

The risk of oesophago-gastric cancer in symptomatic patients in primary care: a large case-control study using electronic records.

Oesophago-gastric cancer diagnosis in primary care

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Abstract

Background

Over 15,000 new oesophago-gastric cancers are diagnosed annually in the UK, with most being advanced disease. We identified and quantified features of this cancer in primary care.

Methods

Case-control study using electronic primary care records of UK patients aged ≥ 40 years. Cases with primary oesophago-gastric cancer were matched to controls on age, sex and practice. Putative features of cancer were identified in the year before diagnosis. Odds ratios (ORs) were calculated for these features using conditional logistic regression, and positive predictive values (PPVs) calculated.

Results

7,471 cases and 32,877 controls were studied. Sixteen features were independently associated with oesophago-gastric cancer (all $p < 0.001$): dysphagia, OR 139(95% confidence interval (CI) 112-173); reflux 5.7(4.8-6.8); abdominal pain 2.6(2.3-3.0); epigastric pain 8.8(7.0-11.0); dyspepsia 6(5.1-7.1); nausea and/or vomiting 4.9(4.0-6.0); constipation 1.5(1.2-1.7); chest pain 1.6(1.4-1.9); weightloss 8.9(7.1-11.2); thrombocytosis 2.4(2.0-2.9); low haemoglobin 2.4(2.1-2.7); low MCV 5.2(4.2-6.4); high inflammatory markers 1.7(1.4-2.0); raised hepatic enzymes 1.3(1.2-1.5); high white cell count 1.4(1.2-1.7); high cholesterol 0.8(0.7-0.8). The only PPV above 5% in patients ≥ 55 years was for dysphagia. In patients < 55 years all PPVs were below 1%.

Conclusion

Symptoms of oesophago-gastric cancer reported in secondary care were also important in primary care. The results should inform guidance and commissioning policy for upper GI endoscopy.

Keywords

Oesophago-gastric cancer, primary care, symptoms, diagnosis, positive predictive values

Introduction

Oesophago-gastric tumours account for 6% of all UK cancers with 15,500 new diagnoses each year (8,173 oesophageal cancer; 7610 gastric cancer); two-thirds are in men, and 92% of new cases occur in those aged 55 or over (Office for National Statistics, 2010). Worldwide there are almost 1.5 million new cases annually, two-thirds gastric and one third oesophageal. In Western countries gastric cancer is decreasing in incidence, but the increase in oesophageal cancer more than outweighs this fall, leading to an overall increase (NHS Information Centre, 2010). Mortality is very high, with 5-year survival approximately 7% for oesophageal and 12% for gastric cancers (Rachet et al, 2009).

There are presently no screening tests available for oesophago-gastric cancer, other than surveillance of patients with Barrett's oesophagus, though this accounts for less than 5% of all new oesophageal cancer diagnoses (Hvid-Jensen et al, 2011). Therefore, diagnosis largely depends upon presentation with symptoms, generally to primary care (Hamilton 2010). However, symptoms are often vague and are also common in benign conditions. Indeed, dyspepsia is experienced by 40% of the population, though only 5% report it to their doctor (National Prescribing Centre, 2006). Furthermore, treatment of dyspepsia with acid suppressants may hide symptoms of gastric cancer and delay diagnosis (Talley et al, 1993). In the UK, selection of patients for investigation is guided by publications from the National Institute for Health and Clinical Excellence (NICE) (NICE, 2004) (NICE, 2005). These recommendations were based almost entirely upon secondary care studies (that is, the referred population), and describe several 'alarm' symptoms (Meineche-Schmidt, 2002) (Varadarajulu et al, 2005) (Vakil et al, 2006). Even so, the yield of upper gastro-intestinal cancer with alarm symptoms is only 4%, many of these cancers being at an advanced stage (Kapoor et al, 2005). Liberalising access to endoscopy in an attempt to increase the number of early-stage cancers is an option, but this strategy could increase the number of endoscopies up to tenfold with no increase in the number of cancers diagnosed (Agreus et al, 2001).

In addition, public awareness of dysphagia as an alarm symptom for oesophageal cancer is poor and may contribute to patient delay in seeking advice (Tentzeris et al, 2011). An awareness campaign for the UK is currently under consideration. Thus, it is timely to study the features of oesophago-gastric cancer as presented to primary care. It is also logical to study the two cancer sites collectively, as they share a common diagnostic test – endoscopy. The aim of this study was to identify and quantify the clinical features of oesophago-gastric cancer in primary care, ultimately to improve selection of patients for investigation.

