disease factors (such as tumour aggressiveness) as tumour morphology is unlikely to rapidly change. Therefore it can be hypothesised that if such changes are observed, they are more likely to reflect changes in patient and healthcare factors.

Tumour factors

Cancer site (and sub-site/sub-type)
Most evidence relates to 4 only cancers, i.e. colorectal, lung, breast cancer, and upper GI (oesophago-gastric) cancers **(Appendix 2)**.

Overall, reported frequencies of emergency diagnosis varied significantly across different cancer types, from 2% for melanoma to more than 60% for brain and central nervous system tumours.[5, 24, 37] Frequencies >30% are reported for patients with brain and central nervous system, cancer of unknown primary, pancreatic, lung, stomach, acute leukaemia and multiple myeloma. At the other end of the spectrum, melanoma, breast, oropharyngeal, oral, uterine, testicular and prostate cancer present as emergencies in < 10% of all cases.

As remarked previously, these findings suggest a correlation between the 'symptom signature' (or diagnostic difficulty) of different cancers and reported proportions of patients diagnosed as emergencies.[38] Cancers where most patients present with visible or palpable symptoms/signs (e.g. melanoma and breast cancer) have typically low proportions of emergency presenters, whereas the opposite is true for cancers where most patients present with non-specific symptoms (e.g. pancreatic cancer or multiple myeloma). It is however also important to consider the role of minimal prior symptoms in some cancers (e.g. seizure as first symptom of brain cancer) and primary care test utilisation for others (e.g. acute lymphocytic leukaemia, often diagnosed after a full blood count investigation).

Beyond general variation by major organ site, variation in tumour sub-site or subtype is also described for a small number of cancers (colorectal, colon, oesophago-gastric cancer and leukaemias) (**Box 2**).

Grade/Histology

Only one American study considered the effect of cancer grade and histology on the likelihood of emergency presentations.[3] A higher proportion of high grade (poorly differentiated/undifferentiated/anaplastic) colorectal cancers were found to present as an emergency than low (well/moderately differentiated) grade colorectal cancers (32% vs 28%). Mucinous adenocarcinoma or signet ring cell tumours were more likely to present as an emergency than 'other adenocarcinoma' (31% vs 28%).

Tumour or host biomarkers

We found no relevant evidence about tumour or host biomarkers predisposing to emergency presentation. Such associations however are highly likely, in spite of lack of evidence currently. For example, within a given organ (e.g. ovary or pancreas), certain types of tumours may be associated with higher or lower risk of emergency presentation.

[INSERT BOX 2]

5. Healthcare utilisation and presenting symptoms among prior consultees

Consistent with our prior theoretical framing, judging the potential for preventing emergency presentations requires consideration of whether patients had presented previously, and if so with what symptoms.

5a. Prior healthcare utilisation

*Prior **primary care** utilisation*

Seven studies (five from UK, and one each from Sweden and the US) studying patients with ovarian, lung, and colorectal cancer documented that most (between two thirds and four-fifths) of emergency presenters have had prior primary care consultation. [4, 11, 25-28, 40]

Evidence from a national English data source indicates that about 30% of emergency presentations are generated by direct emergency referral to hospital services by primary care physicians. [23] Concordantly, evidence from three small primary care studies indicates that up to 20% of cancer patients who have consulted their general practitioner are referred as an emergency.[25-27] Whether this patient group has also had prior 'elective' primary care presentations (before the contact with primary care leading to the emergency) is unclear.

In some patients an investigation plan and/or referral has been made but an emergency presentation occurs in the interval between referral and planned investigation or specialist assessment. Other than one study [26], evidence on this patient group is poorly described in the current literature. A quarter of the 39 emergency presenters in the Barrett et al study had an emergency admission while waiting for a specialist appointment. [26] These patients may benefit from shortening of intervals to investigations or assessment. [41]

Despite relatively high proportion of patients with prior consultations (80%) among emergency presenters, when compared to cancers diagnosed electively, they are less likely to have consulted in primary care prior to diagnosis.[4, 11, 40] This indirectly suggests that among patients subsequently diagnosed with cancer, prior consultations may well lower the risk of diagnosis as an emergency, supporting the need for improving access and reducing barriers to help-seeking where those are present. [42]

*Prior **secondary care** utilisation*

After excluding periods of 1-2 months before diagnosis (to avoid accounting for hospital care directly relating to the emergency presentation itself), three studies on colorectal cancer patients (two from US and one from UK) reported higher rates of prior inpatient and emergency admissions in emergency presenters compared with electively-diagnosed cancer patients. [3, 4, 40]

These findings may indicate that cancer patients who are diagnosed as emergencies may have higher levels of co-morbidity unrelated to their cancer; or suggest that emergency presenters are clustered within a patient group with higher than average use of Accident and Emergency department as opposed to primary

care services either due to personal choice [43] or primary care access barriers, including insurance status in the US health system. [3, 4]

Investigations prior to emergency presentation

Three studies on colorectal cancer reported that patients who had investigations prior to their colorectal cancer diagnosis were less likely to present as emergencies.[3, 11, 39] For example, Gunnarsson et al. reported lower prior colonoscopy and other investigations use in emergency presenters compared with electively diagnosed cancer patients (i.e. 10% vs 63% of emergency vs non-emergency presenters had a prior colonoscopy, while the respective figures for abdominal imaging studies were 15% vs 61%). Whether these prior investigations were performed for screening or the evaluation of symptoms was not reported in any of these three studies. These findings nonetheless indicate that prior endoscopic or imaging investigations may minimise the risk of diagnosis of cancer as an emergency.

