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# Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review

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**Background:** It is unclear whether more timely cancer diagnosis brings favourable outcomes, with much of the previous evidence, in some cancers, being equivocal. We set out to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations.

**Methods:** Systematic review of the literature and narrative synthesis.

**Results:** We included 177 articles reporting 209 studies. These studies varied in study design, the time intervals assessed and the outcomes reported. Study quality was variable, with a small number of higher-quality studies. Heterogeneity precluded definitive findings. The cancers with more reports of an association between shorter times to diagnosis and more favourable outcomes were breast, colorectal, head and neck, testicular and melanoma.

**Conclusions:** This is the first review encompassing many cancer types, and we have demonstrated those cancers in which more evidence of an association between shorter times to diagnosis and more favourable outcomes exists, and where it is lacking. We believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of improved survival, earlier-stage diagnosis and improved quality of life, although these benefits vary between cancers.

Symptomatic diagnosis of cancer is important and has been the subject of considerable innovation and intervention in recent years to achieve timelier and earlier-stage diagnosis (Emery *et al*, 2014); the English National Awareness and Early Diagnosis Initiative has made a major contribution to this effort (Richards and Hiom, 2009; Richards, 2009a). We know that patients value timely

diagnostic workup, and that later stage at diagnosis is one of the contributory factors to poor cancer outcomes (Richards, 2009b). However, it is less clear whether more timely cancer diagnosis brings favourable outcomes. Systematic reviews in breast cancer reported that delays of 3–6 months were associated with lower survival (Richards *et al*, 1999), and in colorectal cancer it was

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concluded that there were no associations between diagnostic delays and survival and stage (Ramos *et al*, 2007, 2008; Thompson *et al*, 2010). Other reviews have been published for gynaecological cancers (Menczer, 2000), bladder (Fahmy *et al*, 2006), testicular (Bell *et al*, 2006), lung (Jensen *et al*, 2002; Olsson *et al*, 2009), paediatric cancers (Brasme *et al*, 2012a, b) and head and neck cancers (Goy *et al*, 2009; Seoane *et al*, 2012), all with equivocal findings. No review to date has undertaken this work in a range of different cancer types.

Longer time to diagnosis may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. Conversely, harm may be caused by earlier detection of cancers without improving survival (lead-time), and detection of slow-growing tumours not needing treatment (over-diagnosis) (Esserman *et al*, 2013). A scoping review, undertaken before the review reported here, showed that observational studies in many cancers reported no association or an inverse relationship between longer diagnostic times and better outcomes (Neal, 2009). We therefore undertook a systematic review of the literature aiming to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations only.

## MATERIALS AND METHODS

We undertook a systematic review in two phases. The original review was conducted in 2008–10, and the literature from inception of databases to February 2010 was searched; the update was conducted in 2013–14, and the literature from February 2010 to November 2013 was searched. The original review did not include breast or colorectal cancer (because of prior systematic reviews); however, these were included in the update (as we knew of more papers published in these cancers). The review adhered to principles of good practice (Egger *et al*, 2001; NHS Centre for Reviews and Dissemination, 2001). Reporting is in line with the PRISMA recommendations (Moher *et al*, 2009).

A search strategy was developed for Medline (Figure 1) and adapted for other search sources. A range of bibliographic databases were searched for relevant studies. These were as follows:

- MEDLINE, MEDLINE in-process, EMBASE, CINAHL, PsychINFO
- Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, NHS Economic Evaluation database.

Reference lists of studies included in this and previous reviews were hand-searched for relevant studies.

One reviewer screened the titles and abstracts of all records for relevance, and assessed potentially relevant records for inclusion. A second reviewer checked the decisions; disagreements were resolved by discussion or, if necessary, by a third reviewer. A study or analysis was included in the review if it:

- Reported patients with symptomatic diagnosis of primary cancer (screen- and biomarker-detected cancers were excluded).
- Primarily aimed to determine the association of at least one time interval to diagnosis or treatment (patient, primary care, secondary care or a combination), allowing assessment against accepted definitions (Weller *et al*, 2012). The outcomes of interest were any measure of survival or mortality; any description of stage, including extent or severity of disease at diagnosis and response to treatment; or quality of life.

- Was available as full text in English.

Data extraction for all included studies was done by one researcher and checked by another. We extracted data relating to the following:

- Characteristics of included studies: study aim, population, location, setting, definitions of time intervals, data collection methods used and outcome measures.
- Clinical outcomes: included the measure of association, associations of intervals with outcomes and reported interpretation.

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1. Exp neoplasms/
2. (time adj4 diagnos$).ti,ab.
3. (time adj4 consult$).ti,ab.
4. (time adj4 treat$).ti,ab.
5. (time adj4 refer$).ti,ab.
6. (time adj4 present$).ti,ab.
7. (time adj4 interv$).ti,ab.
8. (time adj4 therap$).ti,ab.
9. or/2-8
10. (delay$ adj4 diagnos$).ti,ab.
11. (delay$ adj4 consult$).ti,ab.
12. (delay$ adj4 treat$).ti,ab.
13. (delay$ adj4 refer$).ti,ab.
14. (delay$ adj4 present$).ti,ab.
15. (delay$ adj4 interv$).ti,ab.
16. (delay$ adj4 therap$).ti,ab.
17. (delay$ adj4 seek$).ti,ab.
18. (delay$ adj4 care$).ti,ab.
19. (delay$ adj4 detect*).ti,ab.
20. or/10-19
21. (interval adj4 diagnos$).ti,ab.
22. (interval adj4 consult$).ti,ab.
23. (interval adj4 treat$).ti,ab.
24. (interval adj4 refer$).ti,ab.
25. (interval adj4 present$).ti,ab.
26. (interval adj4 therap$).ti,ab.
27. or/21-26
28. (late adj4 diagnosis).ti,ab.
29. (late adj4 detect*).ti,ab.
30. (late adj4 present$).ti,ab.
31. or/28-30
32. (duration adj4 symptom$).ti,ab.
33. Wait$ time$.mp.
34. 9 or 20 or 27 or 31 or 32 or 33
35. 1 and 34
36. limit 35 to (english language and humans and yr="2010 -current")
37. Editorial or letter or practice guideline or biography or case reports or clinical conference or comment or consensus development conference or NIH or guideline or newspaper article or patient education handout
38. Cells[Mesh] or Mass screening[Mesh] or genetic screening[Mesh] or pregnancy[Mesh]
39. Pharmaceutical preparations[Mesh]
40. Chemical. hw
41. #37 or #38 OR #39 or #40
42. 36 NOT 41

The original search strategy was found to be too sensitive and produced a large number of non-relevant references. This was revised and refined to capture all relevant articles. The number of databases searched was also more extensive for the original search, but on investigation, it was evident that all included articles had been found on databases subsequently chosen for the updated review.

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Figure 1. Search strategy (medline).

<p><b>Sample representativeness:</b> <i>Is the sample representative of the relevant cancer patient population? The population may be quite specific, typified by age, stage, ethnicity or other factors.</i>  <b>Yes:</b> <i>only if this is clearly reported</i>  <b>Can't tell:</b> <i>if it's reported in an ambiguous way</i>  <b>Not reported:</b> <i>if it doesn't say</i>  <i>If none of the above, please qualify with free text (this may be a majority of studies)</i></p>
<p><b>Characteristics reporting:</b> <i>Was the reporting of participant characteristics complete?</i>  <b>Yes:</b> <i>only if this is clearly and fully reported</i>  <b>Can't tell:</b> <i>is if it's reported in an ambiguous way</i>  <b>Not reported:</b> <i>if it doesn't say</i>  <i>If none of the above, please qualify with free text (this may be the majority of studies, for example those who just give age and gender)</i></p>
<p><b>Representativeness of participants:</b> <i>Were participants who participated (or whose data were used) representative of the sample from which they (or it) were sourced?</i>  <b>Yes:</b> <i>only if this is clearly and fully reported</i>  <b>Can't tell:</b> <i>is if it's reported in an ambiguous way</i>  <b>Not reported:</b> <i>if it doesn't say</i>  <b>Not applicable:</b> <i>if all of the sample participated, for example, database study</i>  <i>If none of the above, please qualify with free text</i></p>
<p><b>Bias minimisation in measurement of symptom duration:</b> <i>Were steps taken (as stated by the investigators) to minimise and check for, biases and inaccuracies introduced owing to the method used for measurement of symptom duration?</i>  <b>Yes:</b> <i>if clear evidence of this, please list information as free text: MANDATORY</i>  <b>No:</b> <i>if no evidence of this</i>  <b>Can't tell:</b> <i>if unclear (this includes where results may be reported but no mention in methods)</i></p>
<p><b>Independent variable assessment:</b> <i>Was the assessment symptom duration (explanatory variable) conducted independent of the assessment of the outcome variable?</i>  <b>Yes:</b> <i>if reported as done</i>  <b>No:</b> <i>if clearly reported that same researcher did it</i>  <b>Not reported:</b> <i>if it doesn't say</i>  <b>Not applicable:</b> <i>if the method does not require this to be done, for example, database study</i></p>
<p><b>A priori definition of outcome variable:</b> <i>Was the outcome variable specified/defined a priori?</i>  <b>Yes</b>  <b>No</b></p>
<p><b>Appropriate definition of outcome variable:</b> <i>Was the outcome variable clearly defined?</i>  <b>Yes:</b> <i>for example, type of stage, type of survival, not necessary to enter detail</i>  <b>No:</b> <i>anything other than yes</i></p>
<p><b>Multivariate analysis:</b> <i>Was multivariate analysis conducted?</i>  <b>Yes</b>  <b>No</b></p>
<p><b>Prognostic adjustment:</b> <i>Was adjustment for important prognostic factors conducted as part of the analysis?</i>  <b>Yes:</b> <i>if clear evidence of this, (for example: performance status, age, smoking, co morbidity), please qualify with free text MANDATORY</i>  <b>No:</b> <i>if no evidence of this</i>  <b>Can't tell:</b> <i>if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY</i></p>
<p><b>Outlier adjustment for symptom duration:</b> <i>Was adjustment for outliers conducted as part of the analysis?</i>  <b>Yes:</b> <i>if clear evidence of this, please qualify with free text MANDATORY</i>  <b>No:</b> <i>if no evidence of this</i>  <b>Not applicable:</b> <i>for example if there were no symptom durations greater than 2 years or less for more quickly diagnosed cancers</i>  <b>Can't tell:</b> <i>if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY</i></p>
<p><b>Confounder adjustment:</b> <i>Was adjustment for confounders (identified in advance of the study) conducted as part of the analysis?</i>  <b>Yes:</b> <i>if clear evidence of this, please qualify with free text MANDATORY</i>  <b>No:</b> <i>if no evidence of this</i>  <b>Can't tell:</b> <i>if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY</i></p>

We also identified studies (update only 2010–13) that addressed the so-called 'waiting time paradox' (see text).

Figure 2. Bias assessment tool.

