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Association Between Use of Acid-Suppressive Drugs and Risk of Gastric Cancer

A Nested Case-Control Study

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Abstract

Background: The risk of gastric cancer could be influenced by acid-related diseases or by the use of acid-suppressive drugs, such as histamine H_2 receptor antagonists and proton pump inhibitors (PPIs).

Objective: To assess the association between exposure to acid-suppressive drugs and the risk of gastric cancer.

Methods: A nested case-control study was conducted among people registered in the Quebec health insurance plan (Canada). Cases represented a random sample of subjects diagnosed with gastric cancer between 1995 and 2003 who were matched on age and sex to at least four controls (using incidence density sampling). The index date was the date of cancer diagnosis for the cases, which was the index date for the matched controls. The exposure definition in the 5 years preceding the index date was based on the defined daily doses of acid-suppressive drugs and categorized into quartiles.

Results: The study included 1598 gastric cancer cases and 12 991 controls. The adjusted odds ratios for the association between exposure to acid-suppressive drugs and risk of gastric cancer were 1.47 (95% CI 1.23, 1.76), 1.32 (95% CI 1.10, 1.58), 1.48 (95% CI 1.24, 1.77) and 1.18 (95% CI 0.97, 1.44) for the first, second, third and fourth exposure quartiles, respectively. Similar results were obtained when use of H_2 receptor antagonists and PPIs were assessed separately (odds ratios for the association between PPIs and the risk of gastric cancer were slightly higher compared with H_2 receptor antagonists and risk of gastric cancer).

Conclusions: A minor increase in the risk of gastric cancer was observed if exposure to either H_2 receptor antagonists or PPIs occurred within the past 5 years. However, this association is probably not causal since it is most likely due to confounding by indication.

Background

Although the incidence and mortality of gastric cancer has decreased in the past few decades, it remains the second leading cause of cancer death worldwide.[1,2] The risk of gastric cancer could be affected by long-term irritation of the tissues lining the stomach.[3-5] This effect could be caused by acid-related diseases (ARDs), i.e. those characterized by a high acid content or a mix of acid and pancreatobiliary secretions, which irritate and harm the lining of the stomach.[3-5]

The risk of gastric cancer could also be influenced by the ingestion of different acid-suppressive drugs used for treating ARDs.[3] The first class of these drugs, the histamine H_2 receptor antagonists, introduced in the 1970s, prevents histamine from stimulating acid production. The newer class of drugs used to treat ARD is the proton pump inhibitors (PPIs), which inhibit the gastric parietal cell proton pumps.[6] Thus, H_2 receptor antagonists and PPIs reduce the symptoms of ARDs by reducing acid production in the stomach. Although PPIs are one of the most commonly prescribed classes of medications in the primary care setting and are usually associated with frequent long-term use, the long-term safety of these drugs remains unknown.

There is epidemiological evidence that exposure to acid and mixed refluxates in gastro-oesophageal reflux disease (GORD) increases the likelihood for the development of oesophageal adenocarcinoma.[3,4,7-10] Moreover, the use of acid-suppressive drugs, mainly H_2 receptor antagonists, has not been shown to be associated with the development of gastro-oesophageal cancers. Chow et al.[3] found a significant 2-fold risk of adenocarcinomas of the oesophagus and gastric cardia in patients with a history of oesophageal reflux. This was not observed in patients who used H_2 receptor antagonists. In another study, recurrent symptoms of reflux were strongly associated with the risk of oesophageal adenocarcinoma (odds ratio [OR] 7.7; 95% CI 5.3, 11.4) and adenocarcinoma of the cardia (OR 2.0; 95% CI 1.4, 2.9).[4] Farrow et al.[7] found that the frequency of GORD symptoms was associated with an increased risk of oesophageal adenocarcinoma (OR 5.5 for daily symptoms; 95% CI 3.2, 9.3), but not with oesophageal squamous cell carcinoma, gastric cardia adenocarcinoma and non-cardia gastric adenocarcinoma. In the same study, the use of H_2 receptor antagonists was not associated with any of the four groups of gastro-oesophageal cancers. More recently, Garcia Rodriguez et al.[10] found that oesophagus-related indication for long-term acid-suppressive drugs was associated with an increased risk of oesophageal adenocarcinoma (OR 5.42; 95% CI 3.13, 9.39), whereas peptic ulcer indication was associated with an increased risk of gastric non-cardia adenocarcinoma (OR 4.66; 95% CI 2.42, 8.97).