5b. *Preceding symptomatic presentations*

Identifying symptoms associated with higher risk of subsequent diagnosis of cancer as an emergency can help to identify patient groups in which emergency presentations may potentially be averted. Thus far, evidence on prior symptoms relates *to patients who consulted previously* – i.e. it *excludes* a substantial group of patients who have not consulted before their emergency diagnosis (see above).

To avoid potential conflation of prior potential cancer symptoms with those directly triggering the emergency presentation event, optimally, prior symptom data should exclude the period of time directly preceding the emergency presentation (e.g. up to a month prior). However only one of the three studies with relevant data consistently applied such a design feature.[28]

Current empirical evidence about associations between prior symptoms and emergency diagnosis chiefly relates to patients diagnosed with colorectal cancer. Colorectal cancer patients diagnosed through emergency presentations are more likely to have previously seen their doctor with abdominal pain [11, 28, 40], change of bowel habit (particularly constipation [11, 28, 40]) and weight loss [11, 28]. They are less likely to have consulted for rectal bleeding [11, 28, 40] and anaemia. [11]

Although limited to colorectal cancer patients, some evidence suggests that patients who present with symptoms of lower predictive value for cancer are more likely to be diagnosed as emergencies. [11, 28, 40] While reducing the referral threshold for suspected cancer may reduce emergency presentations, this will also result in higher proportions of patients without cancer being also referred. Evidence on prior symptoms, clearly differentiating prior symptoms from those prompting the emergency presentation event, is needed for colon and rectal cancers separately, as well as for other malignancies.

6. Healthcare system factors

Most cancer patients initially present to non-specialists. Examining primary care organisation (such as through qualitative studies involving significant event analysis or quantitative studies examining practice-level characteristics and emergency presentation) and the impact of screening services can shed light on potentially remediable factors that contribute to emergency diagnoses. The available evidence mainly relates to studies examining associations between general practice characteristics (activity or performance) and emergency diagnosis.

General practice characteristics

Two English studies reported the association between practice characteristics and emergency presentations. Poorer in-hours primary care access (as measured by patients' ability to get an appointment within two days) (odds ratio 0.85 CI 0.79 – 0.92, p<0.0001 for patients in practices in the highest vs lowest quartiles of Quality and Outcomes Framework (clinical quality) points) [(1)] was found to independently predict the risk of emergency presentation (all cancer site). In the same paper, higher than average proportion of non-UK qualified practice doctors, and smaller practice list size were associated with higher odds of emergency presentation in the practice population. No association was found between continuity and emergency presentation in another primary care study – which however is likely to have under-estimated the true frequency of emergency presentations due to the unrepresentative sample of cases that have been included in this study. [(44)]

Access to primary care was examined by 2 North-American studies – both in the context of colorectal cancer. In a Canadian study, having a regular source of primary care was associated with a lower risk of diagnosis of colorectal cancer as an emergency (odds ratio 0.70 CI 0.65 – 0.77, no p-value "yes" vs "no" to regular source) [(39)]. Using a data item included in the US Medicare-SEER dataset, Pruitt et al. examined associations with 'prior preventable hospitalisations', as a proxy measure for access to primary care services. Patients with preventable hospitalisations a year before diagnosis were more likely to be diagnosed with cancer as emergencies than those without (e.g. emergency diagnosis rates of 50% vs 27% in colorectal cancer patients with and without preventable hospitalisation respectively). [(3)]

Primary care performance characteristics

In an English ecological study that reported performance characteristics, practices with a lower rate of upper-gastrointestinal endoscopy were associated with a higher emergency presentation risk of gastro-oesophageal cancers. [(45)]

Impact of screening

For cancers with effective screening programmes, no study has examined direct (individual level) associations between screening uptake history and risk of emergency presentation during follow-up periods. However, ecological 'before and after' studies indicate that colorectal cancer screening interventions can decrease the proportion of colorectal cancer patients who are diagnosed as emergencies, [(24, 46-48)] especially in the screening age group of 60-69 year olds (21% in 2006 to 16% in 2012). [(24)] For example, introduction of Faecal Occult Blood Test (FOBT) screening in a UK region was associated with a 47% decrease in the proportions of colorectal cancer patients in the same geographically-defined population who were diagnosed as emergencies between 1999 and 2004.[(46)] Similar

trends were observed in Scotland between 2003 and 2012 (i.e. pre- / post-FOBT screening introduction) with a reported reduction in the absolute proportion of patients diagnosed through emergency presentations from 20% to 13%.[48] Although these ecological studies suggest positive impact of screening on population rates of EP, possibly through the detection of symptomatic cases at an earlier stage, [47, 49] other interventions promoting earlier diagnosis (for example, cancer awareness campaigns) may have also contribute to the observed patterns. No relevant evidence exists for any other cancer (e.g. breast, cervical, lung). It should be noted that the impact of screening programmes on risk of emergency presentation may vary for different countries and healthcare systems, as the nature of screening programmes, and resultant population coverage and programme effectiveness is variable, and influenced by a range of organisational and social factors which are also likely to differ. It has been suggested that racial/ethnic disparities in colorectal cancer screening may explain in major part differences in emergency presentation in the US setting, [3] but the likely impact of inequalities in screening as a source of inequalities in emergency presentation in other countries could vary.

7. Stage at diagnosis

Stage at diagnosis reflects tumour biology (i.e. the intrinsic malignant potential of the tumour at oncogenesis) and at the same time it is also a function of tumour growth over time (and, consequently, a function of time to diagnosis).