- Bias assessment: we envisaged at the outset that there would be considerable variation between included studies in terms of study design, and that many may be of poor quality (Neal, 2009). We therefore considered that the assessment of methodological quality was especially important. However, at that time, there were no widely accepted checklists for checking the quality of prognostic studies, and there was little empirical evidence to support the importance of individual criteria, or study features,

in affecting the reliability of study findings (Altman, 2001). Hence, we decided against the use of quality scoring, and to use a checklist instead of a scale. Judgements on the risk of bias were made according to a number of domains, using a generic list of questions within each domain (Figure 2), based primarily on a framework for assessing prognostic studies (Altman, 2001). For the updated review, and being aware of more recent literature on assessing the quality of prognostic studies, we decided to keep

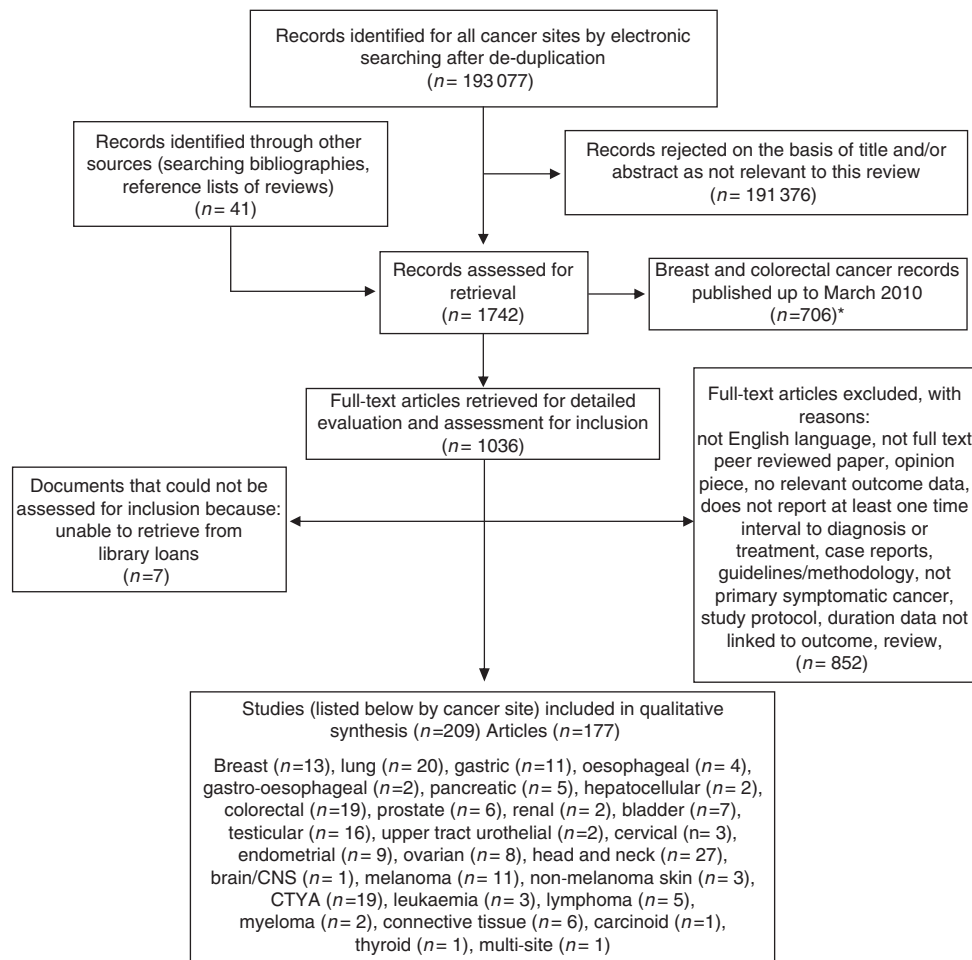


Figure 3. Flow diagram. \*Of those breast and colorectal cancer records published up to March 2010 (n= 706) assessed for retrieval, 330 were retrieved and assessed for inclusion but were not included in the evaluation, as systematic reviews on these cancers had been recently published. The follow-up review, covering the period March 2010 to October 2013, included both breast and colorectal cancers in the qualitative synthesis.

the original questions, as they were in line with the new Quality in Prognosis Studies tool (Hayden *et al*, 2006, 2013). In addition, in the update, we identified studies that addressed the so-called 'waiting time paradox' (Crawford *et al*, 2002), which were likely to be of higher analytical quality. These were defined as follows: 'articles that undertake an analysis or sub-analysis that specifically includes or excludes patients who are either diagnosed very quickly (e.g., within 4–8 weeks, although this will vary between cancers), or have very poor outcomes (e.g., deaths within a short time after diagnosis, e.g., within 4–8 weeks).' Agreement on inclusion in this subset of articles was done by two members of the study team. This is the 'paradox' caused by the inclusion of patients with aggressive disease who invariably present early and have poor outcomes as a result of the aggressive disease, and is a form of confounding by indication.

- Clinical outcomes: the measure of association, associations of intervals with outcomes and interpretation.

We planned to undertake meta-analysis if there were sufficient homogenous studies reporting a similar outcome measure and the same interval for an individual cancer. Narrative synthesis was undertaken otherwise.

## RESULTS

**Study selection.** The number of studies screened, assessed for eligibility, included and reasons for exclusion are shown in

Figure 3. Of the 1036 records identified for full-text review, 177 articles, reporting 209 studies, met the inclusion criteria and entered the narrative synthesis. A number of the articles reported data on more than one cancer, or more than one interval.

### Data collection in the included studies

**Definition of time intervals.** There were 15 different intervals reported in the included studies (Figure 4).

**Clinical and psychological outcomes.** Data collection for the outcome measures was predominantly retrospective review of medical records (using a variety of the following: clinical, pathological, histological and imaging) and cancer registries.

Patient questionnaires were used for studies with psychological outcomes. Most studies used various measures of survival (or mortality) and/or stage as outcome measures.

**Bias assessment.** The bias assessment demonstrates the mixed quality of the studies (Supplementary Online Material). On a positive note, the characteristics and representativeness of the samples were reported in most articles, the definitions and appropriateness of time intervals were well reported and many studies undertook multi-variable analysis. However, the representativeness of the samples was not reported in many articles, and few studies undertook confounder adjustment, prognostic adjustment or attempted bias minimisation. Only seven of the articles made an attempt to address the waiting time paradox (Tørring *et al*, 2011, 2012, 2013; Brasme *et al*, 2012a, b; Elit *et al*, 2013; Gobbi *et al*, 2013; Pruitt *et al*, 2013). Hence, most studies failed to address the premise of confounding by indication–

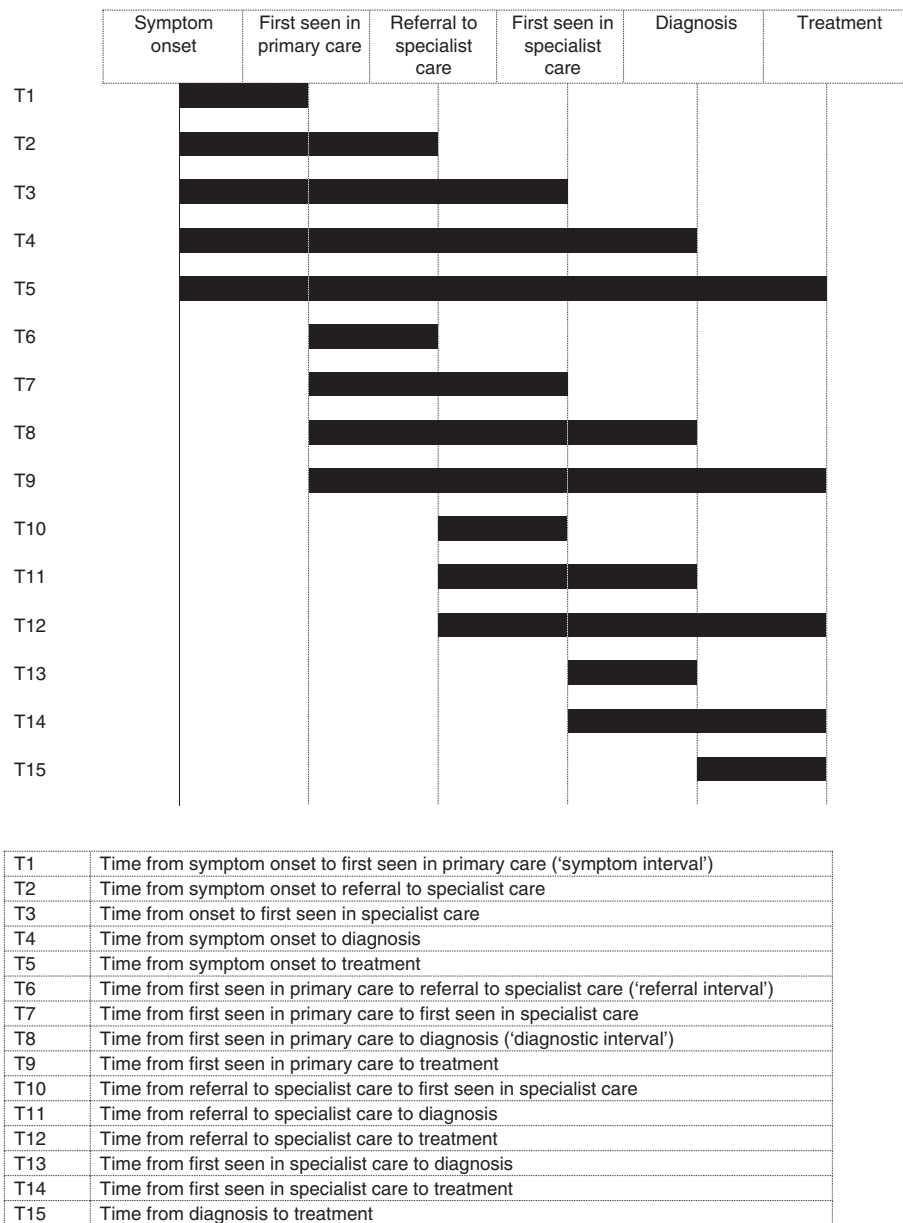


Figure 4. Definitions of time interval.

that is, the relationship between the diagnostic pathway (and hence the time interval) and prognosis.

**Study characteristics.** Of the 177 articles included, there were a total of 401 760 participants, with a range of 13 to 147 682 in individual study size (Supplementary Online Material). There were 88 European studies with 23 from the UK, 9 from Italy, 8 from Spain, 8 from the Netherlands, 7 from Denmark, 7 from Finland, 5 from France, 5 from Norway, 3 from Switzerland, 3 from Sweden, 3 from Germany, 2 from Poland and 1 each from Austria, Belgium, Romania, Greece and joint UK/Denmark. There were 18 studies from Asia, with 5 from India, 4 from Japan, 4 from China, 2 from Hong Kong, 2 from Malaysia and 1 from South Korea. There were 59 studies from the Americas, with 47 studies from the USA, 8 from Canada and 4 from Brazil. In addition, there were three from Turkey, two from Israel, two from Australia, one each from New Zealand, Saudi Arabia, Libya, South Africa and one unspecified.

148 were based in specialist care (106 single site, 38 multisite and 4 unspecified), 21 were population based, 3 were set in primary care, 3 database studies, 1 used hospital cancer registry

data and 1 was unspecified. Study design varied hugely, and it included prospective and retrospective cohort studies, reviews of medical records, database analyses, patient surveys and interviews. The majority of the studies had retrospective designs.

**Synthesis of main findings.** The results of individual studies are presented in Supplementary Online Material. No meta-analyses were possible. The results are reported cancer by cancer. Studies are grouped under 'children teenagers and young adults' where they reported at least a significant proportion of participants aged <25 years.

Summaries for each cancer are reported in Table 1. Studies that reported 'positive' associations (i.e., where there was evidence of shorter intervals being associated with more favourable outcomes) are presented first, followed by studies that reported no associations, followed by those that reported 'negative' associations (i.e., where there was evidence of shorter intervals being associated with less favourable outcomes). In each section, studies reporting survival outcomes (or mortality, but for simplicity just referred to as survival in the table) are presented before those reporting stage and other outcomes. A brief narrative for each cancer is provided below.

For breast cancer, four studies reported positive associations, including one of the studies that addressed the waiting time paradox, and was able to demonstrate the effect of different diagnostic intervals on mortality (Tørring *et al*, 2013). The remainder reported no associations.

The lung studies had mixed findings, with similar numbers of studies reporting positive, negative and no associations, across a range of different time intervals. However, one of the studies reporting a positive association with mortality for

diagnostic intervals addressed the waiting time paradox (Tørring *et al*, 2013).

