The value of alarm features in identifying organic causes of dyspepsia

Lone Galmstrup Madsen MD, Peter Bytzer MD PhD

LG Madsen, P Bytzer. The value of alarm features in identifying organic causes of dyspepsia. Can J Gastroenterol 2000;14(8): 713-720. The unaided clinical diagnosis of dyspepsia is of limited value in separating functional dyspepsia from clinically relevant organic causes of dyspepsia (gastric and esophageal malignancies, peptic ulcer disease and complicated esophagitis). The identification of one or more alarm features, such as weight loss, dysphagia, signs of gastrointestinal bleeding, an abdominal mass or age over 45 years may help identify patients with a higher risk of organic disease. This review summarizes the frequency of alarm symptoms in dyspeptic patients in different settings (such as the community, primary care and specialist clinics). The prevalence of alarm features in patients diagnosed with upper gastrointestinal malignancy or peptic ulcer disease is described. The probability of diagnosing clinically relevant upper gastrointestinal disease in patients presenting with alarm features and other risk factors is discussed. Alarm features such as age, significant weight loss, use of nonsteroidal anti-inflammatory drugs, signs of bleeding and dysphagia may help stratify dyspeptic patients and help optimize the use of endoscopy resources.

Key Words: Age; Alarm features; Dyspepsia; Dysphagia; Gastrointestinal bleeding; Helicobacter pylori; NSAID; Vomiting

Valeur des indices dans l'identification des causes organiques de dyspepsie

RÉSUMÉ : Le diagnostic clinique de dyspepsie sans examen a une valeur plutôt limitée si l'on dissocie la dyspepsie fonctionnelle des causes organiques cliniques de dyspepsie, par exemple une tumeur maligne de l'œsophage ou de l'estomac, un ulcère gastro-duodénal ou une oesophagite compliquée. L'identification d'un ou plusieurs indices comme une perte de poids, la dysphagie, les signes d'hémorragie gastro-intestinale, la présence d'une masse abdominale ou le fait d'avoir plus de 45 ans peut aider à repérer les patients prédisposés à une maladie organique. L'article ci-dessous présente un résumé de la fréquence des indices relevés chez les patients dyspeptiques observés dans différents milieux (cliniques communautaires, spécialisées, centres de soins primaires). Il sera question de la fréquence des indices notés chez les patients chez qui une tumeur maligne du tractus gastro-intestinal supérieur ou un ulcère gastro-duodénal ont été diagnostiqués. L'article traite aussi de la probabilité de poser un diagnostic de maladie gastro-intestinale haute, cliniquement valable, chez les patients qui présentent des indices de maladie et d'autres facteurs de risque. Les indices comme l'âge, une perte de poids importante, l'utilisation d'anti-inflammatoires non stéroïdiens, les signes d'hémorragie et de dysphagie peuvent aider à classer les patients dyspeptiques et à optimiser le recours à l'endoscopie.

Management of the dyspeptic patient who seeks medical care is a great challenge to the physician. Dyspepsia covers a broad spectrum of symptoms with several possible underlying pathophysiological causes. Careful clinical evaluations of symptoms and physical examinations are of limited value in differentiating between peptic ulcer dis-

ease, gastroesophageal reflux disease, gastrointestinal malignancy and functional dyspepsia. In only one-third of patients clinically judged to have ulcer disease is the clinical diagnosis confirmed by endoscopy. Moreover, half of all ulcer patients remain undiagnosed by the clinician. Furthermore, one-third of patients with major lesions on endoscopy

This mini-review was prepared from a presentation made at the 1998 World Congress of Gastroenterology, Vienna, Austria, September 6 to 11, 1998 Department of Medical Gastroenterology, Glostrup University Hospital, DK-2600 Glostrup, Denmark

Correspondence and reprints: Dr Peter Bytzer, Department of Medical Gastroenterology, Glostrup University Hospital, DK-2600, Glostrup, Denmark. Telephone +45-4323-2801, fax +45-4323-3950, e-mail peter.bytzer@dadlnet.dk

