Title: Prevalence of gastrointestinal malignancy in iron deficiency without anaemia: a systematic review and meta-analysis

Short title: Iron deficiency and gastrointestinal cancer

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Declaration of interest: None

Abbreviations: CI, confidence interval; GI, gastrointestinal; IDA, iron deficiency anaemia; IDWA, iron deficiency without anaemia; NSAID, non-steroidal anti-inflammatory drug; NNS, number needed to scope

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ABSTRACT

Background: Iron deficiency anaemia is associated with gastrointestinal (GI) malignancy and is an indication for GI investigations. However, the relevance of iron deficiency without anaemia (IDWA) and the underlying risks of GI malignancy are uncertain. Therefore, the aim of this study was to estimate the prevalence of GI malignancy in patients with IDWA overall and in clinically relevant subgroups.

Methods: We searched MEDLINE and EMBASE for studies that reported on the prevalence or risk of GI malignancy in patients with confirmed IDWA. We performed a random effects meta-analysis of proportions and assessed statistical heterogeneity using the I^2 statistic.

Results: A total of 1923 citations were screened and 5 studies (4 retrospective cohorts, 1 prospective cohort) comprising 3329 participants with IDWA were included in the meta-analysis. Overall pooled random-effects estimates for prevalence of GI malignancy in those with IDWA were low (0.38%, 95% CI 0.00%–1.84%, I^2=87.7%). Older patients (2.58%, 95% CI 0.00%–8.77%); non-screening populations (2.45%, 95% CI 0.16%–6.39%) and men and post-menopausal women (0.90%, 95% CI 0.11%–3.23%) with IDWA were at increased risk of GI malignancy compared to younger patients (0.00%, 95% CI 0.00%–0.21%); screened populations (0.24%, 95% CI 0.00%–1.10%) and pre-menopausal women (0.00%, 95% CI 0.00%–1.05%).

Conclusion: Overall IDWA is associated with a low risk of GI malignancy. Older patients and non-screening populations are at elevated risk and require GI investigations. Those not in these subgroups have a lower risk of GI malignancy and may wish to be monitored following discussion of the risk and potential benefits of GI investigations.

Keywords: Iron deficiency; anaemia; risk of cancer; upper and lower gastrointestinal tract

BACKGROUND

Gastrointestinal (GI) cancers are the most common malignancy worldwide, leading to over 1.6 million deaths per annum[1]. The significant burden from this disease and its association with iron deficiency anaemia (IDA), particularly in those of an older age[2-4], has led to national guidelines recommending further investigation of the GI tract in the presence of IDA[5-8]. Unlike IDA, there is little consensus regarding the need for further investigations in those with iron deficiency without anaemia (IDWA), despite this being a common haematological finding often noted on routine blood tests. The prevalence of IDWA is four times as common as IDA with population cohort studies estimating that 1 in 20 adults have an IDWA[9]. Yet the relevance of IDWA and the underlying risks of GI malignancy are uncertain. As a proportion of IDWA may progress to IDA, one study suggests that all those with IDWA should undergo further GI investigations[10]. Others tentatively recommend further investigations only in those with IDWA and 'higher risk profiles' following discussion of the risks and benefits[6].

Therefore, the aim of this systematic review and meta-analysis was to determine the prevalence and quantify the risk of GI malignancy in those with IDWA overall and according to clinically relevant subgroups. As gastroscopy and colonoscopy are invasive GI investigations with associated risks, this will enable informed clinician and patient decision making for those most at risk from GI malignancy in the investigation of IDWA.

METHODS

The protocol for this systematic review was registered on the PROSPERO database (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42019127611) and conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[11].

Search strategy

We sought relevant published articles and abstracts by searching MEDLINE and EMBASE (both from 1/1/2000 onwards) (appendix 1) using the OVID interface, and manual searches of reference lists of any systematic reviews identified by the previous step. We used the following search terms (including related terms) to search each database: iron deficiency, oesophagus, stomach, small bowel, colon, and carcinoma. No language restrictions were placed on the searches. Searches were up to date as of 5 December, 2019.

Eligibility criteria

Only cross-sectional or cohort studies satisfying the following eligibility criteria were included in the systematic review: (i) at least one adult patient group with confirmed IDWA - no restrictions were placed on the definition of iron deficiency given a lack of a universally applicable definition[12], however the definition was required to be presented for eligibility; (ii) the article presented sufficient data to calculate the proportion with IDWA diagnosed with a GI malignancy. No restrictions were placed on the populations studied, whether screening or symptomatic, the GI investigations undertaken (if any) or the interval between diagnosis of IDWA and GI investigation. Aside from confirmed IDWA, disease cohorts were ineligible for inclusion. Two reviewers (LA and SSMC) independently screened abstracts and selected full text articles for inclusion based on the above criteria. Discrepancies were resolved through discussion between reviewers.