For colorectal cancer, although many studies reported no associations, more studies reported a positive, rather than a negative, association. Indeed, four studies addressing the waiting time paradox were included, three of which reported a positive association (Tørring *et al*, 2011, 2012, 2013) and one a negative association (Pruitt *et al*, 2013). Of the upper gastrointestinal cancers, most studies reported no association, and more reported a

**Table 1. Summary results from narrative synthesis, by cancer**

Positive association	No association	Negative association
<b>Breast</b>		
<b>Survival</b> Diagnostic interval (Tørring <i>et al</i> , 2013) Treatment interval (Yun <i>et al</i> , 2012; Smith <i>et al</i> , 2013)	<b>Survival</b> Treatment interval (Brazda <i>et al</i> , 2010; McLaughlin <i>et al</i> , 2012; Eastman <i>et al</i> , 2013; Mujar <i>et al</i> , 2013; Redaniel <i>et al</i> , 2013; Sue <i>et al</i> , 2013)	
<b>Stage</b> Symptom onset to diagnosis (Ermiah <i>et al</i> , 2012; Warner <i>et al</i> , 2012)	<b>Stage</b> Treatment interval (Wright <i>et al</i> , 2010; Wagner <i>et al</i> , 2011)	
	<b>Other outcomes</b> Treatment interval and risk of recurrence (Eastman <i>et al</i> , 2013)	
<b>Lung</b>		
<b>Survival</b> Diagnostic interval (Tørring <i>et al</i> , 2013) Symptom onset to diagnosis (Maguire <i>et al</i> , 1994)	<b>Survival</b> Symptom onset to treatment (Annakkaya <i>et al</i> , 2007) Patient interval (Loh <i>et al</i> , 2006) Diagnostic interval (Loh <i>et al</i> 2006; Pita-Fernandez <i>et al</i> , 2007; Skaug <i>et al</i> , 2011) Treatment interval (Diaconescu <i>et al</i> , 2011; Yun <i>et al</i> , 2012) Symptom onset to being seen in specialist care (Garcia-Barcala, 2012)	<b>Survival</b> Patient interval (Radzikowska <i>et al</i> , 2012) Treatment interval (Gonzalez-Barcala <i>et al</i> , 2010)
<b>Stage</b> Symptom onset to treatment (Christensen <i>et al</i> , 1997) Treatment interval (Brocken <i>et al</i> , 2012; Murai <i>et al</i> , 2012)	<b>Stage</b> Patient interval (Yilmaz <i>et al</i> , 2008; Tokuda <i>et al</i> , 2009) Diagnostic interval (Pita-Fernandez <i>et al</i> , 2007; Yilmaz <i>et al</i> , 2008)	<b>Stage</b> Diagnostic interval (Gould <i>et al</i> , 2008) Treatment interval (Salomaa <i>et al</i> , 2005) Symptom onset to treatment (Myrdal <i>et al</i> , 2004) Referral interval (Neal, 2007) First seen in secondary care to diagnosis (Brocken <i>et al</i> , 2012)
	<b>Other outcomes</b> Symptom onset to diagnosis and quality of life (Mohan <i>et al</i> , 2006)	
<b>Gastric</b>		
	<b>Survival</b> Treatment interval (Yun <i>et al</i> , 2012) Symptom onset to diagnosis (Maguire <i>et al</i> , 1994; Martin <i>et al</i> , 1997; Windham <i>et al</i> , 2002; Arvanitakis <i>et al</i> , 2006) Patient interval (Lim <i>et al</i> , 1974) Primary care interval (Lim <i>et al</i> , 1974)	<b>Survival</b> Symptom onset to diagnosis (Maconi <i>et al</i> , 2003) Patient interval (Ziliotto <i>et al</i> , 1987)
	<b>Stage</b> Diagnostic interval (Fernandez <i>et al</i> , 2002) Patient interval (Tokuda <i>et al</i> , 2009)	<b>Stage</b> Diagnostic interval (Haugstvedt <i>et al</i> , 1991)
<b>Oesophageal</b>		
<b>Stage</b> Symptom onset to diagnosis (Martin <i>et al</i> , 1997)	<b>Stage</b> Diagnostic interval (Fernandez <i>et al</i> , 2002) Patient interval (Tokuda <i>et al</i> , 2009)	<b>Stage</b> Symptom onset to treatment (Wang <i>et al</i> , 2008)
<b>Gastro-oesophageal</b>		
<b>Other outcomes</b> Treatment interval and morbidity and in-hospital mortality (Grotenhuis <i>et al</i> , 2010)	<b>Survival</b> Referral interval (Sharpe <i>et al</i> , 2010)	
<b>Pancreatic</b>		
<b>Survival</b> Symptom onset to diagnosis (Gobbi <i>et al</i> , 2013) Symptom onset to referral (Raptis <i>et al</i> , 2010)	<b>Survival</b> Treatment interval (Yun <i>et al</i> , 2012)	
	<b>Stage</b> Patient interval (Tokuda <i>et al</i> , 2009)	
	<b>Other outcomes</b> Diagnostic interval and resectability (McLean <i>et al</i> , 2013)	

Table 1. (Continued)

Positive association	No association	Negative association
<b>Hepatocellular</b>		
<b>Survival</b> Treatment interval (Singal <i>et al</i> , 2013)	<b>Stage</b> Patient interval (Tokuda <i>et al</i> , 2009)	
<b>Colorectal</b>		
<b>Survival</b> Diagnostic interval (Tørring <i>et al</i> , 2011, 2012, 2013) Treatment interval (Gort <i>et al</i> , 2010–colon only; Yun <i>et al</i> , 2012–rectal only)  <b>Stage</b> Treatment interval (Guzman-Laura <i>et al</i> , 2011) colon Referral interval (Valentin-Lopez <i>et al</i> , 2012)	<b>Survival</b> Diagnostic interval (Pruitt <i>et al</i> , 2013) Referral interval (Zafar <i>et al</i> , 2011; Currie <i>et al</i> , 2012) Symptom onset to treatment (Thompson <i>et al</i> , 2011) First presentation to diagnosis (Singh <i>et al</i> , 2012) Treatment interval (Roland <i>et al</i> , 2013)  <b>Stage</b> Symptom onset to treatment (Terhaar sive Droste <i>et al</i> , 2010; Cerdan-Santacruz <i>et al</i> , 2011; Deng <i>et al</i> , 2012) Referral interval (Ramsay <i>et al</i> , 2012) Treatment interval (Van Hout <i>et al</i> , 2011) Symptom onset to treatment (Van Hout <i>et al</i> , 2011) Patient interval (Cerdan-Santacruz <i>et al</i> , 2011; Van Hout <i>et al</i> , 2011)  <b>Other outcomes</b> Patient interval and satisfaction (Tomlinson <i>et al</i> , 2012)	<b>Stage</b> Treatment interval (Guzman-Laura <i>et al</i> , 2011) rectal
<b>Prostate</b>		
<b>Survival</b> Diagnostic interval (Tørring <i>et al</i> , 2013) Diagnosis to treatment (O'Brien <i>et al</i> , 2011)	<b>Survival</b> Diagnosis to treatment (Korets <i>et al</i> , 2012; Sun <i>et al</i> , 2012) Referral interval (Neal <i>et al</i> , 2007)  <b>Stage</b> Diagnosis to treatment (Korets <i>et al</i> , 2012; Sun <i>et al</i> , 2012) Patient interval (Tokuda <i>et al</i> , 2009)	
<b>Testicular</b>		
<b>Survival</b> Patient interval (Hanson <i>et al</i> , 1993) Diagnostic interval (Huyghe <i>et al</i> , 2007; Moul <i>et al</i> , 1990–non-seminoma only) Symptom onset to treatment (Prout and Griffin, 1984; Medical Research Council Working Party, Testicular Tumours, 1985)  <b>Stage</b> Symptom onset to treatment (Ware <i>et al</i> , 1980; Wishnow <i>et al</i> , 1990) Patient interval (Ware <i>et al</i> , 1980; Chilvers <i>et al</i> , 1989) Diagnostic interval (Bosl <i>et al</i> , 1981; Moul <i>et al</i> , 1990; Huyghe <i>et al</i> , 2007–non-seminoma only) Patient interval (Hanson <i>et al</i> , 1993)  <b>Other outcomes</b> Diagnostic interval and chance of complete remission (Akdas <i>et al</i> , 1986); and response to treatment (Scher <i>et al</i> , 1983)	<b>Survival</b> Patient interval (Fossa <i>et al</i> , 1981) Symptom onset to treatment (Dieckmann <i>et al</i> , 1987) Symptom onset to treatment Meffan <i>et al</i> , 1991) Diagnostic interval (Moul <i>et al</i> , 1990; Harding <i>et al</i> , 1995–seminoma only; Fossa <i>et al</i> , 1981)  <b>Stage</b> Symptom onset to treatment (Dieckmann <i>et al</i> , 1987) Symptom onset to treatment Meffan <i>et al</i> , 1991) Diagnostic interval (Harding <i>et al</i> , 1995)  <b>Other outcomes</b> Symptom onset to treatment and relapse rate (Napier and Rustin, 2000)	
<b>Renal</b>		
	<b>Stage</b> Patient interval (Tokuda <i>et al</i> , 2009)	<b>Stage</b> Symptom onset to treatment (Holmang and Johansson, 2006)
<b>Bladder</b>		
<b>Survival</b> Symptom onset to diagnosis (Hollenbeck <i>et al</i> , 2010) Symptom onset to referral (Wallace <i>et al</i> , 2002)  <b>Stage</b> Diagnostic interval (Liedberg <i>et al</i> , 2003)	<b>Survival</b> Treatment interval (Gulliford <i>et al</i> , 1991) Referral interval (Wallace <i>et al</i> , 2002) Symptom onset to treatment (Mommson <i>et al</i> , 1983)  <b>Stage</b> Symptom onset to diagnosis (Maguire <i>et al</i> , 1994) Patient interval (Tokuda <i>et al</i> , 2009)	
<b>Upper tract urothelial carcinoma</b>		
<b>Stage</b> Diagnosis to treatment (Waldert <i>et al</i> , 2010)	<b>Survival</b> Diagnosis to treatment (Waldert <i>et al</i> , 2010; Sundi <i>et al</i> , 2012)	
<b>Cervical</b>		
<b>Stage</b> Patient interval (Fruchter and Boyce, 1981)	<b>Survival</b> Treatment interval (Umezu <i>et al</i> , 2012)  <b>Stage</b> Primary care interval (Fruchter and Boyce, 1981) Patient interval (Tokuda <i>et al</i> , 2009)	

Table 1. (Continued)

