The changing prevalence of gastro-intestinal malignancy in adults with iron deficiency anaemia, and identification of additional predictive clinical variables – the IDIOM V study

Orouba Almilaji [1], Carla Smith [2], Lisa Cranham [2], Jonathon Snook [2]

[1] Department of Health Service Research and Policy, Faculty of Public Health and Policy, LSHTM, London UK

[2] Gastroenterology Unit, Poole Hospital, University Hospitals Dorset, UK

Correspondence: Dr Jonathon Snook
Consultant Gastroenterologist, University Hospitals Dorset
Poole Hospital, Longfleet Road, Poole
Dorset BH15 2JB
Tel : 0044 300 0198678
E-mail : Jonathon.Snook@gmail.com

Conflicts of interest: None

Word count (excl summary): 2652

Key Words: Iron Deficiency Anaemia
Cancer
Epidemiology

Abstract

Objective: (1) To determine whether the prevalence of GI cancer in adults presenting with IDA is continuing to fall, and (2) to identify clinical variables with the potential to improve the accuracy of an established system for predicting cancer risk in IDA - the IDIOM score.

Method: (1) An audit of 1253 consecutive adults to the IDA service of a single general hospital in 2022/23, with analysis of outcome of investigation for GI cancer, and the relationship between this outcome a series of eight clinical variables. (2) Refinement of the IDIOM score using an imputation method to combine the development and new predictor datasets.

Results: The prevalence of GI cancer in those undergoing full investigation for IDA was 5.6% (52/934). On univariate logistic regression analysis there were strong negative associations between GI cancer risk and (a) previous colonic imaging within the last five years (OR 0.31, 95% CI 0.08-0.87), and (b) long-term exposure to PPI therapy (OR 0.18, 95% CI 0.09-0.34). Model extension analysis suggested that adding PPI exposure status could improve the accuracy of the IDIOM score : c-statistic - 0.84 v 0.77, calibration slope - 1.01 v 1.05.

Conclusion: The prevalence of GI cancer in adults presenting with IDA continues to fall, strengthening the case for risk stratification and targeting of invasive investigation at those at higher risk. Adding PPI exposure status may improve the value of the IDIOM score, though this requires confirmation in prospective studies.

Key messages

What is already known on this topic

The prevalence of underlying GI cancer in subjects presenting with IDA has been gradually falling over the last 20 years. Age, sex, Hb and MCV are independent predictors of GI cancer risk in the IDA cohort.

What this study adds

The prevalence of underlying GI cancer in subjects with IDA continues to fall, and is very low in those with colonic imaging within the previous 5 years. Long-term PPI therapy is strongly associated with a low GI cancer risk, and may be additional independent predictor.

How this study might affect research, practice or policy

The falling cancer prevalence in the IDA cohort strengthens the argument for risk stratification. Prospective studies are required to determine the place of long-term PPI therapy as an indicator of cancer risk.

Introduction

Iron deficiency anaemia (IDA) is the consequence of impaired bone marrow production of erythrocytes due to depletion of body iron stores. It is a major global healthcare issue, with multiple causes primarily relating to reduced assimilation and / or enhanced loss of iron [1 2]. Around 30% of adult males and non-menstruating females presenting with IDA in the UK prove on investigation to have an underlying mucosal lesion due to inflammatory, vascular or neoplastic pathology in the upper or lower gastrointestinal (GI) tract, which share the common final pathway of chronic GI blood loss [1 - 5].

GI cancer however is by far the most significant cause [5]. It is estimated from population studies in the UK that anaemia with a haemoglobin concentration of less than 100 g/l (of which iron deficiency is the commonest cause) carries a likelihood ratio for underlying colorectal cancer of greater than 10 [6]. In historical case-series, about 10% of IDA referrals to secondary care prove to have underlying GI malignancy [3 4], though whilst referral numbers have risen over the last 20 years, increasing demand on hard-pressed investigation services, the percentage with cancer has gradually fallen [7].