Received for publication September 7, 1999. Accepted September 13, 1999

TABLE 1
Definition and description of traditional alarm features in dyspepsia

Alarm features	Description
Age	Dyspeptic patients older than age 45 to 55 years depending on local incidence of gastric cancer
Weight loss	Significant unintended weight loss; usually defined as more than 3 kg
Vomiting	Persistent vomiting in relation to meals and delayed (longer than 1 h after eating) if occurring repeatedly
Dysphagia	The sensation of food being hindered in its passage from the mouth to the stomach; sometimes associated with odynophagia (pain with swallowing) Oropharyngeal dysphagia: difficulties in initiating swallowing, including coughing and nasal regurgitation Esophageal dysphagia: Food stops in or adheres to the esophagus after swallowing
Active or chronic bleeding	Gastrointestinal bleeding presenting as: Hematemesis: Fresh or 'coffee-ground' vomit Melena: Black, tarry, foul-smelling stools Iron-deficiency anemia: Verified by blood analysis, with no signs or symptoms of bleeding from other sources
Abdominal mass	Presence of an palpable abdominal mass on physical examination

(meaning ulcers, esophagitis or even malignancy) are misclassified as having functional disorders if an unaided clinical diagnosis is trusted (1). To identify dyspeptic patients at higher risk for organic dyspepsia, the identification of alarm symptoms and features may be beneficial. This review examines the value of various alarm features in identifying organic causes of dyspepsia.

ORGANIC CAUSES OF DYSPEPSIA

Dyspepsia is defined as persistent or recurrent abdominal pain or discomfort centred in the upper abdomen, and is considered to originate in the upper alimentary tract. Organic or structural dyspepsia has been defined as an identifiable pathophysiological cause of dyspepsia, associated with improvement of symptoms if the disease is improved or eliminated (2). The organic causes of dyspepsia cover a wide spectrum of conditions, but for the purposes of this review, only clinically relevant organic causes are considered. These causes include positive endoscopic findings that are potentially relevant to the patient's care, such as malignancy, peptic ulcer disease and complicated esophagitis (strictures, ulcerations and Barrett's metaplasia) (1,3-6). The broader term 'specific organic cause' concerns specific lesions in the upper gastrointestinal tract and includes, for example, the differentiation among types and locations of gastric and esophageal cancers, gastric erosions and gastric and duodenal ulcer diseases; the grading of esophagitis and complications of esophagitis such as ulcers, peptic strictures and Barrett's epithelium; and the typing and grading of gastric polyps, gastritis and dysplasia (7-10).

DYSPEPTIC ALARM SYMPTOMS

The following symptoms are usually accepted as alarm features when present in the dyspeptic patient: age over 45 to 50 years, depending on the local incidence of gastrointestinal cancer; a significant, unintended weight loss; severe, persistent vomiting; dysphagia, described as a sensation of delay or difficulty in the passage of a food bolus, occasionally associated with pain; active or chronic upper gastrointestinal bleeding presenting as hematemesis (fresh or 'coffee-ground'

vomit), melena (black, tarry, foul-smelling stools) or iron-deficiency anemia; and a palpable upper abdominal mass (Table 1) (11-15).

Most experts agree that patients having one or more alarm features should be offered prompt endoscopy, whenever possible.

HOW COMMON ARE ALARM SYMPTOMS?

In the community: The prevalence and incidence of alarm symptoms in dyspeptic persons in the community have not been investigated, to the best of our knowledge.

In primary care: In the Western world, only about one-quarter of people with dyspeptic symptoms consult their primary care physician (16). In a Danish primary care study, 10.3% of 7270 dyspeptic patients consulting their general practitioners presented with one or more alarm symptoms. After an average observation time of 31 months, gastrointestinal diseases such as esophagitis, peptic ulcers, cancer or liver cirrhosis had been diagnosed in only 9% to 21%, most commonly in patients presenting with black stools (17).

The frequency of organic causes of dyspepsia in primary care has been established in two large-scale Scandinavian studies with 400 and 612 unselected patients, respectively (18,19). A clinically relevant endoscopic diagnosis was found in 32% to 40% of the patients presenting with esophagitis (15% to 23%), peptic ulcer disease (13% to 16%), erosive duodenitis (2%) or upper gastrointestinal malignancy (1% to 2%).