Positive association	No association	Negative association
<b>Endometrial</b>		
<p><b>Stage</b> Symptom onset to diagnosis (Fruchter and Boyce, 1981; Franceschi <i>et al</i>, 1983; Obermair <i>et al</i>, 1996)</p> <p><b>Other outcomes</b> Symptom onset to treatment and quality of life and satisfaction (Robinson <i>et al</i>, 2012)</p>	<p><b>Survival</b> Symptom onset to diagnosis (Menczer <i>et al</i>, 1995)</p> <p><b>Stage</b> Symptom onset to diagnosis (Pirog <i>et al</i>, 1997) Patient interval (Tokuda <i>et al</i>, 2009)</p>	<p><b>Survival</b> Referral to treatment interval (Crawford <i>et al</i>, 2002) Diagnosis to treatment interval (Elit <i>et al</i>, 2013)</p>
<b>Ovarian</b>		
<p><b>Other outcomes</b> Symptom onset to treatment and quality of life and satisfaction (Robinson <i>et al</i>, 2012)</p>	<p><b>Survival</b> Symptom onset to diagnosis (Nagle <i>et al</i>, 2011) Referral interval (Neal <i>et al</i>, 2007)</p> <p><b>Stage</b> Patient interval (Smith and Anderson, 1985; Tokuda <i>et al</i>, 2009) Symptom onset to diagnosis (Fruchter and Boyce, 1981; Menczer <i>et al</i>, 2009; Nagle <i>et al</i>, 2011)</p>	<p><b>Stage</b> Symptom onset to diagnosis (Lurie <i>et al</i>, 2010)</p>
<b>Head and neck</b>		
<p><b>Survival</b> Patient interval (Koivunen <i>et al</i>, 2001–pharyngeal; Teppo and Alho, 2008–pharyngeal and laryngeal cancers (separately)) Diagnostic interval (Alho <i>et al</i>, 2006–head and neck unspecified; Teppo <i>et al</i>, 2003–laryngeal; Teppo and Alho, 2008–laryngeal) Symptom onset to treatment (Hansen <i>et al</i>, 2004–laryngeal) Treatment interval (Sidler <i>et al</i>, 2010–nasopharyngeal)</p> <p><b>Stage</b> Patient interval (Kumar <i>et al</i>, 2001–oral; Brouha <i>et al</i>, 2005b–oral and pharyngeal cancer (separately); Lee <i>et al</i>, 1997–nasopharyngeal; Sheng <i>et al</i>, 2008–nasopharyngeal; Tromp <i>et al</i>, 2005–head and neck unspecified; Tokuda <i>et al</i>, 2009–head and neck unspecified; Tromp <i>et al</i>, 2005–head and neck unspecified) Diagnostic interval (Allison <i>et al</i>, 1998–aerodigestive tract; Al-Rajhi <i>et al</i>, 2009–nasopharyngeal) Symptom onset to diagnosis (Allison <i>et al</i>, 1998–aerodigestive tract; Al-Rajhi <i>et al</i>, 2009–nasopharyngeal) Symptom onset to referral (Pitchers and Martin, 2006–oropharyngeal)</p> <p><b>Other outcomes</b> Diagnostic interval and risk of recurrence (Teppo <i>et al</i>, 2005–laryngeal)</p>	<p><b>Survival</b> Patient interval (Teppo <i>et al</i>, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane <i>et al</i>, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen <i>et al</i>, 2001–pharyngeal) Symptom onset to diagnosis (Wildt <i>et al</i>, 1995–oral) Symptom onset to treatment (McGurk <i>et al</i>, 2005–head and neck unspecified) Treatment interval (Caudell <i>et al</i>, 2011–head and neck unspecified; Brouha <i>et al</i>, 2000–laryngeal)</p> <p><b>Stage</b> Patient interval (Allison <i>et al</i>, 1998–upper aerodigestive tract; Al-Rajhi <i>et al</i>, 2009–nasopharyngeal; Brouha <i>et al</i>, 2005a–laryngeal cancer; Wildt <i>et al</i>, 1995–oral; Teppo <i>et al</i>, 2009–vestibular schwannoma) Diagnostic interval (Teppo <i>et al</i>, 2009–vestibular schwannoma; Ho <i>et al</i>, 2004–oropharyngeal) Symptom onset to diagnosis (Miziara <i>et al</i>, 1998–laryngeal; Scott <i>et al</i>, 2005–oral) Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) Symptom onset to treatment (McGurk <i>et al</i>, 2005–head and neck unspecified)</p> <p><b>Other outcomes</b> Patient interval and risk of recurrence (Teppo <i>et al</i>, 2005–laryngeal)</p>	
<b>Brain/CNS</b>		
<p><b>Other outcomes</b> Symptom onset to diagnosis and progressive neurological deterioration (Balasa <i>et al</i>, 2012)</p>		
<b>Melanoma</b>		
<p><b>Survival</b> Patient interval (Temoshok <i>et al</i>, 1984, Montella <i>et al</i>, 2002) Diagnostic interval (Temoshok <i>et al</i>, 1984; Metzger <i>et al</i>, 1998; Montella <i>et al</i>, 2002; Tørring <i>et al</i>, 2013)</p> <p><b>Stage</b> Patient interval (Richards <i>et al</i>, 1999) Symptom onset to diagnosis (Helsing <i>et al</i>, 1997)</p>	<p><b>Stage</b> Patient interval (Cassileth <i>et al</i>, 1982, Schmid-Wendtner <i>et al</i>, 2002; Carli <i>et al</i>, 2003; Baade <i>et al</i>, 2006) Diagnostic interval (Cassileth <i>et al</i>, 1982, Schmid-Wendtner <i>et al</i>, 2002; Baade <i>et al</i>, 2006) Symptom onset to diagnosis (Krige <i>et al</i>, 1991; Baade <i>et al</i>, 2006)</p>	
<b>Non-melanoma skin</b>		
<p><b>Stage</b> Patient interval (Tokuda <i>et al</i>, 2009)</p> <p><b>Other outcomes</b> Symptom onset and presentation to specialist care and increase in tumour size (Alam <i>et al</i>, 2011)</p>	<p><b>Other outcomes</b> Symptom onset to treatment and larger lesions (Renzi <i>et al</i>, 2010)</p>	



Table 1. (Continued)

Positive association	No association	Negative association
<b>CTYA</b>		
<p><b>Survival</b> Symptom onset to diagnosis (Marwaha <i>et al</i>, 2010b–leukaemia; Ferrari <i>et al</i>, 2010–soft tissue sarcomas) First seen in specialist care to diagnosis (Marwaha <i>et al</i>, 2010a–leukaemia)</p> <p><b>Stage</b> Diagnostic interval (Wallach <i>et al</i>, 2006–retinoblastoma)</p> <p><b>Other outcomes</b> Symptom onset to treatment and extra-ocular disease (Erwenne and Franco, 1989–retinoblastoma)</p>	<p><b>Survival</b> Symptom onset to diagnosis (Kameda-Smith <i>et al</i>, 2013–soft tissue sarcomas; Sethi <i>et al</i>, 2013–posterior fossa tumours) Diagnostic interval (Lins <i>et al</i>, 2012–leukaemia; Crawford <i>et al</i>, 2009–primary spinal cord tumours) Patient interval (Yang <i>et al</i>, 2009 –osteosarcoma) Symptom onset to diagnosis (Brasme <i>et al</i>, 2012a, b–medulloblastoma; Loh <i>et al</i>, 2012–paediatric solid tumours; Butros <i>et al</i>, 2002–retinoblastoma)</p> <p><b>Stage</b> Patient interval (Yang <i>et al</i>, 2009 –osteosarcoma; Simpson <i>et al</i>, 2005–Ewing’s sarcoma) Symptom onset to diagnosis and eye loss (Butros <i>et al</i>, 2002–retinoblastoma)</p> <p><b>Other outcomes</b> Patient interval and eye loss (Goddard and Kingston, 1999–retinoblastoma) Treatment interval and relapse rate (Wahl <i>et al</i>, 2012–leukaemia)</p>	<p><b>Survival</b> Patient interval (Kukal <i>et al</i>, 2009–brain tumours) First symptom to treatment (Erwenne and Franco, 1989–retinoblastoma)</p> <p><b>Stage</b> Diagnostic interval (Crawford <i>et al</i>, 2009–primary spinal cord tumours; Halperin <i>et al</i>, 2001–medulloblastoma; Bacci <i>et al</i>, 1999–Ewing’s sarcoma)</p>
<b>Leukaemia</b>		
	<p><b>Survival</b> Diagnostic interval (Friese <i>et al</i>, 2011 (chronic lymphocytic)) Symptom onset to diagnosis (Prabhu <i>et al</i>, 1986 (chronic myeloid)) Treatment interval (Bertoli <i>et al</i>, 2013 (acute myeloid))</p>	
<b>Lymphoma</b>		
	<p><b>Survival</b> Symptom onset to diagnosis (Jacobi <i>et al</i>, 2008 (follicular); Maguire <i>et al</i>, 1994 (unspecified); Norum, 1995 (Hodgkin’s))</p>	<p><b>Survival</b> Symptom onset to diagnosis (Kim <i>et al</i>, 1995; Foulc <i>et al</i>, 2003 (both Sezary syndrome))</p>
<b>Myeloma</b>		
<p><b>Survival</b> Symptom onset to diagnosis (Kariyawan <i>et al</i>, 2007)</p> <p><b>Other outcomes</b> Symptom onset to diagnosis and complications at diagnosis (Kariyawan <i>et al</i>, 2007; Friese <i>et al</i>, 2009)</p>		
<b>Connective tissue</b>		
<p><b>Survival</b> Symptom onset to treatment (Ruka <i>et al</i>, 1988 (soft tissue sarcoma)) Symptom onset to diagnosis (Saitna <i>et al</i>, 2008 (soft tissue sarcoma)) Symptom onset to diagnosis (Nakamura <i>et al</i>, 2011 (soft tissue sarcoma))</p>	<p><b>Survival</b> Symptom onset to diagnosis (Rougraff <i>et al</i>, 2007 (soft tissue sarcoma); Wurtz <i>et al</i>, 1999 (osteosarcoma))</p> <p><b>Stage</b> Symptom onset to diagnosis (Bacci <i>et al</i>, 2002 (osteosarcoma))</p>	
<b>Carcinoid</b>		
	<p><b>Survival</b> Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004)</p> <p><b>Stage</b> Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004)</p>	
<b>Thyroid</b>		
	<p><b>Stage</b> Patient interval (Tokuda <i>et al</i>, 2009)</p>	
<b>Multisite</b>		
<p><b>Survival</b> Diagnostic interval (Tørring <i>et al</i>, 2013 (breast, lung, colorectal, prostate and melanoma combined))</p>		

negative, rather than a positive, association. For pancreatic cancer, two of the five studies reported a positive association, one of which addressed the waiting time paradox (Gobbi *et al*, 2013). The other three studies reported no association.

Two of the prostate studies reported a positive association for survival/mortality, one of which addressed the waiting time paradox (Tørring *et al*, 2013); the others reported no association. Two of the bladder studies reported a positive association; the others reported no association. For testicular cancer, 15 studies

reported positive associations, and the remainder had no associations.

For gynaecological cancers, of the four studies examining cervix, one reported a positive association; the others reported no association. For endometrial and ovarian cancers, there were similar numbers of studies with positive, negative and no associations. One of the endometrial studies that reported a negative association addressed the waiting time paradox (Elit *et al*, 2013).

For head and neck cancers (pharyngeal, laryngeal, oral and others), there were a large number of studies and these were equally divided between those reporting a positive association and those reporting no association. No studies reported a negative association.

For melanoma, eight studies reported positive associations, one of which addressed the waiting time paradox (Tørring *et al*, 2013); the remainder reported no associations. For non-melanoma skin, two studies reported positive associations and one reported no association.

There were a large number of studies covering the various cancers in children, teenagers and young adults. The findings of these were very mixed, with the biggest group showing no associations, and smaller but similar number of studies reporting both positive and negative associations. One of the 'no association' studies addressed the waiting time paradox (Brasme *et al*, 2012a, b).

For lymphoma, three studies reported no association or a negative association. For leukaemia, the three studies reported no associations. There were only two studies in myeloma, although both of these reported positive outcomes. For the various connective tissue cancers, three studies each reported a positive association and no association. The other cancer groups (brain/central nervous system, carcinoid, hepatocellular, renal, thyroid, upper tract urothelial carcinoma and multisite) only had one or two included studies.

## DISCUSSION

**Summary of main findings.** This review is unique in that it has assessed the literature for a range of different cancer types, and hence we are able to make recommendations for policy practice and research that are not limited to one cancer (or group of cancers). The number of included studies in this review has shown the importance of this question to patients, clinicians and researchers. However, even within specific cancer types, there is only moderate consensus as to the nature of any associations between various time intervals in the diagnostic process and clinical outcomes, with some studies showing no associations, some studies showing better outcomes with shorter time intervals and some the opposite. There are more reports of an association between times to diagnosis and outcomes for breast, colorectal, head and neck, testicular and melanoma, with reports from a smaller number of studies for pancreatic, prostate and bladder cancers. The time intervals in the studies varied, making it impossible to draw consensus as to which intervals may be more, or less, important. Moreover, the methodological quality of many of these papers is mixed, despite a recent consensus paper on design and reporting of such studies (Weller *et al*, 2012). There is some evidence from papers published more recently that address the waiting time paradox in their analyses (Tørring *et al*, 2011, 2012, 2013; Brasme *et al*, 2012a, b; Elit *et al*, 2013; Gobbi *et al*, 2013; Pruitt *et al*, 2013), with most, but not all, of these reporting longer intervals being associated with poorer outcomes, particularly mortality. This is important and begins to provide more robust evidence about the relationship between time to diagnosis and outcomes.

**Findings within the context of the literature.** The previous cancer-specific reviews (Menczer, 2000; Jensen *et al*, 2002; Bell *et al*, 2006; Fahmy *et al*, 2006; Ramos *et al*, 2007, 2008; Goy *et al*, 2009; Olsson *et al*, 2009; Thompson *et al*, 2010; Brasme *et al*, 2012a, b), with the exception of the breast cancer (Richards *et al*, 1999), and to a lesser extent head and neck (Seoane *et al*, 2012), have been largely equivocal, probably because of the poor quality of the included studies. Our findings are largely in keeping with these

reviews, although we have provided much more evidence than previous reviews for testicular cancer (Bell *et al*, 2006) and head and neck cancers (Goy *et al*, 2009). We have also identified more recent and probably higher-quality papers providing better evidence for colorectal cancer than covered in previous reviews (Ramos *et al*, 2007, 2008; Thompson *et al*, 2010). We provide review findings for the first time for many cancers. We are also aware of further articles being published since the end date of our review. For example, one of these replicated the methods of one of the papers in our review (Tørring *et al*, 2011) on a sample of 958 colorectal cancers in Scotland, and reported that longer diagnostic intervals did not adversely affect cancer outcomes (Murchie *et al*, 2014). Another has reported that time to diagnosis in 436 Ewing tumours in France was not associated with metastasis, surgical outcome or survival (Brasme *et al*, 2014). One of our main findings, of the poor quality of reporting of time to diagnosis studies, replicates the findings of a recent paediatric systematic review (Launay *et al*, 2013).