Several studies have consistently reported that cancer patients who are diagnosed as emergencies are more likely to have advanced stage cancers (**Box 3**). In a recent report published on the routes to diagnosis by stage for 10 cancer sites in England, 30% of EP patients have stage 4 cancers at diagnosis, compared to 17% and 14% of those diagnosed through a fast-track ("2-week-wait") and non-urgent (non-2-week-wait) referral respectively. [(21)] The same source indicates that proportion of emergency presenters diagnosed at stage 4 varies notably between the different (10) studied cancers, from 18% and 20% for melanoma and prostate, to 44% and 45% for lung and ovarian cancer respectively.

[INSERT BOX 3]

8. Patient factors

8a. Sociodemographic inequalities in the frequency of emergency diagnosis of cancer, and interactions between patient characteristics and cancers

In part socio-demographic associations with risk of emergency presentations may reflect disease factors (e.g. age differences in tumour sub-types, or anatomical differences between the two sexes). However, some of these differences may reflect socio-cultural influences on patient help-seeking behaviour, or healthcare inequalities. How overall socio-demographic inequalities vary for different cancers may be particularly revealing of the potential to reduce emergency presentations.

Age

Cancer patients at the either extremes of age (the youngest and the very old patients) are more likely to be diagnosed as emergencies.

Adults: In general older age is associated with higher risk of emergency diagnosis, with the risk in patients above the age of 80 being particularly pronounced.[1-6, 8, 10, 11, 14, 29, 39, 40, 44, 45, 50] For example, English patients above age 85 and over are 2.5 times as likely as those age 65 – 74 to present as an emergency (for all non-gender specific cancers), [37]; similarly, for colorectal cancer patients age 90 are at 3 times greater risk compared to those age 70 [2].

> ***Interactions between age and cancer*:** When considering age as a 'main effect', variation in this relationship between different cancers can be masked. Specifically, some cancers exhibit a more positive association between increasing (adult) age and risk of emergency diagnosis, while for others there is a more complex J- or U-shaped pattern. For acute lymphocytic leukaemia there is a negative association (increasing age being associated with lower risk of emergency presentation).[37] Interactions between cancer and age are likely to reflect disease factors.

Children and young adults: The majority of studies excluded patients below the age of 25, with the exception of two relevant studies in the peer-reviewed evidence and two items of grey literature [5, 14, 18, 24]. More than half (54%) of patients aged 0-14 are diagnosed as emergencies [5]. For most of the cancer groups examined, patients aged 0-14 years in England were more likely to be diagnosed as an emergency than those aged 15-24 years; leukaemias and central nervous system (CNS) tumours were most likely to be diagnosed as an emergency, with 69% and 57% of 0-14 year olds with leukaemias and CNS tumours respectively being diagnosed as an emergency. [18]

Socioeconomic status

There is substantial evidence for an association between measures of lower socioeconomic status and greater risk of diagnosis of cancer as an emergency, as also recently reported by a systematic review specifically focused on lung and colorectal cancer. [1-4, 10, 14, 29, 37, 39, 44, 45, 50, 51] Different studies have defined socioeconomic status either using direct measures (e.g. individual income or insurance status), or ecologically (based on the socioeconomic characteristics of a small area population where an individual resides). Given the increasing use of ecological measures, we use the terms deprivation and socioeconomic

status interchangeably hereafter in the paper. In the US, deprivation and being insured by MedicAid (an insurance program for socioeconomically deprived patients) have also been implicated in their associations with increased EP for lung and colorectal cancer.[3, 4]

> ***Interactions between socioeconomic status and cancer*:** Although evidence for a cancer-deprivation relationship is present for most non-gender specific cancers, there is at present only one study which examined cancer-specific associations between socioeconomic status and EP across a range of different (27) cancers. A positive association (greater risk of emergency presentation among the most deprived patients) was particularly strong for patients with oral, oropharyngeal, and anal cancers – possibly indicating socioeconomic patterning of normalisation of relatively indolent initial symptoms (oral/oropharyngeal cancer) or stigma associated with reporting of symptoms in sensitive areas (anal cancer).[37]

Sex

Overall variation in risk of emergency presentation by sex is relatively small and largely a reflection of variable cancer site case-mix [37]. While women have been found to be at increased risk of EP in some studies,[1, 2, 4, 6, 8, 39, 45, 50] few other studies found no association between sex and risk of emergency diagnosis.[10, 29, 40]

> **Interactions between sex and cancer; and sex and socioeconomic status:** The risk of emergency presentation is notably higher for women with bladder cancer compared to men with bladder cancer, most likely reflecting difficulties of suspecting the diagnosis of bladder cancer in women.[37, 52] There are also interactions between sex and socioeconomic status, with Swedish men of the lowest income quartile being more likely than lowest income women to be diagnosed with colorectal cancer as an emergency.[29]

Ethnicity

Non-white patients [2] and those of Asian background [1] in the UK, as well as African-Americans in the US [3, 4] have been found to be more likely to present as an emergency (Box 4). For example, in a large-scale American study on colorectal cancer conducted by Pruitt, African Americans were 28% more likely than White Americans to have an emergency diagnosis and emergency surgery for colorectal cancer [3].