Although long-term PPI therapy is highly effective and well tolerated when used to control reflux oesophagitis, some authors have observed that the use of PPIs is associated with an increased incidence of gastric corpus mucosal atrophy, which might be a precursor to gastric cancer.[11] However, so far, no evidence demonstrating that the increasing risk of gastric cancer is a result of PPI use has been found. Other investigators have suggested that chronic *Helicobacter pylori* infection might be more significant. In this situation, the PPI-induced hypergastrinaemia and low acidity in the stomach might significantly increase the risk of gastric cancer, especially for those patients with atrophic gastritis.[12] Observations from Carter et al.[13] showed that the formation of atrophic gastritis is associated with the infection of *H. pylori*, not the use of acid-suppressive drugs.

Although the use of H_2 receptor antagonists and PPIs might be markers of an increased risk of oesophageal and gastric adenocarcinoma, rather than being independent causes, the important public health implications of a potential association between acid-suppressive drugs and risk of gastro-oesophageal cancers, particularly with the wide use of these drugs, calls for further studies to shed more light on this issue. Thus, the objective of this study was to assess the association between exposure to acid-suppressive drugs and the risk of developing gastric cancer.

Methods

Source Population

A nested case-control study was conducted among a cohort of subjects registered in the Quebec health insurance plan databases, also known as the Régie de l'Assurance-Maladie du Québec (RAMQ). Two services are covered by the provincial insurance plan, which has been operating since 1969: medical services and pharmaceutical services.[14] The medical services claims database includes information on all physician visits and other medical services offered in private clinics or hospitals to all individuals who have established residence in Quebec, Canada (a population of about 7.4 million in 2003).[15] On the other hand, the pharmaceutical services claims database includes information on all dispensed drugs to all elderly patients in Quebec (>65 years of age), an estimated 0.9 million individuals. Also covered by the RAMQ prescription drug plan are the recipients of social assistance (an estimated 0.55 million). Since 1997, all working residents of Quebec who do not have a private drug insurance plan (an estimated 1.7 million) have also been also covered.[15]

The source population was the dynamic cohort defined by registration with the RAMQ from 1 January 1995 to 31 December 2003, including all people living in Quebec who were eligible for outpatient prescription drug benefits for at least 5 years, and with no prior history of cancer. The study was approved by the ethics committee of the University of Montreal Hospital Centers.

Cases and Controls

For reasons of maintaining confidentiality, RAMQ provided information for a random sample of subjects with first-time diagnosis of gastric cancer between 1 January 1995 and 31 December 2003 (cases). Identification of gastric cancer cases was based on the International Classification of Disease (ICD) codes 151.0–151.9.[16]

For each person diagnosed with gastric cancer, incidence density sampling (with matching on age and sex) was used to select at least four controls from the dynamic source population (individuals covered by the RAMQ prescription drug plan).

Inclusion criteria for cases and controls were a minimum of 5 years of coverage with the RAMQ prescription drug plan and no prior history of cancer. The index date for the cases was the date of cancer diagnosis. For the controls, the index date was the date of cancer diagnosis of the cases to which the controls were matched.

Drug Exposure

Information on all prescribed medications dispensed to cases and their controls were extracted from the RAMQ databases. In these databases, information recorded for each drug claim includes encrypted patient identifiers, drug identifiers, drug format, date when the prescription was dispensed, dosage, number of units dispensed and the duration of the dispensed prescription.

For the purpose of quantifying exposure to acid-suppressive drugs prior to the index date, information on dispensed prescriptions of H_2 receptor antagonists and PPIs in the 5-year period prior to the index date were extracted.

In order to assess the effect of exposure to different acid-suppressive drugs on the risk of gastric cancer, the following three patient group categories were considered (medication of interest): (i) users of any acid-suppressive drug (H_2 receptor antagonists and/or PPIs); (ii) users of H_2 receptor antagonists only, restricted to PPI non-users; and (iii) users of PPIs only, restricted to H_2 receptor antagonist non-users. Two exposure definitions were used to assess the association between exposure to the medication of interest in the 5-year period prior to the index date and the risk of gastric cancer: 'yes/no' and defined daily dose (DDD). Exposure to acid-suppressive drugs in the 6-month period immediately preceding the index date was excluded from all analyses to avoid protopathic bias (i.e. the early symptoms of an undiagnosed gastric cancer could have been the reason for the use of acid-suppressive drugs). This 6-month period was selected using a procedure to