**Strengths and weaknesses.** This is the largest and most comprehensive review in this field, and the first 'all-cancer' systematic review. The huge heterogeneity in both the outcomes and the time intervals used, within each cancer site, precluded meta-analyses. Another systematic review has recently reported similar difficulty in comparisons between studies (Lethaby *et al*, 2013). As previously stated, the review only contains studies in colorectal and breast cancer for 2010–13, and only these studies identified during the second round of searches were assessed to determine whether their analyses addressed the waiting time paradox. Survival, or mortality, is the most objective outcomes for these studies. However, many of the included studies in the review reported stage, or some other proxy. This may explain why stage and survival outcomes differ. Stage categorisation also varied, and some of the studies may be affected by *post-hoc* upstaging. A further problem with the literature is that of confounding by indication. Symptoms of more advanced cancer are likely to present differently and be investigated more promptly, as are patients presenting with so-called 'red-flag' symptoms. We were unable to assess for publication bias; indeed, if there was any publication bias, we cannot predict in which direction this would act.

**Implications for policy, practice and research.** Our main conclusion from this review is that we believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of earlier-stage diagnosis, improved survival and improved quality of life. The amount of benefit varies between cancers; at present, there is more evidence for breast, colorectal, head and neck, testicular and melanoma, with evidence from a smaller number of studies for pancreatic, prostate and bladder cancers. There is either insufficient evidence or equivocal findings in the other cancers. The findings need replicating in using similar analytical methods, ideally also to address how much of a difference expedited diagnosis of different cancers would make on outcomes, and at which points in the diagnostic journey matters most. Until we have well-designed and well-analysed prospective studies to answer this question, it is difficult to determine the likely effect of interventions to reduce patient and diagnostic intervals on outcomes. This knowledge would inform the development of targeted intervention studies, to improve outcomes.

Hence, we recommend that policy, and clinicians, should continue the current emphasis on expediting symptomatic diagnosis, at least for most cancers. This can be achieved by clinicians having a high index of suspicion of cancer, the use of diagnostic technologies and rapid access to diagnostic investigations and fast-track pathways for assessment (Rubin *et al*, 2014). Finally, we recommend the need for more high-quality research in

### Box 1. Key quality criteria for studies that examine the relationship between time intervals in cancer diagnosis and outcomes.

Good studies will report the definition of intervals in compliance with definitions in the Aarhus statement (Weller *et al*, 2012). The most common intervals reported are as follows:

- Patient interval – the time from when bodily changes and/or first symptoms are noticed to presentation of this change or symptom to a health care professional
- Diagnostic interval – the date from first presentation to a health care professional to diagnosis
- Referral interval – the date from referral to specialist care to being seen in specialist care

Good studies will report key dates in the diagnostic journey in a standardised way, with a full description. This includes, for example, the following:

- Dates when patients first notices bodily changes or symptoms and when they decide to seek help
- Date of first presentation of potential cancer symptom – including how such symptoms were defined
- Date of diagnosis – clear reporting of how this date was obtained and what date it actually represents (e.g., date of tissue diagnosis, date when patient informed)
- Dates of referral / investigation – including definitions of which were included and why

Good studies will fully describe appropriate data collection methods for time intervals. These will vary by interval, and different approaches to data collection (e.g., interviews, questionnaires, medical records, database studies) will give different answers. Data collection from patients is preferred for studies measuring patient intervals. Precise details regarding data collection methods are preferred. Good studies will fully describe and justify outcome measures. Mortality or survival is preferred, but some measure of stage (or other measure of disease severity or treatment modality) is also a useful endpoint. Studies capturing patient experience and quality of life and psychological outcomes are also needed.

Good studies will use a design that addresses bias and confounding (including confounding by indication); this includes measures to address the waiting time paradox.

the area for a number of reasons. First, we suspect that many clinicians continue to believe that there are no associations between time and clinical outcomes.

A considerable number of studies fail to address basic issues of bias and thus equate the absence of evidence with evidence of absence. Second, it is likely that more timely diagnosis may have a greater or lesser impact between different cancers. This is important to ascertain, because it will inform policy and practice. We recommend, where possible, re-analysis of pooled (and similar) data from some of the studies included in this review, and new studies using linked data sets, across all cancers, such that similar analyses can be conducted between cancers. We also recommend that such studies should ideally focus on survival or mortality as the outcome, as this is the 'gold-standard' outcome, although stage is also a valuable end point. There is also a dearth of studies reporting patient experience; we therefore recommend further work that examined the relationship between patient perceptions of 'delay' and quality of life and psychological outcomes. Suggested key quality criteria for future studies are summarised in Box 1. Other work should focus on the organisation and function of health services, and subsequent time intervals and outcomes. Furthermore, we recommend that, wherever possible, this work

should be conducted and reported in keeping within the recommendations of the Aarhus Statement (Weller *et al*, 2012).

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### REFERENCES

- Akdas A, Kirkali Z, Remzi D (1986) The role of delay in stage Iii testicular tumors. *Int Urol Nephrol* **18**: 181–184.
- Alam M, Goldberg LH, Silapunt S, Gardner ES, Strom SS, Rademaker AW, Margolis DJ (2011) Delayed treatment and continued growth of nonmelanoma skin cancer. *J Am Acad Dermatol* **64**: 839–848.
- Alho O, Teppo H, Mantyselka P, Kantola S (2006) Head and neck cancer in primary care: presenting symptoms and the effect of delayed diagnosis of cancer cases. *Can Med Assoc J* **174**: 779–784.
- Allison P, Franco E, Black M, Feine J (1998) The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma. *Oral Oncol* **34**: 147–153.
- Al-Rajhi N, El-Sebaie M, Khafaga Y, Al-Zahrani A, Mohamed G, Al-Amro A (2009) Nasopharyngeal carcinoma in Saudi Arabia: clinical presentation and diagnostic delay. *East Mediterr Health J* **15**: 1301–1307.
- Altman DG (2001) Systematic reviews of evaluations of prognostic variables. In *Systematic Reviews in Health Care: meta-analysis in Context*, Egger M, Smith GD, Altman DG (eds) 2nd ed. BMJ Books: London.
- Annakkaya A, Arbak P, Balbay O, Bilgin C, Erbas M, Bulut I (2007) Effect of symptom-to-treatment interval on prognosis in lung cancer. *Tumori* **93**: 61–67.
- Arvanitakis C, Nikopoulos A, Giannoulis E, Theoharidis A, Georgilas V, Fotiou H, Tourkantonis A (2006) The impact of early or late diagnosis on patient survival in gastric cancer in Greece. *Hepatogastroenterology* **39**: 355–357.
- Baade P, English D, Youl P, McPherson M, Elwood J, Aitken J (2006) The relationship between melanoma thickness and time to diagnosis in a large population-based study. *Arch Dermatol* **142**: 1422–1427.
- Bacci G, Di Fiore M, Rimondini S, Baldini N (1999) Delayed diagnosis and tumor stage in Ewing's sarcoma. *Oncol Rep* **6**: 465–466.
- Bacci G, Ferrari S, Longhi A, Forni C, Zavatta M, Versari M, Smith K (2002) High-grade osteosarcoma of the extremity: differences between localized and metastatic tumors at presentation. *J Pediatr Hematol Oncol* **24**: 27–30.
- Balasa AF, Gherasim DN, Gherman B (2012) Clinical evolution of primary intramedullary tumors in adults. *Rom J Neurol* **11**: 165–171.
- Bell D, Morash C, Dranitsaris G, Izawa J, Short T, Klotz LH, Fleshner N (2006) Does prolonging the time to testicular cancer surgery impact long-term cancer control: a systematic review of the literature. *Can J Urol* **13**: 30–36.
- Bertoli S, Berard E, Huguet F, Huynh A, Tavitian S, Vergez F, Dobbstein S, Dastugue N, Mansat-De Mas V, Delabesse E, Duchayne E, Demur C,