Data extraction and quality assessment

Two reviewers (LA and SSMC) independently extracted data from each selected article for study characteristics (study population, study design, setting, location, recruitment period, sample size, 'normal' haemoglobin definition, iron deficiency definition, investigations performed, indication for blood tests, prevalence definition, number of GI malignancies detected in the study population); patient characteristics (mean age, gender, ethnicity, prevalence of: menstruation, smoking, alcohol, vegetarianism, veganism and non-steroidal anti-inflammatory use); the number of patients with IDWA and of these, the number diagnosed with GI malignancy. Two reviewers (LA and SSMC) used a modified Newcastle Ottawa Scale for cross-sectional studies[13] adapted for the purpose of this systematic review, to appraise the internal validity of selected studies (Supplementary appendix 2). Using this scale, studies were scored across three domains: selection (three questions); comparability and outcome (one question each). Assessment for questions relating to sample size and statistical analysis were omitted as they were deemed not applicable to the research question. Therefore, for individual studies the highest possible score was eight points. Discrepancies were resolved through consensus discussion between reviewers. We contacted authors for additional information where required.

Statistical analysis

The primary outcome was a composite of any GI malignancy (oesophageal, gastric, small bowel or colorectal). We used the STATA program, *metaprop*[14], to perform a meta-analysis of proportions extracted from each study. Presented confidence intervals for individual studies were calculated using the binomial exact method[15]. Proportions were transformed to stabilize their variances using Freeman-Tukey double arcsine transformation[16], prior to calculation of pooled estimates using the random effects model proposed by DeSimonian and

Laird[17]. Confidence intervals for the pooled estimates were calculated using the Wald method. We estimated the percentage of variation across all studies due to heterogeneity, rather than chance, using I^2; with values of 25%, 50% and 75% respectively indicating low, moderate and high heterogeneity. To quantify risk of GI cancer in clinically relevant subgroups, and explore heterogeneity, pre-specified subgroup analyses were conducted by screening status, age, and menopausal status. Heterogeneity between subgroups was determined (P values for heterogeneity <0.1 were regarded as statistically significant).

We determined the Number Needed to Scope (NNS) as the number of individuals required to undergo GI investigations to detect one case of GI malignancy[18] i.e. the reciprocal of the prevalence of GI malignancy based on our meta-estimates. This was calculated overall and per subgroup (screening status, age, and menopausal status).

Analyses were performed with STATA version 15.1 (StataCorp LP, College Station, Texas, USA).

RESULTS

Results of systematic review

Search and selection of studies

Among 1923 unique articles identified from the literature search, twenty-eight full-text articles were assessed for eligibility, of which five were ultimately eligible for inclusion[9, 10, 19-21] (Figure 1). The twenty-three excluded articles were excluded on the basis of existing disease (six studies)[22-27], or an absence of patients with IDWA (seventeen studies)[28-44].

Study characteristics

The characteristics of selected studies are shown in table 1. Four were retrospective cross-sectional studies and one was a prospective cross-sectional study. Of the four retrospective cross-sectional studies, two were performed in Europe (Spain and Belgium)[20, 21], one in South Korea[10] and one in Israel[19]. The sole prospective cross-sectional study originated from the United States of America[9]. Three studies were conducted in hospital-based settings in asymptomatic and symptomatic patients[10, 20, 21] with the remaining two studies conducted in a nationwide cohort (NHANES)[9] and a population of young male army recruits up to the age of 30 years[19]. Three of the studies consisted of participants that had blood tests to assess for iron deficiency and anaemia, as part of a routine medical screening[9, 10, 19]. In total, 3329 participants were recruited and assessed across all studies with the largest study comprising of 1858 participants[19]. Three studies defined a normal haemoglobin (Hb) as Hb ≥ 13 g/dL in men or Hb ≥ 12g/dL in women[10, 20, 21]. The study in male army recruits defined a normal Hb as ≥ 14 g/dL[19] whilst the NHANES study defining a normal Hb as being greater than the fifth percentile[9]. Three studies defined iron deficiency as either a ferritin ≤ 50 mcg/l[21] or ≤ 20mcg/l[19, 20] with one of these studies also accepting a transferrin saturation < 15% as an indicator of iron deficiency regardless of ferritin[19]. The NHANES study based iron deficiency exclusively on an iron saturation < 15%[9] and a single study

defined iron deficiency as a combination of ferritin ≤ 50 ng/ml and total iron binding capacity ≥ 300mg/dl[10]. The prevalence of GI malignancy (excluding adenomas) was defined in the NHANES study, the population of asymptomatic young male army recruits and study from Spain as a GI malignancy within less than 2 years, up to 3 years and within 1 year, respectively, following detection of IDWA. Gastroscopy and colonoscopy in all participants as investigations for GI malignancy in the context of IDWA was only done in two studies[10, 20]. The remaining studies investigated IDWA utilizing a combination of gastroscopy, colonoscopy and/or imaging (CT/MRI/capsule) without stating the exact number or proportion of participants who had undergone these investigations for their IDWA[9, 19, 21].