In endoscopy clinics: In an effort to reduce the cost of endoscopic procedures, many gastrointestinal units have implemented systems of open access endoscopy, where specialists perform endoscopies without prior consultation. Only a minority of patients who consult their general practitioner because of dyspepsia are referred for endoscopy; hence, study populations from endoscopy units represent a selected subsample from primary care.

In studies from endoscopy units, alarm symptoms such as gastrointestinal bleeding or anemia (19% to 22%), dysphagia (6% to 16%), persisting nausea or vomiting (6%), anorexia or weight loss (5%) and abnormal upper gastrointestinal x-ray

(6%) are frequent referral indications (5,6,20). However, the most common reason for referral is isolated dyspepsia, which accounts for 28% to 45% of referrals (5,6). The frequency of clinically relevant endoscopic findings in patients referred for open access endoscopy is 30% to 60% (5,6,21).

In specialist clinics: Dyspeptic patients referred to gastroenterology specialist units are highly selected, resulting in a higher prevalence of alarm symptoms and organic disease. Procedures requested from gastroenterologists were compared with procedures requested from nongastroenterologists; the frequency of positive findings was significantly higher in endoscopies requested from gastroenterologists (62%) than in those requested from nongastroenterologists (52%) (5).

PREVALENCE OF ALARM SYMPTOMS IN ORGANIC DYSPEPSIA

Most of the literature on alarm symptoms in dyspepsia is based on retrospective data, resulting in a great risk of recall bias. It is uncertain whether the recorded symptoms led to the examination and to the diagnosis that followed. It is possible that the patient was not aware of a specific symptom before the diagnosis was made, meaning that symptoms other than alarm symptoms were responsible for the referral.

The following section describes the prevalence of alarm symptoms in the organic diseases associated with dyspepsia and the prevalence of organic disease in patients who present with an alarm feature.

Gastric cancer – Age: Gastric cancer is rare in patients younger than 40 years, and the incidence rises with increasing age. In a study of 76 cases of gastric cancer in patients younger than 55 years, only five patients had no alarm symptoms before diagnosis (22). Furthermore, in a retrospective study of 3607 dyspeptic patients under the age of 45 years without alarm symptoms, only two of 17 patients with suspicious lesions at endoscopy had histologically proven gastric carcinoma (0.055%) (23). Thus, in young patients with uncomplicated dyspepsia (no alarm features), upper gastrointestinal cancer is extremely rare (24,25).

Weight loss: The most common symptom in gastric cancer is weight loss, which is present in 60% to 70% of patients at the time of diagnosis (22,25,26). A study from Norway recorded the amount of weight loss during the time before diagnosis of gastric cancer (27). Only 30% had no weight loss before diagnosis. Twenty-six per cent had 1 to 5 kg weight loss and 44% had weight loss of more than 5 kg; the median weight loss per month was 1.7 kg. Weight loss reduced the probability of gastric resection, from 85% in patients with no weight loss to 53% in those who had lost more than 10 kg preoperatively. In most other studies, the duration and magnitude of weight loss have been poorly defined.

Dysphagia: Dysphagia is usually associated with structural diseases in the esophagus. However, dysphagia has also been reported in 10% to 30% of patients with gastric carcinomas (6,25,26), often in patients whose cancer is located in the cardia region and always in patients with more advanced disease (28).

Bleeding: Anemia and signs of upper gastrointestinal bleeding are present in 20% to 40% of patients with advanced gastric cancer (6,25,26). In early gastric cancer, anemia is uncommon at presentation, and a history of bleeding is present in less than 25% (28).

Vomiting: Persistent vomiting and nausea are present in about one-third of patients with gastric cancer, most often in advanced stages or when a tumour invades the pylorus (29-31). In early gastric cancer, only 8% to 10% of patients report anorexia, nausea or vomiting (28,31).