A rising referral rate and falling cancer prevalence strengthen the case for risk stratification of IDA referrals [8]. The perfect risk stratification tool should be based on clinical parameters that are objective and readily available for all subjects at low cost. It should provide complete discrimination between those with cancer anywhere in the GI tract, and those without. The IDIOM (Iron Deficiency as an Indicator Of Malignancy) score is based on the observation that four objective clinical variables - age, sex, Hb (haemoglobin concentration) and MCV (mean red cell volume) - are independent predictors of GI cancer risk in IDA [4 9]. It is a validated estimator of the likelihood of underlying GI cancer in the individual case, giving the

percentage probability of GI malignancy ranging from <2% to >20%, with an area under the receiver operated curve (AUROC) of 70 - 77% [10] – leaving room for improvement.

The primary aim of the current study was to undertake an audit of the outcome of investigation of serial referrals to a single IDA service, focussing particularly on the prevalence and distribution of underlying GI cancer, to determine whether the percentage with underlying cancer continues to fall. The secondary aim was a hypothesis-generating exercise, to assess whether a further eight universally available clinical variables (detailed in the Method section) might show potential for improving the IDIOM scoring system.

Method

Clinical aspects

Clinical information was recorded at the time of initial assessment for consecutive new adult cases attending the IDA Clinic at Poole Hospital between 1.1.22 and 31.8.23. All had documentary evidence of underlying iron deficiency, defined as a serum ferritin below the lower limit of normal (30 ug/l for males, 13 ug/l for females) and / or a transferrin saturation of < 15% [5].

The data collected included information regarding the four variables contributing to the original IDIOM score (sex, age, Hb and MCV) plus eight new variables. These eight were selected on the grounds that they were universally available and relatively objective, with reason for supposing that they might be markers of underlying GI malignancy. They were :

Laboratory parameters (continuous variables) :

a. Platelet count – normal range : 150 – 400 $x10^9$/l

b. Mean cell haemoglobin concentration (MCHC) – normal range : 320 – 360 g/l

Clinical history (binary variables) of :

c. Unintentional weight loss of ≥ ½ stone over the preceding year.

d. Colonic imaging in the last five years - colonoscopy or CT colonography - regardless of indication, study quality or findings.

e. Hollow-organ GI cancer in the index case or any first degree relative.

Pharmacological exposure (binary variables) regularly for ≥1 year to :

f. Aspirin and/or a non-steroidal anti-inflammatory drug (NSAID)

g. A proton pump inhibitor (PPI)

h. An oral anticoagulant (OAC) – vitamin K antagonist or direct-acting.

The completeness and outcome of GI investigation was subsequently recorded. Our standard practice for confirmed IDA is to advise examination of the upper and lower GI tract unless a study of adequate quality has been done within two years.

Subjects were excluded from the analysis if they were unwilling or insufficiently fit to complete appropriate investigation for IDA, if iron deficiency was not felt to be the major cause of their anaemia, or if their clinical information dataset was incomplete.

Statistical aspects

The secondary aim of this analysis was to assess whether incorporating new predictors of GI cancer risk could improve the performance of a previously developed prediction model, the IDIOM score. This original model was built using an entirely independent dataset, published as IDIOM III [9] - the development dataset.

As the new dataset reported here contained only 52 cases of GI cancer, it wasn't feasible to evaluate the impact of all new variables on GI cancer risk. So instead, we focused on one clinical variable – exposure to proton pump inhibitor (PPI) therapy - as this showed by far the strongest association with GI cancer risk on univariate logistic regression (Table 2). It should be stressed that we had no *a priori* hypothesis linking PPI therapy to the risk of finding GI cancer on investigation of IDA, so this part of the analysis should be regarded as exploratory - and hypothesis-generating.

To extend the prediction model, we used the imputation method [11]. We combined the new dataset and the development dataset to produce a prediction model containing the original predictors of the IDIOM score plus PPI status. Since values for PPI status were systematically

missing from the development dataset, we used multiple imputation with chained equations to impute missing PPI values ten times [12]. In each of the completed datasets, we fitted a logistic regression model and obtained an overall estimate of the regression coefficient using Rubin's rules - averaging the estimates across the ten completed datasets [13].

The combined dataset included 252 GI cancer cases. Merging the two datasets was appropriate, as there was no overlap in patient data between them. This approach allowed us to leverage all available data to evaluate the effect of PPI status on GI cancer risk.

We assessed the discrimination and calibration of the extended model. Discrimination refers to the model's ability to differentiate between patients with and without GI cancer, measured by the concordance statistic (c), which is equivalent to the area under the ROC curve in binary logistic regression. A c-statistic of 0.5 indicates random chance, while a value of 1.0 represents perfect discrimination. Calibration measures the agreement between predicted probabilities and observed outcomes, assessed using the calibration slope, where an ideal value is 1.0.