Patient characteristics

The mean age of recruited participants between studies was between 21 to 83 years (table 2). Of all recruited participants, 72% were male. Only one study excluded patients with menorrhagia, vegetarianism and non-steroidal anti-inflammatory drugs (NSAIDs)[10].

Study outcomes

The risk of GI malignancy in IDWA ranged between 0 – 1.8% for four studies whilst a single study set in a geriatric hospital-based population reported the risk of GI malignancy in IDWA as 15%. Notably, the actual number of cases (n=3) and participants (n=20) in this particular study were small[21]. Few studies stratified the risk of GI malignancy in those with IDWA based on age. In the NHANES study, all cases of GI malignancy in those with IDWA were at least ≥ 50 years. Similarly, in the study performed in Spain the only case of colorectal cancer in IDWA was found in a participant ≥ 70 years. However, in the same study a pedunculated gastric polyp in a female < 50 years was subsequently found to have adenocarcinoma infiltrating the stalk[20]. The study of asymptomatic young men with IDWA appeared to have no risk of GI malignancy[19]. Similarly, sub-analyses by the NHANES I study reported that the

risk of GI malignancy in pre-menopausal women was lower (0.00%; 95% CI 0.00% – 1.05%) than that of men and post-menopausal women (0.90%; 95% CI 0.11% to 3.23%).

Results of the meta-analysis

All five studies from the systematic review were included in the meta-analysis with a total of 13 GI malignancies found in 3329 participants (Figure 2). Overall, the random-effects estimates for the prevalence of GI malignancy in those with IDWA were low (0.38%; 95% CI 0.00% – 1.84%) with high heterogeneity (I^2 = 87.7%). Meta-analysis of studies that had sufficient subgroup data allowing stratification by age showed that the prevalence of GI malignancy in those with IDWA is predominantly in those who are older (≥ 50 years of age) (2.58%; 95% CI 0.00% – 8.77%)[9, 20, 21] with little risk in those < 50 years (0.00%; 95% CI 0.00% – 0.21%)[9, 19, 20]. Meta-analysis of screened populations showed that the prevalence of GI malignancy in IDWA is lower (0.25%; 95% CI 0.00% - 1.10%) than that of non-screened populations (2.45%; 95% CI 0.16 % - 6.39%).

Overall, the NNS was 263 (95% CI 54 - ∞). Stratifying by age we found that the NNS in those ≥ 50 years was 39 (95% CI 11 - ∞) and in those < 50 years was ∞ (95% CI 476 - ∞). For screened populations the NNS was 417 (95% CI 91 - ∞) and for non-screened populations was 41 (95% CI 15 - 625) with the NNS for premenopausal women, and men and post-menopausal women being ∞ (95% CI 95 - ∞) and 111 (95% CI 31 - 909) respectively.

Study quality and risk of bias

Based on our modified Newcastle-Ottawa Scale (appendix 2) studies assessed scored between 5 and 7 (maximum score = 8). One study received a score of 7[9], three studies received scores of 6[10, 19, 20] and one study scored 5[21]. Only two studies were truly representative of the wider population[9, 10] with the remaining three studies focused on those who were

elderly[21], asymptomatic young and male[19], or had been referred to secondary care for gastroscopy and colonoscopy[20]. The possibility of selection bias was deemed to be low provided the findings from these three studies were applied to similar populations. Three studies had participation rates of 100%[10, 19, 20] whilst the two remaining studies either had participation rates of < 70%[9] or did not report on this[21].

DISCUSSION

There is a lack of consensus on whether IDWA requires further investigation. To the best of our knowledge, the present analysis is the first to systematically review the prevalence of GI malignancy in those with IDWA and to quantify the risk of those most likely to have malignant GI pathology. Our results show that the overall risk of GI malignancy is low in those with IDWA. However, this risk is elevated in those of an older age (≥ 50 years) and non-screening populations. These findings would suggest that these subgroups of patients should have their IDWA investigated further, whilst those not in these categories may wish to be kept under observation instead of proceeding to GI investigations following discussion of the risks and potential benefits of such procedures.