[INSERT BOX 4]

8b. Pre-diagnosis comorbidity and performance status

Co-morbid illness has been consistently reported to be a risk factor for EP. Patients with increasing comorbidities (especially 3 or more) are more likely to be diagnosed with cancer in an emergency setting [2-4, 8, 14, 44, 45]. Patients with dementia and those with cerebrovascular disease are 2.5 and 1.7 times as likely to present as emergencies than those without these comorbid conditions (e.g. odds ratio 2.46 CI 2.18 – 2.79 for dementia).[2]. On the other hand, no independent associations between comorbidity and emergency presentation risk were reported for chronic respiratory disease, diabetes and cardiovascular disease.[2, 11] Two studies using data from clinical audit initiatives found that poorer performance status was associated with higher risk of emergency diagnosis.[8, 10]

8c. Psychosocial factors

A Swedish study examined the potential role of marriage, as a marker of social isolation: it found that unmarried patients with colorectal cancer were more likely to be diagnosed as emergencies than their married counterparts (odds ratio 1.24, 95% CI 1.04 – 1.49 unmarried vs married patients), after adjustment for other confounders.[29] Other psychosocial factors which have been found to be associated with screening uptake and help-seeking behaviour include fear of cancer or fatalism, [53] and measures of cognitive (awareness), emotional or attitudinal barriers, [42, 54, 55] but no associations with emergency presentation were reported in the reviewed evidence.

Discussion

We considered evidence on the definitions, frequency and potential for preventing emergency presentation of cancers taking into account available evidence to the end of 2015. It is notable that current evidence relates only to 6 developed countries, and overwhelmingly relates to UK patient populations and the English Routes-to-Diagnosis project **(Box 5)**. However, given the consistency of the evidence within studies from these 6 countries, it is highly unlikely that emergency presentation is anything but a global challenge, as also recently highlighted by a study in European hospitals.[22] Studying emergency presentations in other international populations should be addressed by future research.

[INSERT BOX 5]

In most of the evidence emergency presentations are most commonly defined contextually, for example as diagnosis of cancer shortly after presentation to an emergency department or an emergency admission. For colorectal cancer patients only, at times contextual definitions are supplemented with information on clinical symptoms or emergency surgery. Only a minority of studies bases the definition of emergency presentation on the evaluation of clinical records. Nonetheless, use of administrative data analysis offers great advantages in terms of identification of inequalities and should be further explored and refined.

Associations between emergency presentations and a range of both potentially modifiable (e.g. prior consultations) and non-modifiable (e.g. tumour grade) factors have been described. However, quantifying the exact aetiological contribution of modifiable and non-modifiable influences remains poorly described in current literature. Recently a notable downward trend in the proportion of emergency presentations has been reported in England. [24] This strongly indicates that modifiable patient and healthcare factors do play a role, and possibly reflects the impact of public health campaigns (such as 'Be Clear on Cancer' in England) and healthcare interventions aiming to improve cancer diagnosis (such as the introduction of clinical guidelines for fast track assessment of patients at higher risk of cancer). [56, 57];

Early diagnosis interventions will be effective in reducing emergency presentations of cancer. For example, screening interventions (particularly for colorectal cancer) can help to prevent emergency presentations. Consequently efforts to increase uptake in the general population and decrease inequalities are needed. The development of effective screening tests for a number of cancers for which no such tests exist currently can lead to reductions in emergency presentations. However, such initiatives may also result in harm, such as over-diagnosis and over-treatment following screening. While reducing referral or investigation thresholds may reduce emergency presentations, it will also result in higher proportions of patients without cancer being also referred. Detailed description of these issues is outside the scope of this review.

A substantial minority of emergency presenters have no prior contact with the formal healthcare system. This may indicate the influence of biopsychosocial factors such as normalization of symptoms and not appreciating the seriousness of symptoms, particularly in the presence of co-morbid conditions and older age. [42, 55, 58, 59] Other contextual and cultural factors moderating the way in which people recognise, interpret and act on their symptoms include the influence of family and friends, fatalism, [53, 60] and fear of

cancer diagnosis and its treatment. [61] Access to appropriate use of healthcare services and concerns about wasting doctors' time could also act as barriers to help-seeking for these patients. [62] This growing evidence base indicates the need for ongoing development of public health education campaigns about cancer.

Nonetheless, the majority of patients have seen a general practitioner previously, while some have had contact with secondary care services (including emergency services). [31] Interventions that shorten diagnostic intervals and support / streamline the diagnostic process should therefore help reduce the proportion of emergency presentations.

Patients who present as an emergency are less likely to receive treatment with curative intent; and have worse (particularly short-term) survival. Both these associations are partly explained by stage at diagnosis but are maintained as independent associations even after adjustment. Therefore, although these observations may reflect unmeasured tumour aggressiveness, they may also indicate suboptimal diagnostic work-up and treatment in emergency presenters. Improvements in outcomes may therefore be possible by re-configuring how out-of-hours emergencies are covered by specialist medical and surgical oncology services. [11]

It has been previously argued that: "*Interventions should aim to reduce the proportion of patients with cancer who are diagnosed as emergencies to the absolute minimum dictated by tumor aggressiveness, having removed the potential influence of either healthcare or patient factors*". [16] Concordantly and give our review, we propose and advocate the following recommendations for informing clinical practice, public health policy and research.

RECOMMENDATIONS BOX

1. Defining and measuring emergency diagnoses

a. **Definitions:** Studies should explicitly describe whether they define emergency presentations contextually (i.e. if emergency care services were used) and/or clinically (i.e. if criteria about potentially life threatening symptoms and/or requirement for emergency treatment are met). *

b. Studies **using algorithmic definitions** in electronic health records should: i) aim to incorporate validation components based on direct inspection of random sub-samples of patient records *; ii) describe algorithms adequately to enable comparisons between countries/healthcare systems with different data infrastructures and diagnostic pathways. *

c. Studies **using patient records reviews** [20, 31, 32] can be optimally supported by data collection instruments which: i) explicitly consider the potential influence of contributing tumour (disease, biological), patient and healthcare (provider or organisational) factors; ii) allow judgements about the potential preventability of emergency presentations.