- Sarry A, Lauwers-Cances V, Laurent G, Attal M, Recher C (2013) Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. *Blood* **121**: 2618–2626.
- Bosl G, Vogelzang N, Goldman A, Fraley E, Lange P, Levitt S, Kennedy B (1981) Impact of delay in diagnosis on clinical stage of testicular cancer (1981) *Lancet* **2**: 970–972.
- Brasme JF, Chalumeau M, Oberlin O, Valteau-Couanet Gaspar N (2014) Time to diagnosis of Ewing tumours in children and adolescents is not associated with metastasis or survival: a prospective multi-center study of 436 patients. *J Clin Oncol* **32**: 1935–1940.
- Brasme JF, Grill J, Doz F, Lacour B, Valteau-Couanet D, Gaillard S, Delalande O, Aghakhani N, Puget S, Chalumeau M (2012a) Long time to diagnosis of medulloblastoma in children is not associated with decreased survival or with worse neurological outcome. *PLoS One* **7**: e33415.
- Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Bons-Letouzey C, Chalumeau M (2012b) Delays in the diagnosis of paediatric cancers a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol* **13**: e445–e459.
- Brazda A, Estroff J, Euhus D, Leitch AM, Huth J, Andrews V, Moldrem A, Rao R (2010) Delays in time to treatment and survival impact in breast cancer. *Ann Surg Oncol* **17**(Suppl 3): 291–296.
- Brocken P, Kiers Berni AB, Looijen-Salamon MG, Dekhuijzen PNR, Smits-van der Graaf C, Peters-Bax L, de Geus-Oei L, van der Heijden HFM (2012) Timeliness of lung cancer diagnosis and treatment in a rapid outpatient diagnostic program with combined 18FDG-PET and contrast enhanced CT scanning. *Lung Cancer* **75**: 336–341.
- Brouha X, Op De Coul B, Terhaard C, Hordijk G (2000) Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? *Clin Otolaryngol Allied Sci* **25**: 215–218.
- Brouha X, Tromp D, de Leeuw J, Hordijk G, Winnubst J (2005a) Laryngeal cancer patients: analysis of patient delay at different tumor stages. *Head Neck* **27**: 289–295.
- Brouha X, Tromp D, Hordijk G, Winnubst J, de Leeuw J (2005b) Oral and pharyngeal cancer: analysis of patient delay at different tumor stages. *Head Neck* **27**: 939–945.
- Butros L, Abramson D, Dunkel I (2002) Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences. *Pediatrics* **109**: E45.
- Carli P, De Giorgi V, Palli D, Maurichi A, Mulas P, Orlandi C, Imberti G, Stanganelli I, Soma P, Dioguardi D, Catricalá C, Betti R, Cecchi R, Bottoni U, Bonci A, Scalvenzi M, Giannotti B (2003) Dermatologist detection and skin self-examination are associated with thinner melanomas results from a survey of the italian multidisciplinary group on melanoma. *Arch Dermatol* **139**: 607–612.
- Cassileth B, Clark W, Heiberger R, March V, Tenaglia A (1982) Relationship between patients early recognition of melanoma and depth of invasion. *Cancer* **49**: 198–200.
- Caudell J, Locher J, Bonner J (2011) Diagnosis-to-treatment interval and control of locoregionally advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg* **137**: 282–285.
- Cerdan-Santacruz C, Cano-Valderrama O, Cardenas-Crespo S, Torres-Garcia A, Cerdan-Miguel J (2011) Colorectal cancer and its delayed diagnosis: have we improved in the past 25 years? *Rev Esp Enferm Dig* **103**: 458–463.
- Chilvers C, Saunders M, Bliss J, Nicholls J, Horwich A (1989) Influence of delay in diagnosis on prognosis in testicular teratoma. *Br J Cancer* **59**: 126–128.
- Christensen E, Harvald T, Jendresen M, Aggestrup S, Petterson G (1997) The impact of delayed diagnosis of lung cancer on the stage at the time of operation. *Eur J Cardiothorac Surg* **12**: 880–884.
- Crawford J, Zaninovic A, Santi M, Rushing EJ, Olsen CH, Keating RF, Vezina G, Kadom N, Packer RJ (2009) Primary spinal cord tumors of childhood: effects of clinical presentation, radiographic features, and pathology on survival. *J Neurooncol* **95**: 259–269.
- Crawford S, Davis J, Siddiqui N, de Caestecker L, Gillis C, Hole D, Penney G (2002) The waiting time paradox: Population based retrospective study of treatment delay and survival of women with endometrial cancer in Scotland. *Br Med J* **325**: 196.
- Currie A, Evans J, Smith N, Brown G, Abulafi A, Swift R (2012) The impact of the two-week wait referral pathway on rectal cancer survival. *Colorectal Dis* **4**: 848–853.
- Deng S, An W, Gao J, Yin J, Cai Q, Yang M, Hong S, Fu X, Yu E, Xu X, Zhu W, Li Z (2012) Factors influencing diagnosis of colorectal cancer: a hospital-based survey in china. *J Dig Dis* **13**: 517–524.
- Diaconescu R, Lafond C, Whittom R. Treatment delays in non-small cell lung cancer and their prognostic implications (2011) *J Thorac Oncol* **6**: 1254–1259.
- Dieckmann K, Becker T, Bauer H (1987) Testicular tumors: presentation and role of diagnostic delay. *Urol Int* **42**: 241–247.
- Eastman A, Tammaro Y, Moldrem A, Andrews V, Huth J, Euhus D, Leitch M, Rao R (2013) Outcomes of delays in time to treatment in triple negative breast cancer. *Ann Surg Oncol* **20**: 1880–1885.
- Egger M, Smith GD, Altman DG (eds) (2001) *Systematic Reviews in Health Care: meta-analysis in Context*, 2nd edn. BMJ Books: London.
- Elit L, O'Leary E, Pond G, Seow H (2013) Impact of wait times on survival for women with uterine cancer. *J Clin Oncol* **51**: 67.
- Emery J, Shaw K, Williams B, Maaza D, Fallon-Ferguson J, Varlow M, Trevena L (2014) The role of primary care in early detection and follow-up of cancer. *Nat Rev Clin Oncol* **11**: 38–48.
- Ermiah E, Abdalla F, Buhmeida A, Larbesh E, Pyrhonen S, Collan Y (2012) Diagnosis delay in Libyan female breast cancer. *BMC Res Notes* **5**: 452.
- Erwenne CM, Franco EL (1989) Age and lateness of referral as determinants of extra-ocular retinoblastoma. *Ophthalmic Paediatr Genet* **10**: 179–184.
- Esserman LJ, Thompson IM, Reid B (2013) Overdiagnosis and overtreatment in cancer. An opportunity for improvement. *JAMA* **310**: 797–798.
- Fahmy NM, Mahmud S, Aprikian AG (2006) Delay in the surgical treatment of bladder cancer and survival: systematic review of the literature. *Eur Urol* **50**: 1176–1182.
- Fernandez E, Porta M, Malats N, Belloc J, Gallén M (2002) Symptom-to-diagnosis interval and survival in cancers of the digestive tract. *Dig Dis Sci* **47**: 2434–2440.
- Ferrari A, Miceli R, Casanova M, Meazza C, Favini F, Luksch R, Catania S, Fiore M, Morosi C, Mariani L (2010) The symptom interval in children and adolescents with soft tissue sarcomas. *Cancer* **116**: 177–183.
- Fossa DF, Klepp O, Elgio RF, Eliassen G, Melsom H, Urnes T, Wang M (1981) The effect of patient's and doctor's delay in patients with malignant germ cell tumours. *Int J Androl* **4**: 134–144.
- Foulc P, N'Guyen JM, Dréno B (2003) Prognostic factors in Sezary syndrome: a study of 28 patients. *Br J Dermatol* **149**: 1152–1158.
- Franceschi S, La Vecchia C, Gallus G, Decarli A, Colombo E, Mangioni C, Tognoni G (1983) Delayed diagnosis of endometrial cancer in Italy. *Cancer* **51**(6): 1176–1178.
- Friese CR, Abel GA, Magazu LS, Neville BA, Richardson LC, Earle CC (2009) Diagnostic delay and complications for older adults with multiple myeloma. *Leuk Lymphoma* **50**: 392–400.
- Friese CR, Earle CC, Magazu LS, Brown JR, Neville BA, Hevelone ND, Richardson LC, Abel GA (2011) Timeliness and quality of diagnostic care for medicare recipients with chronic lymphocytic leukemia. *Cancer* **117**: 1470–1477.
- Fruchter RG, Boyce J (1981) Delays in diagnosis and stage of disease in gynecologic cancer. *Cancer Detect Prev* **4**: 481–486.
- Gobbi PG, Bergonzi M, Comelli M, Villano L, Pozzoli D, Vanoli A, Dionigi P (2013) The prognostic role of time to diagnosis and presenting symptoms in patients with pancreatic cancer. *Cancer Epidemiol* **37**: 186–190.
- Goddard AG, Kingston JE (1999) Delay in diagnosis of retinoblastoma: Risk factors and treatment outcome. *Br J Ophthalmol* **83**: 1320–1323.
- Gonzalez-Barcala FJ, Garcia-Prim JM, Alvarez-Dobano JM, Moldes-Rodríguez M, Garcia-Sanz MT, Pose-Reino A, Valdes-Cuadrado L (2010) Effect of delays on survival in patients with lung cancer. *Clin Transl Oncol* **12**: 836–842.
- Gort M, Otter R, Plukker JTM, Broekhuis M, Klazinga NS (2010) Actionable indicators for short and long term outcomes in rectal cancer. *Eur J Cancer* **46**: 1808–1814.
- Gould MK, Ghaus SJ, Olsson JK, Schultz EM (2008) Timeliness of care in veterans with non-small cell lung cancer. *Chest* **133**: 1167–1173.
- Goy J, Hall SF, Feldman-Stewart D, Groome P (2009) Diagnostic delay and disease stage in head and neck cancer: a systematic review. *Laryngoscope* **119**: 889–898.
- Grotenhuis BA, van Hagen P, Wijnhoven BPL, Spaander MCW, Tilanus HW, van Lanschot JJB (2010) Delay in diagnostic workup and treatment of esophageal cancer. *J Gastrointest Surg* **14**: 476–483.
- Gulliford MC, Petruckevitch A, Burney PG (1991) Survival with bladder cancer, evaluation of delay in treatment, type of surgeon, and modality of treatment. *Br Med J* **303**: 437–440.

- Guzman-Laura KP, Bolibar RI, Alepuz MT, Gonzalez D, Martin M (2011) Impact on the care and time to tumor stage of a program of rapid diagnosis and treatment of colorectal cancer. *Rev Esp Enferm Dig* **103**: 13–19.
- Halperin EC, Watson DM, George SL (2001) Duration of symptoms prior to diagnosis is related inversely to presenting disease stage in children with medulloblastoma. *Cancer* **91**: 1444–1450.
- Hansen O, Larsen S, Bastholt L, Godballe C, Jørgensen KE (2005) Duration of symptoms: impact on outcome of radiotherapy in glottic cancer patients. *Int J Radiat Oncol Biol Phys* **61**: 789–794.
- Hanson PR, Belitsky P, Millard OH, Lannon SG (1993) Prognostic factors in metastatic nonseminomatous germ cell tumours. *Can J Surg* **36**: 537–540.
- Harding M, Paul J, Kaye SB (1995) Does delayed diagnosis or scrotal incision affect outcome for men with non-seminomatous germ cell tumours? *Br J Urol* **76**: 491–494.
- Haugstvedt TK, Viste A, Eide GE, Soreide O (1991) Patient and physician treatment delay in patients with stomach cancer in Norway is it important. *Scand J Gastroenterol* **26**: 611–619.
- Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* **144**: 427–437.
- Hayden JA, van der Windt D, Cartwright JL, Cote P, Bombardier C (2013) Assessing bias in studies of prognostic factors. *Ann Intern Med* **158**: 280–286.
- Helsing P, Faye R, Langmark F (1997) Cutaneous malignant melanoma. Correlation between tumor characteristics and diagnostic delay in Norwegian patients. *Eur J Dermatol* **7**: 359–361.
- Ho T, Zahurak M, Koch WM (2004) Prognostic significance of presentation-to-diagnosis interval in patients with oropharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* **130**: 45–51.
- Hollenbeck BK, Dunn RL, Ye Z, Hollingsworth JM, Skolarus TA, Kim SP, Montie JE, Lee CT, Wood DP, Miller DC (2010) Delays in diagnosis and bladder cancer mortality. *Cancer* **116**: 5235–5242.
- Holmang S, Johansson SL (2006) Impact of diagnostic and treatment delay on survival in patients with renal pelvic and ureteral cancer. *Scand J Urol Nephrol* **40**: 479–484.
- Huyghe E, Muller A, Mieusset R, Bujan L, Bachaud JM, Chevreau C, Plante P, Thonneau P (2007) Impact of diagnostic delay in testis cancer: results of a large population-based study. *Eur Urol* **52**: 1710–1716.
- Jacobi N, Rogers TB, Peterson BA (2008) Prognostic factors in follicular lymphoma: a single institution study. *Oncol Rep* **20**: 185–193.
- Jensen AR, Mainz J, Overgaard J (2002) Impact of delay on diagnosis and treatment of primary lung cancer. *Acta Oncol* **41**: 147–152.
- Kameda-Smith MM, White MAJ, George EJS, Brown JIM (2013) Time to diagnosis of paediatric posterior fossa tumours: an 11-year West of Scotland experience 2000–2011. *Br J Neurosurg* **27**: 364–369.
- Kariyawan CC, Hughes DA, Jayatilake MM, Mehta AB (2007) Multiple myeloma: causes and consequences of delay in diagnosis. *QJM* **100**: 635–640.
- Kim YH, Bishop K, Varghese A, Hoppe RT (1995) Prognostic factors in erythroid mycosis fungoides and the Sezary syndrome. *Arch Dermatol* **131**: 1003–1008.
- Koivunen P, Rantala N, Hyryn Kangas K, Jokinen K, Alho OP (2001) The impact of patient and professional diagnostic delays on survival in pharyngeal cancer. *Cancer* **92**: 2885–2891.
- Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM (2012) Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. *Br J Urol Int* **110**: 211–216.
- Krige JE, Isaacs S, Hudson DA, King HS, Strover RM, Johnson CA (1991) Delay in the diagnosis of cutaneous malignant melanoma. A prospective study in 250 patients. *Cancer* **68**: 2064–2068.
- Kukal K, Dobrovoljac M, Boltshauser E, Ammann RA, Grotzer MA (2009) Does diagnostic delay result in decreased survival in paediatric brain tumours? *Eur J Pediatr* **168**: 303–310.
- Kumar S, Heller RF, Pandey U, Tewari V, Bala N, Oanh KT (2001) Delay in presentation of oral cancer: a multifactor analytical study. *Natl Med J India* **14**: 13–17.
- Launay E, Morfouace M, Deneux-Tharoux C, Gras le-Guen C, Ravaud P, Chalumeau M (2013) Quality of reporting of studies evaluating time to diagnosis: a systematic review in paediatrics. *Arch Dis Child* **99**: 244–250.
- Lee AWM, Foo W, Law SC, Poon YF, Sze WM, O SK, Tung SY, Lau WH (1997) Nasopharyngeal carcinoma—presenting symptoms and duration before diagnosis. *Hong Kong Med J* **3**: 355–361.
- Lethaby CD, Picton S, Kinsey SE, Phillips R, van Laar M, Feltbower RG (2013) A systematic review of time to diagnosis in children and young adults with cancer. *Arch Dis Child* **98**: 349–355.
- Liedberg F, Anderson H, Månsson A, Månsson W (2003) Diagnostic delay and prognosis in invasive bladder cancer. *Scand J Urol Nephrol* **37**: 396–400.
- Lim BS, Dennis CR, Gardner B, Newman J (1974) Analysis of survival versus patient and doctor delay of treatment in gastrointestinal cancer. *Am J Surg* **127**: 210–214.
- Lins MM, Amorim M, Vilela P, Viana M, Ribeiro RC, Pedrosa A, Lucena-Silva N, Howard SC, Pedrosa F (2012) Delayed diagnosis of leukemia and association with morbid-mortality in children in Pernambuco, Brazil. *J Pediatr Hematol Oncol* **34**: e271–e276.
- Loh AHP, Aung L, Ha C, Tan A-M, Quah TC, Chui C-H (2012) Diagnostic delay in pediatric solid tumors: a population based study on determinants and impact on outcomes. *Pediatr Blood Cancer* **58**: 561–565.
- Loh LC, Chan LY, Tan RY, Govindaraju S, Ratnavelu K, Kumar S, Raman S, Vijayasingham P, Thayaparan T (2006) Time delay and its effect on survival in Malaysian patients with non-small cell lung carcinoma. *Malays J Med Sci* **13**: 37–42.
- Lurie G, Wilkens LR, Thompson PJ, Matsuno RK, Carney ME, Goodman MT (2010) Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: a case analysis. *Gynecol Oncol* **119**: 278–284.
- Maconi G, Kurihara H, Panizzo V, Russo A, Cristaldi M, Marrelli D, Roviello F, de Manzoni G, Di Leo A, Morgagni P, Bechi P, Bianchi Porro G, Taschieri AM (2003) Gastric cancer in young patients with no alarm symptoms: focus on delay in diagnosis, stage of neoplasm and survival. *Scand J Gastroenterol* **38**: 1249–1255.
- Maguire A, Porta M, Malats N, Gallén M, Piñol JL, Fernandez E (1994) Cancer survival and the duration of symptoms—an analysis of possible forms of the risk-function. *Eur J Cancer* **30A**: 785–792.
- Martin IG, Young S, Sue-Ling H, Johnston D (1997) Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. *Br Med J* **314**: 467–470.
- Marwaha RK, Kulkarni KP, Bansal D, Trehan A (2010a) Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. *Ann Hematol* **89**: 249–254.
- Marwaha RK, Kulkarni KP, Bansal D, Trehan A (2010b) Pattern of mortality in childhood acute lymphoblastic leukemia: experience from a single center in northern India. *J Pediatr Hematol Oncol* **32**: 366–369.
- McGurk MC, Chan C, Jones J, O'regan E, Sherriff M (2005) Delay in diagnosis and its effect on outcome in head and neck cancer. *Br J Oral Maxillofac Surg* **43**: 281–284.
- McLaughlin JM, Anderson RT, Ferketich AK, Seiber EE, Balkrishnan R, Paskett ED (2012) Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. *J Clin Oncol* **30**: 4493–4500.
- McLean SR, Karsanji D, Wilson J, Dixon E, Sutherland FR, Pasiaka J, Ball C, Bathe OF (2013) The effect of wait times on oncological outcomes from periampullary adenocarcinomas. *J Surg Oncol* **107**: 853–858.
- Medical Research Council Work Party, Testicular Tumours (1985) Prognostic factors in advanced non-seminomatous germ-cell testicular tumours results of a multicenter study. *Lancet* **1**: 8–11.
- Meffan PJ, Delahunt B, Nacey JN (1991) The value of early diagnosis in the treatment of patients with testicular cancer. *NZ Med J* **104**: 393–394.
- Menczer J (2000) Diagnosis and treatment delay in gynecological malignancies: does it affect outcome? *Int J Gynecol Cancer* **10**: 89–94.
- Menczer J, Chetrit A, Sadetzki S (2009) The effect of symptom duration in epithelial ovarian cancer on prognostic factors. *Arch Gynecol Obstet* **279**: 797–801.
- Menczer J, Krissi H, Chetrit A, Gaynor J, Lerner L, Ben-Baruch G, Modan B (1995) The effect of diagnosis and treatment delay on prognostic factors and survival in endometrial carcinoma. *Am J Obstet Gynecol* **173**: 774–778.
- Metzger S, Ellwanger U, Stroebel W, Schiebel U, Rassner G, Fierlbeck G (1998) Extent and consequences of physician delay in the diagnosis of acral melanoma. *Melanoma Res* **8**: 181–186.
- Miziara ID, Cahali MB, Murakami MS, Figueiredo LA, Guimaraes JR (1998) Cancer of the larynx: correlation of clinical characteristics, site of origin,