Palpable abdominal mass: There are no physical findings associated with early stages of gastric cancer. The presence of a palpable abdominal mass generally indicates longstanding growth with regional extension and is only present in 5% of those with advanced gastric cancer (26,31).

Other risk factors for gastric cancer: The incidence of gastric cancer is decreasing worldwide, but countries such as Japan, China, Russia and South America continue to have much higher rates of gastric cancer than Western countries. Over the past 50 years in the United States, the incidence of gastric cancer has declined from 33 to 10 cases per 10⁵ men and from 30 to five cases per 10⁵ women. Racial and ethnic background are also important. In the United States, African Americans, Hispanic Americans and Native Americans are 1.5 to 2.5 times more likely to have gastric carcinoma than white Americans (29), and the disease remains approximately twice as common in men as in women.

Considerable evidence supports a genetic role in the pathogenesis of gastric cancer. Case-control studies indicate that first-degree relatives (eg, parents or siblings) have a twofold to threefold increased risk of contracting the disease (32,33). This suggests that a family history for gastric cancer should be observed in approximately 10% to 15% of the registered cases (33).

Epidemiological studies have demonstrated a statistically significant relation between the seroprevalence of *Helicobacter pylori*, and incidence and mortality rates of gastric cancer (34). Many studies report *H pylori* infection rates of 40% to 90% in patients with gastric cancer, depending on local infection rates (35,36). The precise role of *H pylori* infection in gastric carcinogenesis remains unclear, although it is associated with the development of chronic atrophic gastritis (29), a well established precursor of gastric cancer. Nevertheless, gastric carcinoma develops in only a small proportion of infected persons, and the effects of prevention or treatment of *H pylori* infection on gastric cancer are unknown.

Onset of dyspeptic symptoms at the time of diagnosis of gastric cancer is common, and 73% of patients with gastric cancer had a previous history of dyspepsia. Two-thirds of patients had experienced dyspeptic symptoms for more than one year (8).

Esophageal cancer – Age: Compared with patients with gastric cancer, patients with esophageal cancer are, on average, 10 years older at the time of diagnosis. Thus, esophageal cancer is seldom seen in patients younger than 50 to 55 years. In a retrospective study of 73 patients with esophageal cancer (all types) younger than 55 years, all had reported one or more

alarm symptoms (22). In a Danish study of 1013 patients with adenocarcinoma of the esophagus, only 59 patients (6%) were younger than 50 years (37).

Dysphagia, vomiting and weight loss: Dysphagia is the most common esophageal alarm symptom and is present in 60% to 85% of patients with esophageal cancer (6,22). Persistent vomiting occurs with increased tumour size and esophageal stricture formation in about one-third of patients (22). Weight loss is reported by 65% of patients (22,37).

Bleeding and a palpable abdominal mass: Signs of upper gastrointestinal bleeding are not typical of esophageal cancer. In a survey of 73 cancers, 5.5% presented with anemia and only 2.7% presented with hematemesis or melena (22). The frequency of abdominal mass in esophageal cancer is unknown, but is more than likely low.

Other risk factors: Gastroesophageal reflux, especially if severe and long-standing, is associated with an increased risk of adenocarcinoma of the esophagus (10). Heartburn, regurgitations or both, occurring at least once a week for five years or more, were reported by 38% of 356 patients with esophageal cancer (10). The association between reflux symptoms and cancer was present only in patients with esophageal adenocarcinoma and not in patients with squamous cell cancer. Fifty-three per cent of patients with adenocarcinoma and 6% of patients with squamous cell carcinomas experienced reflux symptoms at night (10). Barrett's esophagus, which predisposes patients to adenocarcinomas (38), was present in 62% of patients with adenocarcinoma of the esophagus. The true prevalence is probably much higher. Large tumours tend to overgrow and conceal the underlying specialized tissue from which they arise (39).

Peptic ulcer disease: A chronic peptic ulceration (such as a duodenal or gastric ulcer) is present in approximately 15% to 25% of cases of new-onset dyspepsia (40).