2. Preventing emergency presentations in patients without prior relevant healthcare utilisation

a. Given that some emergency presenters have no prior relevant consultations, [4, 11, 20, 25-27, 32, 39, 40, 44] evidence is needed to help better understand the characteristics of these patients and their possible

preceding symptoms, together with potential access (including insurance coverage) or psychosocial barriers to help-seeking in this patient group.

3. *Preventing emergency presentations in patients with prior relevant consultations / healthcare utilisation*

More evidence is needed on the prior consultations / healthcare utilisation patterns in these patients to identify higher risk groups. It is important that symptoms suggestive of cancer at an earlier stage and acute symptoms triggering the emergency presentation event itself are distinguished in such studies. [28]

4. Optimising organisational / healthcare system factors

a. Supporting the diagnostic process by reducing thresholds for specialist referral and enabling access to investigations could help prevent some emergency presentations. *

b. New models of diagnostic services (such as multidisciplinary one stop diagnostic clinics) for patients with atypical / 'vague' symptoms should help reduce emergency presentations, [63] given that some emergency presentations occur while patients are awaiting or undergoing elective investigation. [25-28, 31, 32]

c. As screening for colorectal cancer may reduce emergency presentations, [46-48] policy initiatives and research are needed to increase its population uptake and decrease related inequalities. Future development of effective screening programmes (e.g. for lung cancer) could further reduce emergency presentations *.

d. Initiatives to increase use of early detection interventions for symptomatic patients or in the context screening should encompass the evaluation of potential harms from over-diagnosis and cost-effectiveness, which are increasingly being considered in clinical practice and research studies. [64]

5. Improving outcomes in emergency presenters

a. Research is needed to understand the associations between emergency presentation and lower use of curative treatments, and the reasons why emergency presenters have poorer survival compared with electively diagnosed patients of the same stage. [10, 14, 21]

b. Reconfiguration of out-of-hours coverage of emergencies by specialist oncology service may help to improve clinical outcomes in patients diagnosed through an emergency presentation. [11]

6. Emergency diagnosis of cancer as a likely global challenge

a. Given that evidence is currently restricted to patient populations from only 6 countries, researchers and policy makers should urgently address the evidential gap on the global burden of emergency presentations; doing so requires substantial global investment in cancer registration and the conduct of comparative studies.*

b. Understudied patient groups include paediatric and young adult cancer patients, and those with rarer cancers [18]; international policy initiatives and research should aim to address these evidential gaps as a priority. *

** Statements based on indirect evidence and consensus between the authors.*

Box 1. Review Criteria

Database Sources
We searched PubMed, EMBASE, CINAHL, Web of Science, and the Cochrane Library from their inception, using the search terms "emergency or emergencies or urgent", and "presentation or diagnosis or diagnose*", and "neoplasm or cancer". We restricted the search to human studies, without time (ie. From database inception) or language restrictions. An initial search was completed in February 2015, and updated in December 2015. Endnote was used to facilitate title and abstract inspection, and de-duplication.

Eligibility Criteria
We searched for population-based evidence about the frequency and predictors of diagnosis of cancer as an emergency. We included all empirical studies based on population-based evidence which examined "emergency diagnosis" or "emergency presentation" of cancer as an outcome or independent variable. We excluded case series arising from single hospital centres (because of concerns about generalisability), case reports, conference abstracts, commentaries and reviews.

Box 2. Variation in frequency by tumour sub-site or sub-type

In the few studies examining 'colon' and 'rectal' cancers separately, the average frequency of emergency diagnosis was approximately two-fold greater for colon cancer (e.g. 31% vs 15% for rectal cancer in Abel et al.) [6, 11, 29, 37, 39]These findings may reflect differences in the nature of preceding symptoms or anatomical differences leading to variable risks of obstruction or perforation in either sub-site. Variation in the proportion of patients who are diagnosed as emergencies has also been reported for different colon sub-sites, although the evidence is inconsistent about whether the risk is greater for left- or right-sided tumours. [3, 6, 39].

Similarly oesophageal and stomach cancers vary in emergency presentation frequencies, with average reported rates being 20% and 31% respectively [1, 5, 8, 37] These differences may reflect that a relatively high proportion of patients with oesophageal cancer present with a 'red flag' symptom (dysphagia).

Within haematological cancers, higher frequency of emergency presentations are reported in non-Hodgkins compared to Hodgkin's patients. [37] Similarly higher frequencies were reported for patients with acute compared to chronic leukaemias, with about half of all patients with acute leukaemia presenting as emergencies. [1, 37]

Box 3. Associations between stage and emergency presentation for different cancers

Colorectal: odds ratio between 1.28 to 4.8, all p<0.05 for late vs early stages [3, 4, 6, 14, 40]
Lung: odds ratio between 1.65 to 2.70, all p<0.05 for late vs early stages [4, 10, 14]
Cervical: *odds ratio 14.7, 95% CI 11.1 – 19.6 for TNM stage 4 vs 1 at diagnosis [14]
Breast: *odds ratio 13.9, 95%CI 3.2 – 59.7 for TNM stage 4 vs 1 at diagnosis [14]
Prostate: *odds ratio 5.9, 95% CI 5.0 – 7.0 for TNM stage 4 vs 1 at diagnosis [14]
Oesophago-gastric: 20 vs 13% of emergency cases for Stage IV vs I/II p<0.001 [8]