Table I. Characteristics of the gastric cancer cases and their controls

Characteristic	Cases	Controls	p-Value
Total	**1 598**	**12 991**	
Mean age in years (%)	75.5 (9.3)	75.9 (8.8)	0.09
Females [n (%)]	765 (47.9)	6 296 (48.5)	0.66
Year of diagnosis [n (%)]			
1995	173 (10.8)		
1996	142 (8.90)		
1997	162 (10.1)		
1998	166 (10.4)		
1999	169 (10.6)		
2000	162 (10.1)		
2001	203 (12.7)		
2002	214 (13.4)		
2003	207 (13.0)		
Acid-suppressive drugs [n (%)]			
none	919 (57.5)	8 728 (67.2)	<0.0001
histamine H_2 receptor antagonists only	257 (16.1)	1 772 (13.6)	
PPIs only	248 (15.5)	1 402 (10.8)	
any	174 (10.9)	1 089 (8.38)	
In the year prior to date of diagnosis [mean (SD)]:			
number of drug dispensings	41.0 (48.0)	38.5 (50.1)	0.03
total length of hospitalizations (d)	3.66 (10.6)	2.54 (10.5)	0.67
number of visits to GPs	4.89 (5.08)	4.32 (4.53)	<0.0001
number of visits to specialists	9.24 (11.9)	5.65 (9.48)	<0.0001
number of visits to emergency rooms	0.94 (1.91)	0.69 (1.61)	<0.0001

GPs = general practitioners; **PPIs** = proton pump inhibitors; **SD** = standard deviation.

identify the best lag-time to be applied in studies where control for protopathic bias is required.[17]

In the 'yes/no' exposure definition, a subject was considered to be exposed if he/she had at least one dispensed prescription of the medication of interest during the study period (i.e. between 6 months and 5 years prior to the index date). A subject was categorized as unexposed if no prescription of the medication of interest was dispensed during that period.

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a unit of measurement used to standardize the use of different drugs prescribed for the same indication.[18] The DDD exposure definition was calculated by measuring the number of tablets of the dispensed prescriptions of the medication of interest during the study period, adjusted for the DDD for each individual drug. This measure was further categorized into quartiles.

Data Analyses

Conditional logistic regression was performed to calculate matched ORs and 95% confidence intervals. In the final regression models, five measures relating to health services utilization by cases and controls in the 1-year period (between 6 months and 18 months prior to the index date) were included. These measures were the number of dispensed prescriptions for any drug, the total length of hospitalizations and the number of visits to general practitioners (GPs), specialists and emergency rooms. In order to assess the association between exposure to acid-suppressive drugs and risk of different types of gastric cancer, stratified analyses were performed according to the type of gastric cancer diagnosed (i.e. adenocarcinoma of the gastric cardia, other

gastric adenocarcinomas and unspecified gastric adenocarinomas) while using the two exposure definitions, 'yes/no' and DDD. Data management and analyses were done using SAS version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Between 1 January 1995 and 31 December 2003, the RAMQ identified 1598 gastric cancer cases (22% of individuals diagnosed with gastric cancer in Quebec), who were matched to 12 991 controls on age and sex (ranging from 4 to 16 controls per case). The average age of the cases was 75.5 years (standard deviation [SD] 9.3), and 47.9% were female (table I). Compared with the controls, cases were characterized by a significantly higher number of dispensed prescriptions for any drug as well as the number of visits to GPs, specialists and emergency rooms. No significant difference was found for the total length of hospitalizations prior to the diagnosis (table I).

Table II summarizes the results of the association between the risk of gastric cancer and the use of acid-suppressive drugs as measured by the 'yes/no' exposure definition. The adjusted OR for receiving at least one dispensed prescription of either H_2 receptor antagonists or PPIs and the risk of gastric cancer was 1.37 (95% CI 1.22, 1.53). In the analyses conducted with H_2 receptor antagonists as the medication of interest (restricted to PPI non-users), the adjusted ORs ratio was 1.28 (95% CI 1.08, 1.51), whereas it was 1.46 (95% CI 1.22, 1.74) when PPIs were considered as the medication of interest (restricted to H_2 receptor antagonist non-users).