As an audit of outcome involving the analysis of fully anonymised data with no interventional element and using data collected as part of routine clinical practice, ethics approval was not required. The STROBE guidelines were followed in the reporting of this study [14].

Results

A total of 1253 cases were assessed during the study period, although 239 were unwilling and / or insufficiently fit to complete full investigation for IDA, as defined in the Method section. This relatively high figure reflects the recent trend towards referral of cases with greater morbidity, and the degree of nosocomephobia that persists in the aftermath of the pandemic - particularly in those with major co-morbidities. The wide range of co-morbidities

encountered included failure of one or more major organ, obesity, frailty and old age - often in combination. The other reasons for exclusion were anaemia not felt to primarily reflect iron deficiency (n=59), duplicate entries (n=17) and incomplete datasets (n=4).

Data for 934 investigated cases were therefore available for analysis, and descriptive statistics for this cohort are shown in Table 1, along with baseline data for the 239 who were excluded because investigation was incomplete. Of the 934, a total of 52 (5.6%) proved on investigation to have an underlying malignant neoplasm in the upper (12) or lower (40) GI tract. One case with ileal adenocarcinoma was included in the lower GI category for the purposes of analysis.

The crude prevalence of the eight candidate variables is shown in Table 2, along with the results of univariate logistic regression analysis. A history of colonic examination in the previous five years was significantly lower in those with GI cancer (4/52 - 7.7%) than in those without (186/882 – 21.1%), giving an OR (odds ratio) of 0.31 (95% confidence interval : 0.08-0.87). Put another way, only 4 of 190 (2.1%) of cases with prior colonic imaging had GI cancer – and three of these were in the upper GI tract (2) or ileum (1), so would not have been expected to be revealed by colonic imaging. The one colon cancer diagnosed was a small lesion found 43 months after a colonoscopy of satisfactory quality.

Perhaps the most striking finding of this study was for exposure to long-term PPI therapy, which was far higher in those without GI cancer (69.7%) than in those with (28.8%) – giving an OR of 0.18 (95% CI 0.09-0.34). The remaining variables assessed showed no more than marginal differences between the study groups, with confidence intervals close to or crossing unity (Table 2).

Table 1 Descriptive statistics for the full study cohort, broken down by the presence / absence of underlying GI cancer for those who were fully investigated (NA – information not available).

GI Investigation :	**Complete (n=934)**		**Incomplete (n=239)**
GI cancer found :	No (n=882)	Yes (n=52)	NA
Age – median [IQR] yrs	71.1 [61.0, 78.0]	78.3 [72.9, 83.5]	74.5 [58.5, 84.9]
Sex – F : M ratio	1.56	0.68	1.66
Hb – median [IQR] g/l	110 [99, 118]	94 [81, 109]	104 [93, 115]
MCV – median [IQR] fl	80 [75, 85]	78 [72, 84]	80 [74, 86]

Table 2 The crude prevalence of the eight candidate variables in the study cohort, broken down by the presence / absence of underlying GI cancer, with the results of univariate logistic regression analysis.

	GI cancer?		**Logistic regression**		
	No (882)	**Yes (52)**	**OR**	**95% CI**	**P value**
Platelets – median [IQR] x10^9/l	294 [237, 356]	312 [262, 391]	1.002	0.999, 1.004	.143
MCHC – median [IQR] g/l	318 [311, 325]	314 [306, 322]	0.978	0.959, 0.999	.032
Weight loss – n (%)	117 (13.3%)	12 (23.1%)	1.959	0.909, 3.948	.060
Prior colonic imaging – n (%)	186 (21.1%)	4 (7.7%)	**0.312**	**0.081, 0.869**	**.019**
PH/FH GI Cancer – n (%)	176 (20.0%)	10 (19.2%)	0.955	0.419, 1.983	.999
Aspirin/NSAID – n (%)	267 (30.3%)	9 (17.3%)	0.482	0.204,1.022	.059
PPI – n (%)	615 (69.7%)	15 (28.8%)	**0.176**	**0.088, 0.336**	**<0.001**
OAC – n (%)	203 (23%)	16 (30.8%)	1.486	0.753,2.814	.237

As shown in Table 3, the updated model using the imputation method described retained the same predictors as the original IDIOM model, with a higher c-statistic. It also had a calibration slope closer to 1. Therefore - pending further studies - PPI exposure appears to be a promising candidate for incorporation into the IDIOM scoring system.