10 cancers considered together: 30% of EP patients have stage 4 cancers at diagnosis, compared to 17% and 14% of those diagnosed through a 2-week-wait and non-2-week-wait referrals respectively; the proportion of emergency presenters with stage 4 cancer at diagnosis was 17% for bladder, 33% for breast, 32% for colorectal, 30% for kidney, 59% for lung, 16% for melanoma, 21% for non-Hodgkin's lymphoma, 29% for ovarian, 39% for prostate and 17% for uterine cancer. [21]

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*Adjusted odds ratio for age, sex, co-morbidity (as measured by Charlson index), income deprivation; for TNM Stage 4 vs 1

Box 4. Selected examples of associations between ethnicity and emergency presentation

Type of cancer	Country of Study	Odds of Emergency Presentation
Any of 15 cancers	England [1]	OR 1.16 95% CI 1.08 – 1.24 Asian vs White
Colorectal	England [2]	OR 1.13 95% CI 1.02 – 1.24 Non-white vs White
Colorectal	US [3]	OR 1.28 95% CI 1.20 – 1.37 African-American vs White
Colorectal	US [4]	OR 1.16 95% CI 0.97 – 1.38 African-American vs White
Lung	US [4]	OR 1.42, 95% CI 1.42 – 1.66 African-American vs White

Box 5. The UK Routes to Diagnosis project – an exemplar for health record epidemiological studies to study emergency presentation.

The great majority of epidemiological evidence on emergency diagnosis of cancer currently relates to the English "Routes to Diagnosis" project (Public Health England). Linking information from different sources such as cancer registration, hospital care and screening programme records, patients are assigned to different diagnostic 'routes' (including emergency presentation but also screening detection and urgent or routine referral routes) using algorithms. The project provides for the largest population-based collection of data on the diagnostic route of incident cancer patients anywhere in the world, and can serve as a prototype for similar developments in healthcare systems benefiting from rich collections of electronic patient health records

Appendix 1: Descriptions of included studies / sources of evidence

Study details	Diagnosis period; data source	Population (total cases)	Number of emergency presenters (%)	Cancer studied
Abel et al, Br J Cancer 2015, UK [37]	2006 – 2010; Routes to Diagnosis dataset*	England (age 25+, 749 645)	232 281 (31)	27 non-gender-specific cancers
Barrett, Fam Pract 2006, UK [26]	2002; 5 cases from each participating GP practice	Exeter, Oxford and Sheffield (151)	39 (26)	Colorectal
Barrett, BMC Fam Pract 2008, UK [25]	1998-2002; primary care records	Exeter Primary Care Trust (246)	71	Lung
Barrett, Br J Obs & Gynae 2010, UK [27]	2000-2007; primary care records	Exeter, East and Mid-Devon (women>40yr, 212)	39	Ovarian
Beckett, Lung Cancer 2014, UK [10]	2006-2011; National Lung Cancer Audit in England	England (133,530)	25 675 (19)	Non-small cell lung cancer
Bottle, Br J Cancer 2012, UK [1]	2007 – 2010; Hospital Episodes Statistics	England, (639064) *likely partially nested within Abel/Elliss-Brookes	139 351 (22)	22 cancers
Cleary, Fam Pract 2007, UK [28]	1998-2002; primary care records	Exeter PCT (349)	62	Colorectal
Dejardin, Br J Cancer 2005, France [65]	1995; Cancer registry data	Nationwide (1413)	192	Colorectal
Elliss-Brookes, Br J Cancer 2012, UK [5]	2006-2008; Routes to diagnosis dataset*	England (739 667) *fully nested within Abel except for breast, prostate, cervix, endometrial,	(24%)	15 cancers
Gunnarsson, Eu J Surg Onc 2013, Sweden [29]	1997-2006; Cancer registry	Uppsala-Orebro and Stockholm regions (12293)	2856 (23)	Colon
Gunnarsson, World J Surg 2014, Sweden [11]	2006-2008; Cancer registry, review of primary and secondary care records`	Regional Oncology Centre in Uppsala-Orebro (case control - 854)	263	Colon
McArdle, Br J Surg 2004, UK [6]	1991-1994; Linked secondary care data with cancer registry.	Scotland (3200)	986	Colorectal
McPhail, Br J Cancer 2013, UK [14]	2006-2008; Routes to diagnosis dataset*	England (colorectal and cervical); East of England (prostate, breast, lung) (131,754) *fully nested within Elliss-Brookes	Percentages for individual cancers given	5 cancers including cervical, colorectal, breast, lung and prostate
Nouraei, Laryngoscope 2014, UK [12]	1996-2011; Hospital Episodes Statistics	England (874)	353 (40%)	primary tracheal
Palser, BMJ Open 2013, UK [8]	2007-2009; National Oesophago-gastric cancer audit	England (14102)	(16%)	Oesophageal, Gastric