This systematic review has several limitations that stem from shortcomings and uncertainties from included studies. The clinical relevance of IDWA as an indication for endoscopic investigation is best considered in asymptomatic individuals, since GI symptoms, independent of IDWA, may prompt further investigation regardless of IDWA status. While predominantly asymptomatic individuals will be very likely to contribute to screening populations[10, 19] and in the setting of a population-based cohort study[9], the same cannot be assumed for two of the included hospital-based studies[20, 21], where the prevalence of GI symptoms is relevant and not reported. This may have resulted in an overestimate of the prevalence of GI malignancy overall and separately in the older and younger groups. The interval between diagnosis of IDWA and GI investigation (and/or the end of follow-up) was not reported in three of the studies[9, 19, 20]. It is therefore uncertain whether a reasonable time period was applied in order to define the malignancy as prevalent. In line with current definitions of interval cancers of either the upper or lower GI tract[45], we propose an interval of three years as reasonable. Caution should be applied when attempting to generalize these findings to other patient groups and should consider the varying characteristics of the included study

populations. This will likely have contributed to the substantial heterogeneity (I^2 = 87.7%) observed for the overall meta-estimate. Nevertheless, the overall prevalence of GI malignancy was very low. Interpretation of clinically important subgroups (stratification by age, gender and menopausal status) should be informed by an understanding of the studies contributing to these groups and the precision of the meta-estimates. The younger, male subgroup were predominantly informed by a cross-sectional study of young male recruits to the Israel defence force (n= 1858)[19], followed by a subgroup contributing to NHANES I (n= 420)[9]. Iron deficiency is very common in male army recruits participating in strenuous exercise programs and has similarly been observed in elite athletes[46, 47]. Nevertheless, estimates from these two studies were similar (no GI cancers developed in either group), and the pooled prevalence of GI malignancy in younger patients was very low with high degree of precision (0.00%, 95% CI 0.00% – 0.21%). As expected, the prevalence of malignancy in older patients with IDWA was higher, however the estimates were imprecise (2.58%, 95% CI 0.00 – 8.77%). This uncertain estimate was mainly driven by a selective and small (n=20) cohort of older (mean age 82.8 years) hospital inpatient and outpatients[21]. There is a relative paucity of data to inform the prevalence of GI malignancy in pre-menopausal women and men and post-menopausal women, which were subgroups drawn from the same study[9].

We therefore recommend the conduct of further generalizable cross-sectional population-based studies to more reliably inform the need for GI investigation in patients with IDWA. In particular, precise estimates of the prevalence of GI malignancy in relevant asymptomatic patient subgroups (stratified simultaneously by age groups, and gender) are required, with explicit reasoned definition of the interval between detection of IDWA and investigation/follow-up. Future research should also assess the role of non-invasive testing to further risk-stratify those with asymptomatic IDWA and guide selection for endoscopic investigations. In the appropriate contexts, these may include tissue transglutaminase, faecal

calprotectin and faecal immunochemical testing (FIT). Such investigations may be prudent in order to minimise the number of unnecessary invasive endoscopic investigations in the context that IDWA is a common finding[9]. Certainly, FIT testing is already being explored to aid selection for colonoscopy in the work-up for IDA[34, 48, 49]; and while its diagnostic accuracy has been established in a range of populations[50], its performance, stratified by age and gender, is understudied; and its utility in patients with IDWA is currently unknown.

CONCLUSIONS

In summary, the observational evidence suggests that the prevalence of GI malignancy overall in patients with IDWA is low; however, it appears to be elevated in older and non-screening populations. Our meta-estimates may inform patient and clinician decision making with regards to the appropriateness of further endoscopic investigation in those with IDWA particularly those who are considered low risk. There is a paucity of data to inform the risk according to gender and in post-menopausal women. More population-based research is required to further refine estimates and inform clinical practice.

ADDITIONAL INFORMATION

Grant support: LA is funded by the National Institute of Health Research (NIHR) as a clinical lecturer. The NIHR had no role in in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript.

Ethical approval and consent to participate: This systematic review only includes previously published data and does not include new human data or tissue that requires ethical approval and consent. This research was conducted in accordance with the Declaration of Helsinki.

Availability of data and materials: All data reported in this manuscript are found in the literature as cited in the text. Supplementary information is available for this paper at [insert link].

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TABLE AND FIGURE LEGEND

Table 1: Summary of Study Characteristics

Table 2: Summary of Participant Characteristics

Figure 1: Flow diagram for literature selection process

Figure 2: Forest plot – Estimated prevalence of gastrointestinal malignancy in those with IDWA