

Predictive effect of heartburn and indigestion and risk of upper GI malignancy

Further to our recent publication of two papers in the BJGP^{1,2}, we have been asked to specifically evaluate whether dyspepsia is a significant independent predictor of upper gastro-intestinal malignancy (ie gastro-oesophageal and pancreas) and to consider adding it to the models. These symptoms (heartburn or indigestion) were not included in the original analysis which had focused on more traditional alarm symptoms. We therefore undertook an analysis based on the original derivation cohort from the published studies and identified patients with new onset of (a) heartburn or (b) indigestion (other than where heart burn is explicitly mentioned). We determined the age-sex incidence rates. We added both factors to the Cox models and determined the hazard ratios adjusted for the factors in the original models. We tested for interactions between the new variables and age. We evaluated performance of the new models on the original validation dataset using published methods.

Figure 1 shows age-sex incidence rates of each symptom (where dyspepsia represents either heartburn or indigestion). The crude incidence rate for new onset heartburn in patients aged 30-84 years was 130 (95% CI 128 to 133) per 100,000 person years for men and 196 (95% CI 193 to 199) for women. The incidence rate for indigestion in men was 680 (95% CI 680 to 693) per 100,000 person years for men and 844 (95% CI 836 to 850) for women. Table 1 shows the hazard ratios for heartburn and indigestion in the new Cox models, adjusted for the other factors in the original models (see footnote). There were no age interactions for these symptoms. Both heartburn and indigestion were independently associated with risk of gastro-oesophageal cancer and also pancreatic cancer in both men and women. The adjusted hazard ratios associated with indigestion without heartburn were higher than those associated with heartburn. For example, women with heartburn had a 2.2-fold increased risk of gastro-oesophageal cancer and a 2.5 fold increased risk of pancreatic cancer. Women with indigestion without mention of heartburn had a 4.3-fold increase in gastro-oesophageal cancer and a 3.8-fold increase in pancreatic cancer. The pattern for men was similar. We therefore retained both heartburn and indigestion in both updated models for men and women. The performance of the updated algorithms on the validation cohort was equivalent to that of the original models for gastro-oesophageal cancer and marginally better for pancreatic cancer. The R^2 , D statistic and ROC statistics for gastro-oesophageal cancer were 71%, 3.2 and 0.90 for women and 71%, 3.2 and 0.92 for men. The corresponding values for pancreatic cancer were 62%, 2.6 and 0.84 for women and 64%, 2.7 and 0.86 for men.

In summary, we have identified and quantified two additional symptoms (heartburn and indigestion) which are predictive of both upper GI cancers. We have now included both symptoms in updated models at www.qcancer.org. As with the other symptoms included in the models, it is important to remember that they represent symptoms which have been significant enough for a patient to present to their GP and for their GP to record. Not all patients with such symptoms will have attended their GP and not all such symptoms will be reported or recorded.

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Figure 1: incidence rates of symptoms per 100,000 person years by age and sex in the derivation cohort.