Method

This was a case-control study using data from the General Practice Research Database (GPRD) in the UK. The GPRD maintains an anonymised copy of participating practices' medical records; these contain full details of the patient, including all consultations, recorded symptoms, investigations and diagnoses. The data are subject to stringent checks on validation and quality, and they are regarded as high quality in terms of accuracy, completeness and validity of diagnoses (Khan et al, 2010). We have previously used similar methods for several cancer diagnostic studies (Hamilton, 2007) (Dommett et al, 2012).

Identification of cases and controls

A list of 42 (18 oesophageal, 24 gastric) tumour diagnostic codes (available from the authors) was collated from the GPRD master code library. This has approximately 100,000 codes covering all events in primary care. GPRD staff identified all patients ≥ 40 years with an oesophago-gastric tumour diagnosed between 1st January 2000 and 31st December 2009 and with at least one year of data meeting their quality standards before diagnosis. For each case, the GPRD identified up to five controls, matched by year of birth, sex, and practice, using a computer-generated random sequence. We excluded cases and controls with no consultations in the year before diagnosis of the case (the index date). We included primary oesophago-gastric cancers which had metastasised but excluded cancers from other sites which had spread to the oesophagus or stomach. Controls were excluded if they had ever had oesophago-gastric cancer.

Selection of possible features of oesophago-gastric cancer

We studied all previously described diagnostic features of oesophago-gastric cancer identified in a literature review, supplemented by literature from relevant cancer websites. The GPRD's code list has many synonyms for similar symptoms, often including additional description such as severity or duration. These synonyms were identified and merged. The dyspepsia variable merged codes with either the word 'dyspepsia' or 'indigestion'; the reflux variable included 'regurgitation' as well as 'reflux'; the variable 'epigastric pain' required a precise anatomical description whereas the variable 'abdominal pain' incorporated all other abdominal pain variables without a precise anatomical description. Occurrences of features in the year before the index date were identified. These were only retained if they occurred in $\geq 5\%$ of cases or controls. For laboratory tests, we used the local laboratory range to identify abnormal results; we considered patients without a test to be equivalent to those with a normal result. We merged all hepatic enzyme results into a composite variable, deemed abnormal if any enzyme was raised; similarly, abnormal erythrocyte sedimentation rate, plasma viscosity and C-reactive protein were collated into a single variable called raised inflammatory markers. In order to test for any recording bias between cases and controls we also identified all codes for fractures (making the assumption that the fracture rate would be approximately equal).

Analysis

All analyses were performed using Stata (version 11), (StataCorp, 2010) and our main analytical method was conditional logistic regression. Variables associated with oesophago-gastric cancer with a p-value < 0.1 in the univariable regressions entered multivariable analyses. Multivariable regressions were performed in stages, initially collecting similar variables together, such as those reflecting abdominal pain. Significant variables then entered a second stage, grouping variables into abdominal symptoms, other symptoms, and investigations. For these two stages, a threshold p-value of < 0.05 was used. The final model was derived from all variables surviving the earlier staged regressions, and used a threshold p-value of < 0.01 . All rejected variables were checked to see if they contributed to the final model, and eleven clinically plausible interactions were investigated. We also examined the

possibility that the symptom patterns differed between oesophageal and gastric cancers by repeating the two multivariable models in the single sites: where the odds ratios for features differed materially, an interaction term between the symptom and cancer site was added to the final model.

Calculation of positive predictive values (PPVs)

We calculated PPVs for the risk of oesophago-gastric cancer in patients consulting in primary care using Bayes' theorem (Knottnerus, 2002). In this, the posterior odds of disease = the prior odds \times the likelihood ratio. For the prior odds we used the age-specific national incidence rate of oesophago-gastric cancer for 2008 (Cancer Research UK, 2008). As all 7,471 cases analysed had consulted in primary care, but only 32,877 of 36,212 (90.8%) controls had consulted in the study period, we divided the posterior odds by 0.908 to give predictive values for the consulting population. This analysis was performed in two age groups over and under 55 years to mirror current UK national guidance (NICE, 2004) (NICE, 2005).