Table 3 A comparison of IDIOM score coefficients, c-statistics and calibration slopes for the original model versus the imputation model (: p-value <0.01, *** : p-value<0.001)**

	Original model	**Imputation model**
Intercept	-1.84 ***	-2.36 ***
Sex = male	0.94 ***	0.95 ***
Age	0.06 ***	0.07 ***
MCV	-0.03 **	-0.03 **
Hb	-0.03 ***	-0.02 ***
PPI = yes	-	-1.84 ***
c-statistic	0.77	0.84
Calibration slope	1.05	1.01

Discussion

This study confirms that the prevalence of underlying GI cancer in the cohort of IDA referrals to secondary care has continued to fall over the last 20 years, from a figure of around 10% [3] [4] [7] to 5.6% in the current study. Whilst not designed to identify the cause, the reasons are likely to include a greater proportion of IDA referrals with milder anaemia, recurrent anaemia or a previous colonic examination (not necessarily for IDA) – all of whom are likely to have a relatively low risk of underlying GI cancer. The introduction of FIT over recent years may also be a contributory factor, with diversion of IDA patients with a positive result to the colorectal service.

This falling prevalence strengthens the argument for routine risk stratification in IDA [8], the aim being to identify a sub-group at very low predicted risk of malignancy who might with appropriate counselling, non-invasive testing and safety-netting avoid invasive investigation. This would allow stretched investigational resources to be more usefully targeted at those at predicted higher risk.

Whilst the IDIOM score has been validated as an estimator of the likelihood of underlying GI cancer in the individual case with IDA [9] [10], the AUROC is currently sub-optimal. The question is whether additional clinical variables – meeting the criteria of immediate and universal availability, objectivity and cost outlined above – can be usefully added to it. We explored the potential of eight candidates in this study, selected for the reasons outlined below.

Recognised predictors of visceral malignancy in general include platelet count [15], weight loss [16] and a personal or family history [17], whilst the history of a previous colonic examination might be expected to be associated with a reduced risk of colon cancer [18], the commonest cancer underlying IDA. The MCHC is an objective marker of hypochromia, and therefore falls

with increasing severity of iron deficiency - Hb and MCV behave in the same way, and both have proved to be independent predictors of GI cancer risk in the IDIOM studies [4 9].

The contribution of pharmacological agents to the development of IDA is an under-researched area, but long-term therapy with a PPI or OAC may have a significant role – the latter particularly in those with haemorrhagic lesions, such as cancers in the GI tract [19-22]. The mechanism by which PPI therapy might contribute to the development of IDA also needs to be clarified, but interference with enteric iron absorption has been proposed as the explanation [23-25].

There is some evidence that aspirin and NSAID therapy may be associated with a reduced risk of underlying GI malignancy in IDA [26]. Again the mechanism is uncertain, but suppressing the development of colon cancer [27] and / or predisposing to other causes of IDA - notably peptic ulceration and NSAID enteropathy [28] – may have a role.

In the event, our results on simple logistic regression analysis suggest that any trend towards an association between GI cancer risk and platelet count, MCHC, weight loss, cancer history and exposure to aspirin / NSAIDs or anticoagulants in the IDA cohort is at most weak. Therefore, none of these variables are likely to be useful in a clinical risk prediction system.

The association between GI cancer risk and previous colonic imaging appears to be considerably stronger (OR 0.31). Our findings would suggest in particular that the colon cancer risk in IDA is very low within 5 years of a previous examination of adequate quality. This has resource implications, as many units including our own currently use an arbitrary cut-off of 2 - 3 years. However, the observation is only of relevance to the 20% of the IDA cohort with this history.

The striking - and unexpected - finding in this study is the strong negative association between long-term PPI therapy in the IDA cohort and the presence of GI cancer (OR 0.18). This builds on previous work [21] and reflects the high prevalence (almost 70% in this study) of long-term PPI therapy in those with IDA who prove not to have underlying malignancy. In those with GI malignancy, the prevalence of long-term PPI treatment (just under 29% in this study) is actually similar to that in general population [21 29]. One interpretation of this observation is that PPI exposure is a major contributor to the development of IDA, but only in those without an underlying GI malignancy. The possible role of confounding always needs to be considered in association studies of course, and PPI exposure may simply be a marker of healthcare exposure or some other selection bias - though the strength of the association might argue against this explanation [30].