Age: In a population-based study from Norway, prevalence of peptic ulcerations increased with age, with a pronounced increase in men older than 40 years and in women older than 50 years (41). Peptic ulcer disease is diagnosed in about one-third of all dyspeptic patients over 40 years referred for endoscopy (9,19,41) and in 10% to 15% of dyspeptic patients younger than 40 years (3,11,42).

Bleeding: Upper gastrointestinal bleeding is a common alarm symptom in peptic ulcer disease and was present in 16% of patients with gastric ulcers and 12.5% of patients with duodenal ulcers in a study of 2900 unselected dyspeptic patients (6).

Other risk factors: In most studies, the prevalence of *H pylori* infection is greater than 90% in patients with duodenal ulcers and 70% to 90% in patients with gastric ulcers who are not using nonsteroidal anti-inflammatory drugs (NSAIDs) (43). However, recent reports from a community study and an endoscopy centre suggest that the prevalence of *H pylori* in duodenal ulcer disease, especially among white patients, is considerably lower than previously reported (44).

Peptic ulcer disease is a relapsing condition, and a history of peptic ulceration was reported by 20% of patients with peptic ulcers (45). Of patients with duodenal ulcer disease, 60% to 75% relapse within one year and almost 100%

relapse within four years (46). The relapse rate is affected by *H pylori* infection; in patients with uncomplicated peptic ulcers, recurrence rates were reduced to less than 10% one year after successful eradication therapy (47).

The use of NSAIDs is a risk factor for peptic ulcer disease and an important cause of ulcer complications. In a primary care study, the frequency of NSAID use in dyspeptic patients who had an upper gastrointestinal bleeding event in a one-year follow-up study was 78%, compared with only 33% in the group of nonbleeding dyspeptic patients (48). In a study of 235 patients with life-threatening complications of peptic ulceration (death or emergency surgery), 60% had been taking NSAIDs (49).

PROBABILITY OF ORGANIC DYSPESIA IN PATIENTS WITH ALARM FEATURES

Patients with alarm symptoms and features are at a higher probability of having organic disease. The following section summarizes the studies evaluating the diagnostic value of identifying alarm features in dyspeptic patients. Because endoscopy is the diagnostic gold standard for investigating dyspepsia, the majority of studies are completed in patients referred for endoscopy and not in unselected patients presenting in primary care, where the majority of decisions about management are made.

The relation of various symptoms and demographic characteristics with organic dyspepsia, and with peptic ulceration in particular, have been tested in a number of predictive score models. At least 10 different models have been published (21,50-61). Unfortunately, no single model has been thoroughly validated, and the predictive value of the various symptoms and signs is thus unclear. In three different score models (malignancy, peptic ulcer and uncomplicated esophagitis) to detect major dyspepsia (21,54,62), a total of six, five and eight predictors, respectively, were selected. Only one predictor (previous peptic ulcer) was found in all three models, and partial overlap was found for another three predictors (age, vomiting and smoking). In models designed to predict peptic ulceration, a total of 20 different predictors have been identified. Age, smoking habits and relief by antacids or food were selected by most models, but total overlap of these models was not found for any single predictor. This is partially due to inherent problems in the designing and building of score models, but is also explained by the confusing similarity in symptom presentation between patients with organic dyspepsia and patients with functional complaints.

Age: Age has traditionally been viewed as an independent alarm feature. The presence of gastric cancer is very rare below the age of 45 years, while its incidence increases rapidly thereafter in Western nations (22,25,42). Data from endoscopy departments and population studies suggest that age over 40 years is an independent risk factor for organic dyspepsia (24,41,50), although not all studies agree (6).

Recent data suggest that concern about overlooking underlying cancer is not a valid reason for endoscopy in patients younger than 55 years of age – at least in Western nations (22,25). However, if a higher age threshold is used, a substan-

tial number of patients with peptic ulcer disease will likely be missed (23).

Dysphagia: Dysphagia is most commonly related to pathology of the esophagus. In dyspeptic patients reporting dysphagia, 35% to 74% had a relevant endoscopic diagnosis (5,6). Dysphagia is the most common symptom in esophageal cancer (6,22) and is present in 18.6% of patients with esophagitis (6).