Results

We were initially supplied with 7,657 cases and 37,699 controls: this includes 2,968 cases in whom fewer than five controls were available. The application of exclusions is shown in Figure 1.

(Figure 1)

The demographic features of patients are shown in Table 1, and their clinical features are shown in Table 2. In the year before diagnosis, cases presented to primary care more frequently than controls: median number of consultations 26 (interquartile range 15 to 42) versus 15 (7 to 28); $p < 0.001$ Mann-Whitney test. For the cases and controls respectively, 130 (1.7%) and 521 (1.6%) had a record of a fracture. Barrett's oesophagus was recorded in 209 (2.8%) of cases, and 51 (0.2%) of controls.

(Table 1)

(Table 2)

Multivariable analysis results are shown in Table 3: of cases, only 26.6% had none of the features present in this Table. No interaction terms with age or sex were found. Dysphagia was the only symptom with a markedly different odds ratio between the two separate cancer sites (oesophageal cancer OR 230 (CI 180 to 300); gastric cancer OR 20 (14 to 29)). When expressed as an interaction term in the unified model, the interaction OR for dysphagia was 0.27 (CI 0.21 to 0.33): $p < 0.001$, The ORs for the remaining symptoms were remarkably similar.

(Table 3)

Figure 2 shows PPVs for oesophago-gastric cancer for the symptoms in Table 3 plus low haemoglobin and thrombocytosis for patients aged ≥ 55 years. All PPVs for symptom combinations in patients aged under 55 were $<1\%$ (data not shown). The highest PPV in this age group was for dysphagia, 0.8% (CI 0.4% to 1.5%).

(Figure 2)

Discussion

This is the first study quantifying the risk of oesophago-gastric cancer in primary care that incorporates single and multiple symptoms as well as laboratory results. Most of the symptoms that have been reported from secondary care studies and from patient groups were also strongly associated with oesophago-gastric cancer in this primary care study. This was particularly so for dysphagia, with a risk of cancer of 4.8%. No other isolated symptom had a risk over 1%, even when we restricted the analysis to patients over 55 years of age to match current guidance. In combination, however, several symptom pairs carried higher risks, especially when one of the symptoms was loss of weight. In contrast, no symptom in patients under 55 years had a risk above 1%, even dysphagia.

Strengths and limitations of the study

This study is large, and uses primary care data. This is crucial: selection of patients for investigation is performed by clinicians in primary care, so primary care data must be used to illuminate the selection process. The GPRD is considered by many to be the gold standard of longitudinal patient databases from primary care. It has been used in nearly 1,000 research papers published in peer-reviewed journals and its validity has been well documented (Herrett et al, 2010) (Khan et al, 2010). The patient population in the database is also broadly representative of the UK population. Additionally, laboratory results are transmitted directly to the database, allowing us to use the local normal range to identify abnormal results, as well as minimising transcription errors. A further strength was our decision to study oesophageal and gastric cancers together; it was logical to answer the question of what clinical features should prompt consideration of endoscopy as both cancers share the same investigation. In any case, the associations between symptoms and the individual cancers were remarkably similar (other than for dysphagia).

We could not check the accuracy of diagnosis in the cases by histology, or determine the staging. This is less important than it appears: primary care recording of cancer diagnoses is excellent, especially since maintaining a cancer registry became one of the items in the Quality and Outcomes Framework.

Staging data may have allowed us to identify clinical features particularly associated with early stage cancer: whilst superficially attractive, it is actually valuable to identify all cancers, including those that cannot be cured, as treatment may still be beneficial.

The main limitation of the study is that we had to rely upon the accurate recording by GPs of symptoms. Under-recording of symptoms or signs may have led to some features that may be genuinely associated with oesophago-gastric cancer not being identified, such as upper gastrointestinal bleeding. When calculating PPVs, under-recording is only important if the proportion of symptom under-recording was markedly higher in either cases or controls. We have no reason to believe this is the case (Hamilton, 2009).