Pruitt, BMC Cancer 2014, USA [3]	1992-2005; Linked SEER-Medicare data	Nationwide, aged 66+ (138,376)	21313 (28%)	Colorectal
Rabeneck, Am J Gastroenterol 2006, Canada [39]	1996-2001; Linked Canadian Insitute for Health Information, Ontario Health Insurance Plan, Registered Persons Database	Ontario (age 20+, 41356)	7739 (19%)	Colorectal
Raine, BMJ 2010, UK [50]	1999 – 2006; Hospital Episodes Statistics	England (age 50+, 564821)	182 449 (32%)	Colorectal Breast Lung
Shawihdi, Gut 2014, UK [45]	2006-2008; Linked Hospital Episodes Statistics and Death registry	England (22488) *likely partially nested within Abel/Elliss-Brookes	(28%)	Oesophagogastric
Sheringham, Br J Cancer 2014, UK [40]	2009-2011; Linked cancer registry, primary and secondary care records	North East London (943) *likely partially nested within Abel/Elliss-Brookes	228 (24%)	Colorectal
Sikka, Am J Emerg Med 2012, USA [4]	1996-2000; Linked cancer registry, Medicaid eligibility file and Census Summary File	Michigan (age 65+, 20311)	4278 (21%)	Colorectal Lung
Tataru, Cancer Epidem 2015, UK [9]	2006-2008; Linked Cancer registry, Hospital Episodes Statistics, National Lung Cancer Audit and Routes to Diagnosis dataset*	England (93 783)	35042 (37%)	Non-small cell lung cancer
Tsang, BMC Health Serv Res 2013, UK [44]	1999-2008; Linked primary care records, Hospital Episodes Statistics and Office for National Statistics mortality data	England (5870)	817 (13.9%)	22 cancers
Wallace, Br J Cancer 2014, UK [2]	2007-2011; Linked Hospital Episodes Statistics and National Bowel Cancer Audit	England (82777)	17889 (21%)	Colorectal
Grey Literature				
NCIN Routes to Diagnosis 2006-2013 [19, 24]	2006-2013; Routes to diagnosis dataset	England (2,152,704)	(22%)	56 cancer sites
NCIN Teenagers & Young Adults [18]	2004-2008; Routes to Diagnosis	England, 0-49 year olds (131353)	0-14yr – (54%) 15-49yr – (13%)	10 cancer groups
NCIN Major Resections [7]	2006-2010; Linked cancer registry and Hospital Episodes Statistics	England, excluding 0-14 year olds (971329)	199466 (20.5)	20 cancer sites
NCIN Cancer by Stage [21]	2012-2013: Routes to Diagnosis	England (574487)	118113 (20.6)	10 cancer sites
Jones (2013) [20]	2010-2012: Retrospective audit of primary care records	Thames Valley Cancer Network, 73 GP Practices (1579)	142 (9%)	13 cancer groups and sites
Newsom-Davies (2015) [22]	2006-2008: Hospital case series	European Thoracic Oncology members - 8 sites in Europe: (2315)	534 (23.1)	Lung
* Routes to Diagnosis dataset consists of linked data from National Cancer Data Repository, Hospital Episodes Statistics, National Cancer Waiting Times, NHS screening programmes data in England				

Appendix 2: Frequency of emergency presentation for different cancers

Study	Cancer Site	Total number of cases (N)	Number of EP (n)	Proportion of EP (%)
Colorectal				
Abel (2015)	Colon	97880	30777	31
Gunnarsson (2013)	Colon	12293	2856	23
Gunnarsson (2014)	Colon	1430	158	11
Abel (2015)	Rectal	54076	8177	15
Bottle (2012)	Colorectal	80508	17285	22
Cleary (2007)	Colorectal	349	62	18
Dejardin (2005)	Colorectal	1413	192	14
Elliss-Brookes (2012)	Colorectal	91416	*	26
McArdle (2004)	Colorectal	3200	986	31
	Colon	2068	802	39
	Rectum	1091	170	16
McPhail (2013)	Colorectal	89484	*	26
Pruitt (2014)	Colorectal (emergency diagnosis)	83330	*	29
	Colorectal (emergency surgery)	55046	*	26
Rabeneck (2006)	Colorectal	41356	7739	19
	Colon	21050	4572	22
	Rectal	13216	1636	12
	Other/Synchronous	7090	1531	22
Raine (2010)	Colorectal	186977	60684	33
Sheringham (2014)	Colorectal	943	*	24
Sikka (2010)	Colorectal	9030	*	23
Wallace (2014)	Colorectal	82777	17889	22
Lung				
Abel (2015)	Lung	162543	62498	39
Barrett (2008)	Lung	246	56	23
Bottle (2012)	Lung	62442	24803	40
Elliss-Brookes (2012)	Lung	96735	*	39
McPhail (2013)	Lung	9601	*	36
Raine (2010)	Lung	186741	96521	52
Sikka (2010)	Lung	11281	*	19
Abel (2015)	Mesothelioma	10116	3631	36
Beckett (2014)	NSCLC	133530	25675	19
Tataru (2015)	NSCLC	93783	35042	37
Oesophago-gastric				
Abel (2015)	Oesophageal	32470	7062	22
Bottle (2012)	Oesophageal	18946	3407	18
Elliss-Brookes (2012)	Oesophageal	19449	*	22
Palser (2013)	Oesophageal	9755	*	13
Shawihdi (2014)	Oesophago-gastric	22488	*	28
Abel (2015)	Stomach	29893	9913	33
Bottle (2012)	Stomach	13970	3684	26
Elliss-Brookes (2012)	Stomach	18613	*	33
Palser (2013)	Stomach	4347	*	24
Gender-specific				
Barrett (2010)	Ovarian	212	43	20
Bottle (2010)	Ovarian	12079	3493	29
Elliss-Brookes (2012)	Ovarian	16026	*	32
Bottle (2010)	Cervix	5964	779	13