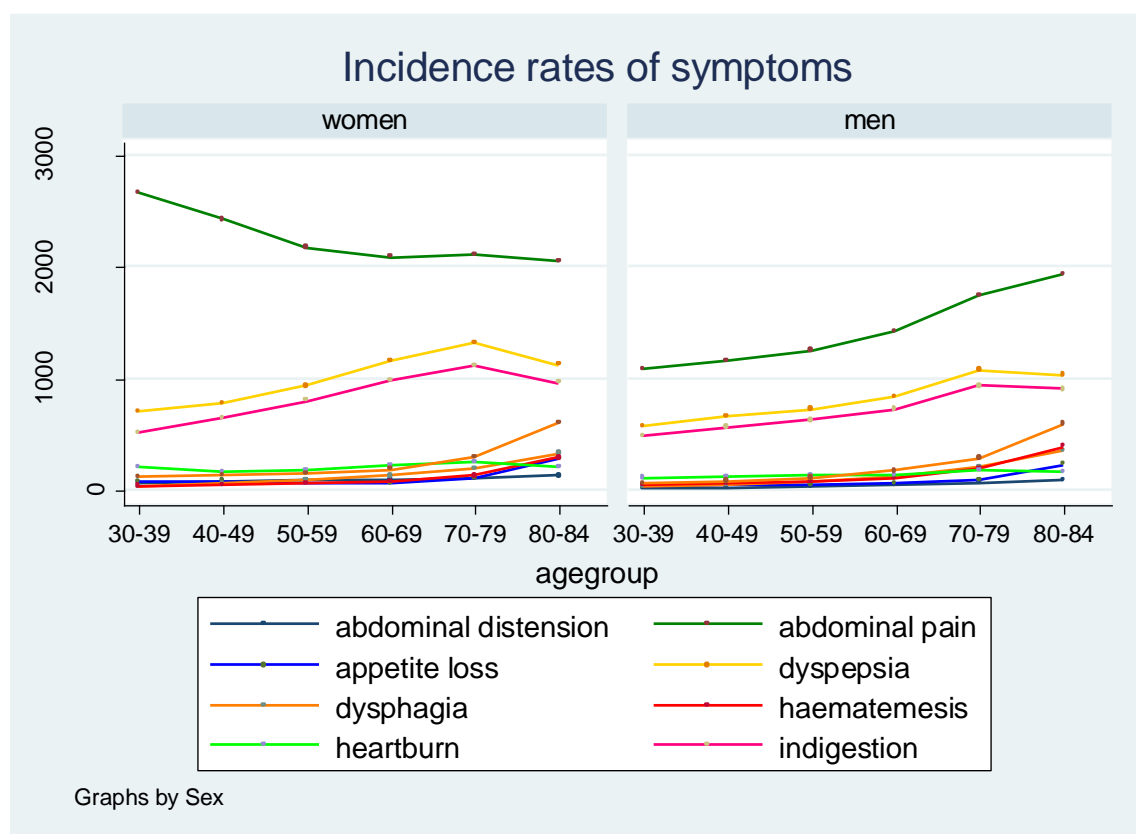


Table1: adjusted hazard ratios (95% CI) for (a) pancreatic cancer and (b) gastro-oesophageal cancer in patients with heart burn or indigestion

	<i>adjusted hazard ratio (95% CI) for pancreatic cancer†</i>	<i>adjusted hazard ratio (95% CI) for gastro-oesophageal cancer±</i>
women		
Heartburn*	2.55 (1.34 to 4.85)	2.16 (1.29 to 3.64)
Indigestion without heart burn*	3.76 (2.83 to 5.01)	4.30 (3.51 to 5.25)
men		
Heartburn*	2.24 (1.11 to 4.55)	2.95 (2.11 to 4.13)
Indigestion without heart burn*	4.64 (3.62 to 5.94)	6.44 (5.64 to 7.36)

*compared with person without heartburn or indigestion

† The models for pancreatic cancer also included fractional polynomial terms for age which were age⁻² and age³ for women and age⁻¹ for men; smoking status (5 levels), type 2 diabetes, chronic pancreatitis, appetite loss, weight loss, abdominal pain, abdominal distension (women), dysphagia (men), constipation (men). The model for men also included interactions between weight loss and the age terms

± The models for gastro-oesophageal cancer included fractional polynomial terms for age. For women the term was age^{0.5}. For men the terms were age⁻², age³. The models for men and women also included smoking status (5 levels), dysphagia, abdominal pain, appetite loss, haematemesis, weight loss, anaemia. The model for women also included interactions between the age term and dysphagia, abdominal pain, appetite loss, haematemesis. The model for men included interactions between the age terms and dysphagia.

Competing Interests and Financial disclosures (as per original paper reproduced here)

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JHC is professor of clinical epidemiology at the University of Nottingham and co-director of QResearch[®] – a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of IT for 60% of general practices in the UK). JHC is also a paid director and co-founder of ClinRisk Ltd which produces software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. The software which implement the algorithms described in this paper are free for anyone to use under the terms of the GNU lesser GPL3. For those who wish to implement software in a closed source setting, then a license fee is payable to ClinRisk Ltd. CC is associate professor of Medical Statistics at the University of Nottingham and a paid consultant statistician for ClinRisk Ltd. This work and any views expressed within it are solely those of the co-authors and not of any affiliated bodies or organisations.

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References

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2. Hippisley-Cox J, Coupland C. Identifying patients with suspected gastro-oesophageal cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract* 2011;61(592):e707-14.