The imputation approach to update the original IDIOM score suggests that the addition of PPI status might improve the predictive value of the model, and the demonstrated improvement in the c-statistic is promising. However, it remains to be seen whether this translates into any meaningful reclassification of risk in clinical practice. We feel strongly that revision of the IDIOM risk score needs validation by analysis of a larger dataset with sufficient GI cancers, particularly as there was no a priori hypothesis.

Additional weaknesses of this study include firstly the high exclusion rate due to incomplete investigation, and the lower than anticipated prevalence of GI cancer in those who were fully investigated. As a result, the number of cancers identified was insufficient for multivariate analysis without an imputation approach. Secondly as a single centre study, the findings may not be more widely applicable. Finally, the analysis does not include results of Faecal Immunochemical Testing (FIT) for haem. The primary reason for this was that whilst FIT is

undoubtedly useful for colon cancer screening in the symptomatic population, a result was not universally available in our cohort due to limited requesting and patient compliance [31]. The place of FIT in risk stratification of the IDA cohort remains to be established [5 31]

In summary, this study confirms that the prevalence of underlying GI cancer continues to fall in adults with unexplained IDA, and that the yield of colon cancer in the IDA cohort is very low in those with a colonic examination of adequate quality within the previous 5 years. It also suggests a strong negative association between long-term PPI exposure and GI cancer risk in the IDA cohort. Whilst independent confirmation of this is clearly required, this may provide an additional term that can be usefully integrated into the IDIOM scoring system.

Acknowledgements

Author contributions: OAM and JAS conceived and designed this study. CS and LC collected the data, whilst OAM analysed it. The manuscript was drafted by OAM and JAS. All authors made significant contributions to the subsequent revision of the paper and approved the final version, and JAS is the guarantor.

Funding sources: none.

Competing interests: none.

Data Sharing Statement: data available on reasonable request.

Ethics approval: as an audit of fully anonymised and routinely collected clinical data, formal Research Ethics approval was not required.

Patient consent for publication: not required.

References

1. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016 ; 387(10021) : 907-16. doi: 10.1016/S0140-6736(15)60865-0.

2. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet 2021 ; 397(10270) : 233-248. doi: 10.1016/S0140-6736(20)32594-0.

3. James MW, Chen CM, Goddard WP, Scott BB, Goddard AF. Risk factors for gastrointestinal malignancy in patients with iron-deficiency anaemia. Eur J Gastroenterol Hepatol 2005 ; 17(11) : 1197-1203. doi:10.1097/00042737-200511000-00008.

4. Castro-Silva A, Sheppard ZA, Surgenor SL, Williams EJ, Thomas PW, Snook JA Clinical risk factors for underlying gastrointestinal malignancy in iron deficiency anaemia : the IDIOM study. Frontline Gastroenterology 2014 ; 5 : 237-242.

5. Snook JA, Bhala N, Beales ILP, et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut 2021 ; 70(11) : 2030-2051. doi:10.1136/gutjnl-2021-325210.

6. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. Br J Cancer 2008 ; 98(2) : 323-7. doi: 10.1038/sj.bjc.6604165.

7. Stone H, Almilaji O, John C et al. The dedicated iron deficiency anaemia clinic – a fifteen-year experience. Frontline Gastroenterology 2022 ; 13 : 20-24. doi.org/10.1136/flgastro-2020-101470.

8. Snook JA. Investigating for GI malignancy in iron deficiency anaemia – the case for risk stratification. Frontline Gastroenterology 2014 ; 5 : 225-226.

9. Almilaji O, Smith C, Surgenor S et al. Refinement and validation of the IDIOM score for predicting the risk of gastro-intestinal cancer in iron deficiency anaemia. BMJ Open Gastroenterology 2020 ; 7 : e000403. doi: 10.1136/bmjgast-2020-000403.

10. Almilaji O, Webb G, Maynard A et al. Broad External Validation of a Multivariable Risk Prediction Model for GI Malignancy in Iron Deficiency Anaemia. Diagn Progn Res 2021 ; 5 : 23. doi.org/10.1186/s41512-021-00112-8.