- stage, histology and diagnostic delay. *Rev Laryngol Otol Rhinol* **119**: 101–104.
- Mohan A, Mohan C, Bhutani M, Pathak AK, Pal H, Das C, Guleria R (2006) Quality of life in newly diagnosed patients with lung cancer in a developing country: is it important? *Eur J Cancer Care* **15**: 293–298.
- Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* **151**: 264–269.
- Mommsen S, Aagaard J, Sell A (1983) Presenting symptoms, treatment delay and survival in bladder cancer. *Scand J Urol Nephrol* **17**: 163–167.
- Montella M, Crispo A, Grimaldi M, De Marco MR, Ascierio PA, Parasole R, Melucci MT, Silvestro P, Fabbrocini G (2002) An assessment of factors related to tumor thickness and delay in diagnosis of melanoma in Southern Italy. *Prev Med* **35**: 271–277.
- Moul JW, Paulson DF, Dodge RK, Walther PJ (1990) Delay in diagnosis and survival in testicular cancer: Impact of effective therapy and changes during 18 years. *J Urol* **143**: 520–523.
- Mujar M, Dahlui M, Yip CH, Taib NA (2013) Delays in time to primary treatment after a diagnosis of breast cancer: does it impact survival? *Prev Med* **56**: 222–224.
- Murai T, Shibamoto Y, Baba F, Hashizume C, Mori Y, Ayakawa S, Kawai T, Takemoto S, Sugie C, Ogino H (2012) Progression of non-small-cell lung cancer during the interval before stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* **82**: 463–467.
- Murchie P, Raja EA, Brewster DH, Campbell NC, Ritchie LD, Robertson R, Samuel L, Gray N, Lee AJ (2014) Time from presentation in primary care to treatment of symptomatic colorectal cancer: effect on disease stage and survival. *Br J Cancer* **111**: 461–469.
- Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Ståhle E (2004) Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax* **59**: 45–49.
- Nagle CM, Francis JE, Nelson AE, Zorbas H, Luxford K, de Fazio A, Fereday S, Bowtell DD, Green AC, Webb PM (2011) Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* **29**: 2253–2258.
- Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A (2011) The symptom-to-diagnosis delay in soft tissue sarcoma influence the overall survival and the development of distant metastasis. *J Surg Oncol* **104**: 771–775.
- Napier MP, Rustin GJ (2000) Diagnostic delay and risk of relapse in patients with stage I nonseminomatous germ cell tumour followed on active surveillance. *Br J Urol Int* **86**: 486–489.
- Neal RD (2009) Do diagnostic delays in cancer matter? *Br J Cancer* **101**: S9–S12.
- Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, Evans J (2007) Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. *Br J Gen Pract* **57**: 212–219.
- NHS Centre for Reviews and Dissemination (2001) *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*, 2nd edn. NHS CRD, University of York: York, UK.
- Norum J (1995) The effect of diagnostic delay in patients with Hodgkin's lymphoma. *Anticancer Res* **15**: 2707–2710.
- Obermair AE, Hanzal E, Schreiner-Frech I, Buxbaum P, Bancher-Todesca D, Thoma M, Kurz C, Vavra N, Gitsch G, Sevela P (1996) Influence of delayed diagnosis on established prognostic factors in endometrial cancer. *Anticancer Res* **16**: 947–949.
- O'Brien D, Loeb S, Carvalho GF, McGuire BB, Kan D, Hofer MD, Casey JT, Helfand BT, Catalona WJ (2011) Delay of surgery in men with low risk prostate cancer. *J Urol* **185**: 2143–2147.
- Olsson JK, Schultz EM, Gould MK (2009) Timeliness of care in patients with lung cancer: a systematic review. *Thorax* **64**: 749–756.
- Pirog EC, Heller DS, Westhoff C (1997) Endometrial adenocarcinoma—Lack of correlation between treatment delay and tumor stage. *Gynecol Oncol* **67**: 303–308.
- Pita-Fernandez S, Montero-Martinez C, Pértiga-Díaz S, Vereja-Hernando H (2007) Relationship between delayed diagnosis and the degree of invasion and survival in lung cancer. *J Clin Epidemiol* **56**: 820–825.
- Pitchers M, Martin C (2006) Delay in referral of oropharyngeal squamous cell carcinoma to secondary care correlates with a more advanced stage at presentation, and is associated with poorer survival. *Br J Cancer* **94**: 955–958.
- Prabhu M, Kochupillai V, Sharma S, Ramachandran P, Sundaram KR, Bijlani L, Ahuja RK (1986) Prognostic assessment of various parameters in chronic myeloid leukemia. *Cancer* **58**: 1357–1360.
- Prout GR, Griffin PP. Testicular tumors: delay in diagnosis and influence on survival (1984) *Am Fam Physician* **29**: 205–209.
- Pruitt SL, Harzke AJ, Davidson NO, Schootman M (2013) Do diagnostic and treatment delays for colorectal cancer increase risk of death? *Cancer Causes Control* **24**: 961–977.
- Radzikowska E, Roszkowski-Sliz K, Glaz P (2012) The impact of timeliness of care on survival in non-small cell lung cancer patients. *Pneumonol Alergol Pol* **80**: 422–429.
- Ramos M, Esteva M, Cabeza E, Campillo C, Llobera J, Aguiló A (2007) Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. *Eur J Cancer* **43**: 2467–2478.
- Ramos M, Esteva M, Cabeza E, Llobera J, Ruiz A (2008) Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer. *Eur J Cancer* **44**: 510–521.
- Ramsay G, MacKay C, Nanthakumaran S, Craig WL, McAdam TK, Loudon MA (2012) Urgency of referral and its impact on outcome in patients with colorectal cancer. *Colorectal Dis* **14**: e375–e377.
- Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR (2010) Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. *Surgeon* **8**: 239–246.
- Redaniel MT, Martin RM, Cawthorn S, Wade J, Jeffreys M (2013) The association of waiting times from diagnosis to surgery with survival in women with localised breast cancer in England. *Br J Cancer* **109**: 42–49.
- Renzi C, Mastroeni S, Passarelli F, Mannooranparampil TJ, Caggiati A, Potenza C, Pasquini P (2010) Factors associated with large cutaneous squamous cell carcinomas. *J Am Acad Dermatol* **63**: 404–411.
- Richards MA, Grob JJ, Avril MF, Delaunay M, Thirion X, Wolkenstein P, Souteyrand P, Dreno B, Bonerandi JJ, Dalac S, Machel L, Guillaume JC, Chevrant-Breton J, Vilmer C, Aubin F, Guillot B, Beylot-Barry M, Lok C, Raison-Peyron N, Chemaly P (1999) Melanoma and tumor thickness: challenges of early diagnosis. *Arch Dermatol* **135**: 269–274.
- Richards MA (2009a) The National Awareness and Early Diagnosis Initiative in England: assembling the evidence. *Br J Cancer* **101**: S1–S4.
- Richards MA (2009b) The size of the prize for earlier diagnosis of cancer in England. *Br J Cancer* **101**: S125–S129.
- Richards MA, Hiom S (2009) Diagnosing cancer earlier: evidence for a national awareness and early diagnosis initiative. *Br J Cancer* **101**: S1–S129.
- Robinson KM, Christensen KB, Ottesen B, Krasnik A (2012) Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: a nationwide Danish study. *Qual Life Res* **21**: 1519–1525.
- Roland CL, Schwarz RE, Tong L, Ahn C, Balch GC, Yopp AC, Anthony T, Mansour JC (2013) Is timing to delivery of treatment a reliable measure of quality of care for patients with colorectal adenocarcinoma? *Surgery* **154**: 421–428.
- Rougraff BT, Davis K, Lawrence J (2007) Does length of symptoms before diagnosis of sarcoma affect patient survival? *Clin Orthop Relat Res* **462**: 181–189.
- Rubin G, Walter F, Emery J, Neal RD, Hamilton W, Wardle J (2014) Research into practice: earlier diagnosis of symptomatic cancer. *Br J Gen Pract* **64**: 428–430.
- Ruka W, Emrich LJ, Driscoll DL, Karakousis CP (1988) Tumor size/symptom duration ratio as a prognostic factor in patients with high-grade soft tissue sarcomas. *Eur J Cancer Clin Oncol* **24**: 1583–1588.
- Saithna A, Pynsent PB, Grimer RJ (2008) Retrospective analysis of the impact of symptom duration on prognosis in soft tissue sarcoma. *Int Orthop* **32**: 381–384.
- Salomaa E, Sällinen S, Hiekkanen H, Liippo K (2005) Delays in the diagnosis and treatment of lung cancer. *Chest* **128**: 2282–2288.
- Scher H, Bosl G, Geller N, Cirrincione C, Whitmore W, Golbey R (1983) Impact of symptomatic interval on prognosis of patients with stage III testicular cancer. *Urology* **21**: 559–561.
- Schmid-Wendtner MH, Baumert J, Stange J, Volkenandt M (2002) Delay in the diagnosis of cutaneous melanoma: an analysis of 233 patients. *Melanoma Res* **12**: 389–394.
- Scott SE, Grunfeld EA, McGurk M (2005) The idiosyncratic relationship between diagnostic delay and stage of oral squamous cell carcinoma. *Oral Oncol* **41**: 396–403.