A study from 1984 examined 90 patients with true dysphagia, defined as difficulty in swallowing solid foods for at least one week (63). A total of 85% of the patients had an abnormality, the most common being peptic strictures (36%), malignant strictures (26%), hiatal hernias with esophagitis (13%) and dysmotility disorders (7%).

Bleeding: Signs of chronic gastrointestinal bleeding were present in 42% to 53% of patients with clinically relevant disease in trials from endoscopy clinics (5,6). In two large series, the causes of upper gastrointestinal bleeding have been described (64,65). Peptic ulcer disease was the most common cause (36% to 45%), followed by esophageal varices (13% to 15%), gastric erosions (6% to 20%), esophagitis (4% to 8%), Mallory-Weiss tears (2% to 7%) and neoplasms (2.6% to 3.7%).

Iron-deficiency anemia in patients with no obvious signs of bleeding is generally considered to be caused by occult gastrointestinal bleeding (66). In studies evaluating more than 300 patients with iron-deficiency anemia, lesions of the gastrointestinal tract consistent with chronic blood loss were identified in the esophagus, stomach or duodenum (41%) (peptic ulcers or severe esophagitis); the small intestine (3%); and the colon (22%) (colon cancer and large adenomas) (67-70). Careful evaluation of gastrointestinal symptoms help in determining the workup (70,71), although the disease may not be localized by the evaluation of symptoms (68,69). The role of gastrointestinal evaluations in premenopausal women with iron-deficiency anemia is not settled. A recent retrospective study of 186 premenopausal women with iron-deficiency anemia found that 23 (12%) had serious gastrointestinal lesions, of which 50% were malignant (gastric or colonic cancer) (71). Although the design of that study limits its generalizability, it shows that gastrointestinal evaluation can lead to important diagnoses, especially in asymptomatic women in whom the severity of iron deficiency anemia is disproportional to menstrual blood loss (66).

Vomiting: The frequency of the detection of organic disease in dyspeptic patients with severe, persistent vomiting is unknown. In patients with vomiting as the cause of referral, endoscopy demonstrated clinically relevant findings in 40% (5). Vomiting was shown to be a valuable predictor of organic disease in a study evaluating a score model for prediction of the endoscopic diagnosis (21).

Weight loss: Dyspeptic patients reporting a significant (usually greater than 3 kg) and unintended weight loss have a higher probability of having organic dyspepsia than those without significant weight loss. Relevant endoscopic findings were found in 30% to 40% of patients reporting anorexia and weight loss (amount not specified) (5,6), and gastric cancer is

diagnosed significantly more often in patients referred because of loss of appetite and weight loss than in patients without these symptoms at presentation (6).

Other factors associated with increased risk of organic dyspepsia – History of peptic ulcers: In the majority of patients, peptic ulcer disease is a relapsing condition. Thus, a previous peptic ulcer is associated with an increased probability of having organic disease in case of altered symptomatology. In 40.5% of patients with a previous peptic ulcer, a relevant endoscopic diagnosis was made, most commonly a duodenal (20.2%) or a gastric ulcer (13.7%) (6). Previous peptic ulcer disease was also shown to be a valuable predictor of a new peptic ulcer in studies evaluating a score model for prediction of the endoscopic diagnosis (21,54,62).

In most centres patients with apparently benign gastric ulcers are commonly followed-up until complete healing occurs. The risk of overlooking a shift to malignancy is increased if endoscopy is performed during acid suppressive treatment. The prescription of proton pump inhibitors and H₂ blockers without an endoscopic diagnosis may delay or even prevent the diagnosis of early gastric cancer because of rapid symptom control. Avoiding antisecretory drugs one to two weeks before endoscopy does not reduce misclassification (72). A British study showed that one in six patients with gastric cancer had been investigated by endoscopy within the three years before their diagnosis, and the majority of these patients had been on antisecretory medication that may have masked an early stage of the cancer (8).

H pylori: With noninvasive test methods to detect *H pylori*, it is possible to screen patients for the presence of infection before endoscopy. A prospective study by McColl and co-workers (73) demonstrated that a positive *H pylori* test was a powerful predictor of underlying ulcer disease; a peptic ulcer was diagnosed in 47% of infected patients compared with only 5% of noninfected patients.