Comparison with existing literature

The prevalence of the common symptoms of oesophago-gastric cancer in cases was lower than in previous secondary care studies (Ojala et al, 1982) (Bodger et al, 2000) (Fransen, 2007) (Berrill et al, 2011). This probably reflects different symptom experience early in the disease, – especially in primary care. There are two possible alternative explanations. The first is under-recording of symptoms as discussed earlier; the second is that most previous studies directly interviewed patients after diagnosis. Such methods may be subject to recall bias, thus reporting higher rates of symptoms than studies using indirect methods, such as ours. Again, this may matter less than it appears: unvoiced symptoms are a well recognised feature of primary care, and can only be combated by using checklists, a procedure rarely used in primary care. The risk from dysphagia in primary care has previously been estimated as 5.4% in men and 2.7% in women (Jones et al, 2007). Our figure of 4.8% (with little difference between the sexes) is similar. Another primary care study using a different dataset has reported associations for six features of cancer (dysphagia, haematemesis, abdominal pain, loss of weight, loss of appetite, anaemia), though without reporting PPVs (Hippisley-Cox, 2011). Our finding of a strong association between a raised platelet count and cancer has been described before

for ovarian and lung cancers, though not for oesophago-gastric tumours (Hamilton et al, 2005) (Stone et al, 2012).

Implications for clinical practice and future research

Selection of patients for investigation – generally by endoscopy – has always been difficult. The ‘alarm’ symptoms, such as loss of weight or dysphagia, are shown in this study to have a sufficiently high PPV to warrant endoscopy, though in the case of weight loss additional symptoms are needed to raise the PPV above 1%. Our figures support current NICE guidance on such symptoms (NICE, 2005). However, using alarm symptoms alone to identify patients for endoscopy will miss over half of patients with cancer, as only 32% of our cases had reported dysphagia, and 8% loss of weight. A previous primary care study agrees with this, suggesting that a symptom-based approach, focusing on single symptoms such as dysphagia, is likely to miss 40% of current oesophago-gastric cancers some of which will be at a curable stage (Jones et al, 2007).

It has long been recognised that certain ‘low-risk but not no-risk’ symptoms are associated with cancer – particularly dyspepsia. The risk is even lower in younger patients, though the decision to use a threshold age of 55 years for investigation was not based on primary care literature, and is hotly contested, especially by patient advocacy groups. There is no generally agreed view of a particular level of risk that warrants cancer investigation: patients, commissioners of care and clinicians will all have a voice in such a decision, which will need to include a health-economic dimension. If a 2% risk is chosen, endoscopy would be offered to patients over 55 for most patients with loss of weight and a second gastrointestinal symptom, as well as all patients with dysphagia. It is only if a lower figure of (say) 1% risk is accepted that a much larger group of patients are selected for endoscopy. This would include most combinations of dyspepsia with a second symptom, plus combinations with epigastric pain. Indeed, there must be considerable overlap between these two symptoms, with many clinicians using them interchangeably (we assigned these symptoms according to the GP’s records, but each GP will have their own personal definition of the two terms).

By lowering the threshold for investigation, many more patients would be identified (as dyspepsia, in particular, was common in cases). This would bring considerable investigative costs. Until prevention

by reduction of alcohol, smoking or obesity reduces the incidence – and this is not likely in the short term – or a screening programme is developed – and again it is difficult to conceive of what this could be – or a biomarker is uncovered, then the only solution to the UK’s marked excess mortality from oesophago-gastric cancer will be a considerable expansion of testing. Currently there is almost a threefold variation within England, with European rates even higher (Department of Health, 2012). This will mean commissioners and clinicians accepting the financial and organisational costs, as well as patients accepting a high initial ‘false-positive rate’ – that is, being selected for endoscopy, yet transpiring not to have cancer. This is not our decision as authors to make, though our research shows that it is naive to believe that more appropriate selection of patients will identify a higher number of cancers without increasing use of investigations.

Conclusion

Although current mortality from oesophago-gastric cancer is very high in the UK, other European countries have better outcomes from the cancer (Abdel-Rahman et al, 2009). It is not known if these better outcomes arise from better access to investigations or public awareness of symptoms, or both. This study has two main uses: first, it can guide GPs in the selection of patients for urgent investigation; and secondly it suggests that selection of patients for investigation using only alarm symptoms will have a limited effect.

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Ethical approval

The study was approved by the Independent Scientific Advisory Committee (ISAC).

Competing interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) No authors have any relationships with companies that might have an interest in the submitted work in the previous 3 years; (2) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (3) All authors have no non-financial interests that may be relevant to the submitted work.

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SS performed the data manipulation and analyses, under the supervision of WH and TJP. SS and WH drafted the article. All six authors made revisions.

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