McPhail (2013)	Cervix	6950	*	12
Bottle (2010)	Prostate	55275	6487	12
Elliss-Brookes (2012)	Prostate	92922	*	10
McPhail (2013)	Prostate	11204	*	7
Bottle (2010)	Testis	4732	445	9
Bottle (2010)	Uterus	16017	1036	7
Elliss-Brookes (2012)	Uterus	18462	*	8
Bottle (2010)	Breast	101506	4170	4
Elliss-Brookes (2012)	Breast	110173	*	5
McPhail (2013)	Breast	12354	*	4
Raine (2010)	Breast	191103	25244	13
Urogenital				
Abel (2015)	Bladder	42234	7834	19
Bottle (2012)	Bladder	48333	3696	8
Elliss-Brookes (2012)	Bladder	25639	*	19
Abel (2015)	Renal	29469	7733	26
Bottle (2012)	Kidney	13653	3157	23
Elliss-Brookes (2012)	Kidney and unspecified urinary organs	20594	*	25
Other gastrointestinal				
Abel (2015)	Pancreas	33295	16364	49
Bottle (2012)	Pancreas	13225	7436	56
Elliss-Brookes (2012)	Pancreas	19896	*	50
Abel (2015)	Small intestine	3399	1863	55
Abel (2015)	Liver	14732	7270	49
Abel (2015)	Anal	3381	345	10
CNS				
Abel (2015)	Brain	16710	11175	67
Bottle (2012)	Brain and CNS	13170	6484	49
Elliss-Brookes (2012)	CNS	11697	*	62
Leukaemia				
Abel (2015)	Hodgkin's	4768	674	14
Abel (2015)	Non-Hodgkin's	46329	12393	27
Bottle (2012)	Non-Hodgkin's	23541	5318	23
Elliss-Brookes (2012)	Non-Hodgkin's	25413	*	27
Abel (2015)	Multiple myeloma	18272	6693	37
Bottle (2012)	Multiple myeloma	9654	2674	28
Elliss-Brookes (2012)	Multiple myeloma	11221	*	37
Abel (2015)	CLL	11892	2950	25
Abel (2015)	CML	1702	656	39
Bottle (2012)	Chronic leukaemia	7192	1716	24
Abel (2015)	AML	9611	5388	56
Bottle (2012)	Acute leukaemia	8336	4087	49
Oral-pharyngeal/ENT				
Abel (2015)	Oral	9801	491	5
Bottle (2012)	Oral	9863	721	7
Abel (2015)	Oropharyngeal	6429	365	6
Abel (2015)	Laryngeal	8283	833	10
Bottle (2012)	Larynx	4764	661	14
Abel (2015)	Thyroid	8254	460	6
Nouraei (2014)	Tracheal	874	353	40
Melanoma				

Abel (2015)	Melanoma	45561	967	2
Bottle (2012)	Melanoma	18933	414	2
Elliss-Brookes (2012)	Melanoma	26660	*	3
Others				
Abel (2015)	Soft-tissue sarcoma	4839	635	13
Abel (2015)	Unknown primary	43290	24805	57
Bottle (2012)	Other	96961	37398	39
* Data not available in study, only percentage and total cases given				

Appendix 3 Population based studies on EP and types of variables considered/mentioned by each

	Site	Stage	Grade	Symptoms	Age	SES	Ethnicity	Gender	Comorbidity	Performance Status	Psychosocial factors	Screening coverage	Prior GP contact	Prior admission	Prior investigation	Practice factors	Temporal change	Treatment	Survival
Abel (2015) [37]					Y	Y		Y									Y		
Barrett (2006) [26]													Y						
Barrett (2008) [25]													Y						
Barrett (2010) [27]													Y						
Beckett (2014) [10]		Y			Y	Y		Y	Y	Y									Y
Bottle (2012) [1]					Y	Y	Y	Y								Y	Y		
Cleary (2007) [28]				Y															
Dejardin (2005) [65]								EP = exposure variable											
Elliss-Brookes (2012) [5]					Y												Y		Y
Gunnarsson (2013) [29]		Y			Y	Y		Y									Y		
Gunnarsson (2014) [11]		Y		Y	Y			Y	Y				Y		Y				Y
McArdle (2004) [6]	Y	Y		Y	Y	Y		Y										Y	Y
McPhail (2013) [14]		Y			Y	Y		Y	Y										Y
Nouraei (2014) [12]																		Y	Y
Palser (2013) [8]		Y			Y	Y		Y	Y	Y								Y	Y
Pruitt (2014) [3]	Y	Y	Y		Y	Y	Y	Y	Y					Y	Y		Y		
Rabeneck (2006) [39]	Y	Y			Y	Y		Y	Y				Y		Y		Y		
Raine (2010) [50]					Y	Y		Y									Y	Y	
Shawihdi (2014) [45]					Y	Y			Y							Y			
Sheringham (2014) [40]		Y		Y	Y			Y					Y	Y					
Sikka (2010) [4]		Y			Y	Y	Y	Y	Y				Y	Y					
Tataru (2015) [9]		Y			Y	Y		Y	Y	Y							Y	Y	Y
Tsang (2013) [44]					Y	Y	Y	Y	Y				Y	Y		Y			

Wallace (2014) [2]				Y	Y	Y	Y	Y						Y		
GREY LITERATURE																
NCIN 2006-2013 (2015) [19, 24]				Y	Y	Y	Y							Y		Y
NCIN Teenagers & Young Adults (2013) [18]				Y			Y							Y		
NCIN Major Resections (2015) [7]							Y								Y	
NCIN Cancer by Stage (2016) [21]		Y		Y	Y	Y	Y									
Jones (2013) [20]								Y		Y	Y	Y	Y			
Newsom-Davies (2015) [22]	Y	Y	Y	Y			Y		Y						Y	

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