The relevance of *H pylori* status as a predictor for endoscopic diagnosis in dyspeptic patients has been confirmed in a large number of publications. These studies have all tested the policy of restricting gastroscopy to young patients without alarm features who are seropositive for *H pylori* (73-84). The results of more than 10,000 patients have been reported and the conclusions are remarkably similar: 25% to 33% of the investigations can be saved without overlooking serious pathology (85). It is particularly important to note that no cancers are missed and that the detection rate for peptic ulcers is well above 95%.

Use of NSAIDs and low dose acetylsalicylic acid: The United States Food and Drug Administration reports that symptomatic gastrointestinal ulcerations (pain, bleeding and perforation) occur in approximately 2% to 4% of patients treated with NSAIDs for one year (86). In contrast, endoscopic clinical research reveals that 10% to 20% of patients taking NSAIDs develop gastric ulcerations within the first three months of medication (87-89). The reason for this prevalence is that NSAIDs are extremely common as both over-the-counter and prescribed medications, and that clinical trials using endoscopy are biased by a selection of patients

having an increased risk of peptic ulcers, diseases and complications. The risk of ulceration is equivalent for all types of NSAIDs, but the relative risk (RR) of ulceration is different depending on the type of NSAID used. Ibuprofen (RR 2.0) and diclofenac (RR 4.2) are less harmful, and indomethacin (RR 11.3) and ketoprofene (RR 23.7) are more harmful (90). Other factors contributing to the risk of NSAID-related ulcers are high age (older than 75 years, odds ratio [OR] 8.9; 60 to 75 years, OR 3.5)(91), previous ulcer history (OR 2.5 to 5) (91,92) and dyspeptic symptoms related to NSAID therapy (OR 8.7) (91).

The risk of upper gastrointestinal bleeding caused by acetylsalicylic acid (ASA) is dose-dependent, with an OR of 2.3 for ASA 75 mg and an OR of 3 to 4 for ASA 300 mg daily (93,94). The role of *H pylori* infection as an additional risk factor for peptic ulcers and associated complications in NSAID users has been debated. A recent case-control study showed that current NSAID users with *H pylori* infection had an almost twofold risk of bleeding from a peptic ulcer compared with NSAID users without *H pylori* (95). This is compatible with the results from a randomized trial in which eradication of *H pylori* before starting NSAID therapy reduced the occurrence of peptic ulcer (96). Other studies have failed to show this relation (97-99).

History of reflux and Barrett's metaplasia: Symptoms of gastroesophageal reflux such as heartburn and regurgitation

are very common in the general population (100,101). The prevalence of an underlying organic cause of reflux symptoms is not known, but at least half of the patients with reflux symptoms referred for endoscopy have a normally appearing esophagus (38).

The esophageal complications of chronic gastroesophageal reflux are reflux esophagitis, strictures and Barrett's metaplasia. The risk of developing Barrett's metaplasia is associated with the duration of reflux symptoms (102), with an OR of 6.4 in patients having symptoms for more than 10 years.

Lifestyle-associated risk factors: Smoking increases the risk of peptic ulcer disease and gastric cancer. Both gastric and duodenal ulcerations are more common in smokers than in non-smokers (103,104). In a survey of 1217 unselected patients with dyspepsia, peptic ulcers were found in 24.7% of smokers, compared with 10.7% of nonsmokers. There was a progressive increase in the prevalence of gastric and duodenal ulcerations in ex-smokers, light smokers (fewer than 15 cigarettes per day) and heavy smokers (more than 15 cigarettes per day), compared with nonsmokers (103). Also, gastric carcinoma was more frequent in smokers (3.6%) than in nonsmokers (0.6%) (103); similar results were found in cohort and case-control studies showing a 1.5- to 3.0-fold increase in the risk of gastric cancer among smokers (105,106). Studies of the relation between alcohol consumption and the risk of gastric cancer have been inconclusive (105,106).

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