11. Nieboer D, Vergouwe Y, Ankerst DP et al. Improving prediction models with new markers: a comparison of updating strategies. BMC Med Res Methodol 2016 ; 16 : 128. doi.org/10.1186/s12874-016-0231-2

12. Van Buuren S. Flexible Imputation of Missing Data. Boca Raton : Taylor & Francis ; 2012.

13. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York : Wiley ; 1987.

14. Vandenbroucke JP, von Elm E, Altman DG et al. STROBE initiative - Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007 ; 147(8) : W163-94. doi: 10.7326/0003-4819-147-8-200710160-00010-w1.

15. Giannakeas V, Kotsopoulos J, Cheung MC, et al. Analysis of Platelet Count and New Cancer Diagnosis Over a 10-Year Period. JAMA Netw Open 2022 ; 5(1) : e2141633. doi:10.1001/jamanetworkopen.2021.41633.

16. Wang QL, Babic A, Rosenthal MH et al. Cancer diagnosis after recent weight loss. JAMA 2024 ; 331(4) : 318-328. doi:10.1001/jama.2023.25869.

17. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology 2010 ; 138(6) : 2044-58. doi: 10.1053/j.gastro.2010.01.054.

18. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Long-Term Risk of Colorectal Cancer After Negative Colonoscopy. Journal of Clinical Oncology 2011 ; 29(28) : 3761-3767. doi:10.1200/JCO.2011.35.9307.

19. Tran-Duy A, Connell NJ, Vanmolkot FH, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case-control study. J Intern Med 2019 ; 285(2) : 205-214. doi: 10.1111/joim.12826.

20. Lam JR, Schneider JL, Quesenberry CP, Corley DA. Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency. Gastroenterology 2017 ; 152(4) : 821-829.e1. doi:10.1053/j.gastro.2016.11.023.

21. Prabhu K, Warricker F, Almilaji O, Williams EJ, Snook JA. The role of prescribed medication in the development of iron deficiency anaemia in adults – a case-control study. BMJ Open Gastroenterology 2024 ; 11:e001305. doi: 10.1136/bmjgast-2023-001305.

22. Johannsdottir GA, Onundarson PT, Gudmundsdottir BR, Bjornsson ES. Screening for anemia in patients on warfarin facilitates diagnosis of gastrointestinal malignancies and pre-malignant lesions. Thromb Res. 2012 ; 130(3) : e20-5.
doi: 10.1016/j.thromres.2012.05.005.

23. Hutchinson C, Geissler CA, Powell JJ, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. Gut 2007 ; 56 : 1291–1295. doi: 10.1136/gut.2006.108613.

24. Betesh AL, Santa Ana CA, Cole JA, Fordtran JS. Is achlorhydria a cause of iron deficiency anemia? Am J Clin Nutr 2015 ; 102(1) : 9-19. doi: 10.3945/ajcn.114.097394.

25. Hamano H, Niimura T, Horinouchi Y et al. Proton pump inhibitors block iron absorption through direct regulation of hepcidin via the aryl hydrocarbon receptor-mediated pathway. Toxicol Lett 2020 ; 318 : 86-91. doi: 10.1016/j.toxlet.2019.10.016.

26. van Everdink J, Callenbach PMC, van der Kleij FGH. Salicylate use: a negative predictive factor for finding pathology explanatory for iron deficiency anaemia. Neth J Med 2020 ; 78(4) : 161-166.

27. Garcia-Albeniz X, Chan AT. Aspirin for the prevention of colorectal cancer. Best Pract Res Clin Gastroenterol 2011 ; 25(4-5) : 461-72. doi: 10.1016/j.bpg.2011.10.015.

28. Shin SJ, Noh CK, Lim SG, Lee KM, Lee KJ. Non-steroidal anti-inflammatory drug-induced enteropathy. Intest Res 2017 ; 15(4) : 446-455. doi: 10.5217/ir.2017.15.4.446.

29. Abrahami D, McDonald EG, Schnitzer M, et al Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study BMJ Open 2020 ; 10 : e041529. doi: 10.1136/bmjopen-2020-041529.

30. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965 ; 58 : 295-300.

31. D'Souza N, Georgiou Delisle T, Chen M, Benton S, Abulafi M; NICE FIT Steering Group. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. Gut 2021 ; 70(6) : 1130-1138. doi: 10.1136/gutjnl-2020-321956.