- Seoane J, Pita-Fernandez S, Gomez I, Vazquez I, Lopez-Cedrun Jose L, De Augustin A, Vareal-Centelles P (2010) Proliferative activity and diagnostic delay in oral cancer. *Head Neck* **32**: 1377–1384.
- Seoane J, Takkouche B, Varela-Centelles P, Tomas I, Seoane-Romero JM (2012) Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis. *Clin Otolaryngol* **37**: 99–106.
- Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM (2013) Delayed diagnosis in children with intracranial germ cell tumors. *J Pediatr* **163**: 1448–1453.
- Sharpe D, Williams RN, Ubhi SS, Sutton CD, Bowrey DJ (2010) The 'two-week wait' referral pathway allows prompt treatment but does not improve outcome for patients with oesophago-gastric cancer. *Eur J Surg Oncol* **36**: 977–981.
- Sheng L, Shui Y, Shen L, Wei Q (2008) Effect of patient-related delay in diagnosis on the extent of disease and prognosis in nasopharyngeal carcinoma. *Am J Rhinol* **22**: 317–320.
- Sidler D, Winterhalder R, Huber G, Haerle SK (2010) Undifferentiated carcinoma of nasopharyngeal type (UCNT): A Swiss single-institutional experience during 1990–2005. *Swiss Med Wkly* **140**: 273–279.
- Simpson PM, Reid R, Porter D (2005) Ewing's sarcoma of the upper extremity: Presenting symptoms, diagnostic delay and outcome. *Sarcoma* **9**: 15–20.
- Singal AG, Waljee AK, Patel N, Chen EY, Tiro JA, Marrero JA, Yopp AC (2013) Therapeutic delays lead to worse survival among patients with hepatocellular carcinoma. *J Natl Compr Canc Netw* **11**: 1101–1108.
- Singh H, Shu E, Demers A, Bernstein CN, Griffith J, Fradette K (2012) Trends in time to diagnosis of colon cancer and impact on clinical outcomes. *Can J Gastroenterol* **26**: 877–880.
- Skaug K, Eide GE, Gulsvik A (2011) Predictors of long-term survival of lung cancer patients in a Norwegian community. *Clin Respir J* **5**: 50–58.
- Smith EC, Ziogas A, Anton-Culver H (2013) Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. *JAMA Surg* **148**: 516–523.
- Smith EM, Anderson B (1985) The effects of symptoms and delay in seeking diagnosis on stage of disease at diagnosis among women with cancers of the ovary. *Cancer* **56**: 2727–2732.
- Sue GR, Lannin Donald R, Killelea B, Tsangaris T, Chagpar AB (2013) Does time to definitive treatment matter in patients with ductal carcinoma in situ? *Am Surg* **79**: 561–565.
- Sun M, Abdollah F, Hansen J, Trinh Q-D, Bianchi M, Tian Z, Briganti A, Shariat SF, Montorsi F, Perrotte P, Karakiewicz PI (2012) Is a treatment delay in radical prostatectomy safe in individuals with low-risk prostate cancer? *J Sex Med* **9**: 2961–2969.
- Sundi D, Svatek RS, Margulis V, Wood CG, Matin SF, Dinney CP, Kamat AM (2012) Upper tract urothelial carcinoma: Impact of time to surgery. *Urol Oncol* **30**: 266–272.
- Temoshok L, DiClemente RJ, Sweet DM, Blois MS, Sagebiel RW (1984) Factors related to patient delay in seeking medical attention for cutaneous malignant melanoma. *Cancer* **54**: 3048–3053.
- Teppo H, Alho OP (2008) Relative importance of diagnostic delays in different head and neck cancers. *Clin Otolaryngol* **33**: 325–330.
- Teppo H, Heikkinen J, Alho OP (2009) Diagnostic delays in vestibular schwannoma. *J Laryngol Otol* **123**: 289–293.
- Teppo H, Hyrynkangas K, Koivunen P, Jokinen K, Alho OP (2005) Impact of patient and professional diagnostic delays on the risk of recurrence in laryngeal carcinoma. *Clin Otolaryngol* **30**: 157–163.
- Teppo H, Koivunen P, Hyrynkangas K, Alho OP (2003) Diagnostic delays in laryngeal carcinoma: professional diagnostic delay is a strong independent predictor of survival. *Head Neck* **25**: 389–394.
- Terhaar sive Droste JS, Oort FA, van der Hulst RW, Coupe VM, Craanen ME, Meijer GA, Morsink LM, Visser O, van Wanrooij RLJ, Mulder CJJ (2010) Does delay in diagnosing colorectal cancer in symptomatic patients affect tumor stage and survival? A population-based observational study. *BMC Cancer* **10**: 332.
- Thompson MR, Asimwe A, Flashman K, Tsavellas G (2011) Is earlier referral and investigation of bowel cancer patients presenting with rectal bleeding associated with better survival? *Colorectal Dis* **13**: 1242–1248.
- Thompson MR, Heath I, Swarbrick ET, Faulds Wood L, Ellis BG (2010) Earlier diagnosis and treatment of symptomatic bowel cancer: can it be achieved and how much will it improve survival? *Colorectal Dis* **13**: 6–16.
- Tokuda Y, Chinen K, Obara H, Joishy SK (2009) Intervals between symptom onset and clinical presentation in cancer patients. *Intern Med* **48**: 899–905.
- Tomlinson C, Wong C, Au HJ, Schiller D (2012) Factors associated with delays to medical assessment and diagnosis for patients with colorectal cancer. *Can Fam Physician* **58**: e495–e501.
- Tørring ML, Frydenberg M, Hamilton W, Hansen RP, Laustrup MD, Vedsted P (2012) Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. *J Clin Epidemiol* **65**: 669–678.
- Tørring ML, Frydenberg M, Hansen RP, Olesen F, Hamilton W, Vedsted P (2011) Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care. *Br J Cancer* **104**: 934–940.
- Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P (2013) Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer* **49**(9): 2187–2198.
- Toth-Fejel S, Pommier RF (2004) Relationships among delay of diagnosis, extent of disease, and survival in patients with abdominal carcinoma tumors. *Am J Surg* **187**: 575–579.
- Tromp DM, Brouha X, Hordijk GJ, Winnubst JAM, de Leeuw RJ (2005) Patient and tumour factors associated with advanced carcinomas of the head and neck. *Oral Oncol* **41**: 313–319.
- Umezu T, Shibata K, Kajiyama H, Yamamoto E, Mizuno M, Kikkawa F (2012) Prognostic factors in stage IA-IIA cervical cancer patients treated surgically: does the waiting time to the operation affect survival? *Arch Gynecol Obstet* **285**: 493–497.
- Valentin-Lopez B, Ferrandiz-Santos J, Blasco-Amaro J-A, Morillas-Sainz J-D, Ruiz-Lopez P (2012) Assessment of a rapid referral pathway for suspected colorectal cancer in Madrid. *Fam Pract* **29**: 182–188.
- Van Hout A, de Wit NJ, Rutten FH, Peeters PHM (2011) Determinants of patient's and doctor's delay in diagnosis and treatment of colorectal cancer. *Eur J Gastroenterol Hepatol* **23**: 1056–1063.
- Vernham GA, Crowther JA (1994) Head and neck carcinoma—Stage at presentation. *Clin Otolaryngol Allied Sci* **19**: 120–124.
- Wagner JL, Warneke CL, Mittendorf EA, Bedrosian I, Babiera GV, Kuerer HM, Hunt KK, Yang W, Sahin AA, Meric-Bernstam F (2011) Delays in primary surgical treatment are not associated with significant tumor size progression in breast cancer patients. *Ann Surg* **254**: 119–124.
- Wahl SK, Gildengorin G, Feusner J (2012) Weekend delay in initiation of chemotherapy for acute lymphoblastic leukemia: does it matter? *J Pediatr Hematol Oncol* **34**: e8–e11.
- Waldert M, Karakiewicz PI, Raman JD, Remzi M, Isbarn H, Lotan Y, Capitanio U, Bansalah K, Marberger MJ, Shariat SF (2010) A delay in radical nephroureterectomy can lead to upstaging. *Br J Urol Int* **105**: 812–817.
- Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S (2002) Delay and survival in bladder cancer. *Br J Urol Int* **89**: 868–878.
- Wallach MA, Balmer A, Munier F, Houghton S, Pampallona S, von der Weid N, Beck-Popovic M (2006) Shorter time to diagnosis and improved stage at presentation in Swiss patients with retinoblastoma treated from 1963 to 2004. *Pediatrics* **118**: e1493–e1498.
- Wang J, Liu F, Gao H, Wei W, Zhang X, Liang Y, Cheng Y (2008) The symptom-to-treatment delay and stage at the time of treatment in cancer of esophagus. *Jpn J Clin Oncol* **38**: 87–91.
- Ware SM, Al-Askari S, Morales P (1980) Testicular germ cell tumors: Prognostic factors. *Urology* **15**: 348–352.
- Warner ET, Tamimi RM, Hughes ME, Ottesen RA, Wong Y-N, Edge SB, Theriault RL, Blayney DW, Niland JC, Winer EP, Weeks JC, Partridge AH (2012) Time to diagnosis and breast cancer stage by race/ethnicity. *Breast Cancer Res Treat* **136**: 813–821.
- Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, van Rijswijk E, Hiom S, Muth C, Beyer M, Neal RD (2012) 'The Aarhus statement: improving design and reporting of studies on early cancer diagnosis'. *Br J Cancer* **106**: 1262–1267.
- Wildt J, Bundgaard T, Bentzen SM (1995) Delay in the diagnosis of oral squamous cell carcinoma. *Clin Otolaryngol Allied Sci* **20**: 21–25.
- Windham TC, Termuhlen PM, Ajani JA, Mansfield PF (2002) Adenocarcinoma of the stomach in patients age 35 years and younger: No impact of early diagnosis on survival outcome. *J Surg Oncol* **81**: 118–124.
- Wishnow KI, Johnson DE, Preston WL, Tenney DM, Brown BW (1990) Prompt orchiectomy reduces morbidity and mortality from testicular carcinoma. *Br J Urol* **65**: 629–633.

- Wright GP, Wong JH, Morgan JW, Roy-Chowdhury S, Kazanjian K, Lum SS (2010) Time from diagnosis to surgical treatment of breast cancer: factors influencing delays in initiating treatment. *Am Surg* **76**: 1119–1122.
- Wurtz LD, Peabody TD, Simon MA (1999) Delay in the diagnosis and treatment of primary bone sarcoma of the pelvis. *J Bone Joint Surg* **81**: 317–325.
- Yang JYK, Cheng FW, Wong KC, Lee V, Leung WK, Shing MM, Kumta SM, Li CK (2009) Initial presentation and management of osteosarcoma, and its impact on disease outcome. *Hong Kong Med J* **15**: 434–439.
- Yilmaz A, Damadoglu E, Salturk C, Okur E, Tuncer LY, Halezeroglu S (2008) Delays in the diagnosis and treatment of primary lung cancer: are longer delays associated with advanced pathological stage? *Ups J Med Sci* **113**: 287–296.
- Yun YH, Kim YA, Park S, Won YJ, Kim DY, Choi IJ, Kim YW (2012) The influence of hospital volume and surgical treatment delay on long term survival after cancer surgery. *Ann Oncol* **23**: 2731–2737.
- Zafar A, Mak T, Whinnie S, Chapman MAS (2011) The 2-week wait referral system does not improve 5-year colorectal cancer survival. *Colorectal Dis* **14**: 177–180.
- Ziliotto AJ, Kunzle JE, De Souza A, Colicchio-Filho O (1987) Evolutionary and prognostic aspects in gastric cancer analysis of 189 cases. *Cancer* **59**: 811–817.



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