The results of the association between exposure to acid-suppressive drugs, as measured by the DDD exposure definition, and the risk of gastric cancer are presented in table III. The adjusted ORs of the four quartiles of DDD exposure definition of either H_2 receptor antagonists or PPIs and risk of gastric cancer were 1.47 (95% CI 1.23, 1.76) for the first quartile, 1.32 (95% CI 1.10, 1.58) for the second quartile, 1.48 (95% CI 1.24, 1.77) for the third quartile and 1.18 (95% CI 0.97, 1.44) for the fourth quartile. When the restriction based on the type of the acid-suppressive drug was applied, similar results were found. However, slightly higher ORs were observed for the association between PPIs and the risk of gastric cancer, compared with that of H_2

Table II. Crude and adjusted odds ratios (ORs) for the association between the use of acid-suppressive drugs (any, histamine H_2 receptor antagonists only and proton pump inhibitors [PPIs] only) and the risk of gastric cancer, as measured by the 'yes/no' exposure definition

Prescriptions	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
H_2 receptor antagonists and/or PPIs	**1 598**	**12 991**		
None	*919*	*8 728*	*1.00 (referent)*	*1.00 (referent)*
At least one	679	4 263	1.51 (1.36, 1.68)	1.37 (1.22, 1.53)
Other variables in the model				
No. of drug dispensings				1.00 (0.98, 1.01)
Total length of hospitalizations (d)				1.01 (1.00, 1.01)
Visits to GPs				1.02 (1.00, 1.03)
Visits to specialists				1.02 (1.02, 1.03)
Visits to emergency rooms				1.03 (1.00, 1.06)
H_2 receptor antagonists	**1 097**	**7 635**		
None	*852*	*6 277*	*1.00 (referent)*	*1.00 (referent)*
At least one	245	1 358	1.33 (1.14, 1.55)	1.28 (1.08, 1.51)
PPIs	**1 071**	**7 158**		
None	*837*	*6 093*	*1.00 (referent)*	*1.00 (referent)*
At least one	234	1 065	1.60 (1.36, 1.87)	1.46 (1.22, 1.74)

a Adjustment was done for the following variables during the year prior to the diagnosis: number of prescriptions to any drug, total length of hospitalizations and number of visits to GPs, specialists and emergency rooms.

GPs = general practitioners.

Table III. Crude and adjusted odds ratios (ORs) for the association between the use of acid-suppressive drugs (any, histamine H_2 receptor antagonists only and proton pump inhibitors [PPIs] only) and the risk of gastric cancer, as measured by the defined daily dose definition

Prescriptions (number of tablets)	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
H_2 receptor antagonists and/or PPIs	**1 598**	**12 991**		
None	*919*	*8 728*	*1.00 (referent)*	*1.00 (referent)*
Q1 (0–42)	175	1 051	1.58 (1.33, 1.88)	1.47 (1.23, 1.76)
Q2 (43–149)	166	1 075	1.47 (1.23, 1.75)	1.32 (1.10, 1.58)
Q3 (150–516)	186	1 049	1.68 (1.42, 2.00)	1.48 (1.24, 1.77)
Q4 (>517)	152	1 088	1.33 (1.11, 1.59)	1.18 (0.97, 1.44)
H_2 receptor antagonists	**1 097**	**7 635**		
None	*852*	*6 277*	*1.00 (referent)*	*1.00 (referent)*
Q1 (0–29)	55	329	1.23 (0.92, 1.65)	1.17 (0.86, 1.59)
Q2 (30–86)	78	374	1.54 (1.19, 1.98)	1.42 (1.09, 1.85)
Q3 (87–299)	55	317	1.28 (0.95, 1.72)	1.25 (0.92, 1.70)
Q4 (>300)	57	338	1.24 (0.93, 1.66)	1.24 (0.92, 1.69)
PPIs	**1 071**	**7 158**		
None	*837*	*6 093*	*1.00 (referent)*	*1.00 (referent)*
Q1 (0–41)	65	283	1.67 (1.26, 2.21)	1.66 (1.24, 2.23)
Q2 (42–119)	53	244	1.58 (1.16, 2.15)	1.37 (1.00, 1.88)
Q3 (120–479)	68	276	1.79 (1.36, 2.36)	1.57 (1.17, 2.10)
Q4 (>580)	48	262	1.33 (0.97, 1.83)	1.20 (0.85, 1.70)

a Adjustment was done for the following variables during the year prior to the diagnosis: number of prescriptions to any drug, total length of hospitalizations and number of visits to general practitioners, specialists and emergency rooms.

Q = quartile.

receptor antagonists and risk of gastric cancer (table III).

Finally, table IV summarizes the results of the analyses stratified by the three types of gastric cancer diagnosed: adenocarcinoma of the gastric cardia, other gastric adenocarcinomas and unspecified gastric adenocarcinomas. No statistically significant association between the adenocarcinoma of the gastric cardia and the two exposure definitions of acid-suppressive drugs were demonstrated. For the other gastric adenocarcinomas, the ORs for the association with receiving at least one dispensing of any acid-suppressive drugs (H_2 receptor antagonists and/or PPIs) and PPIs only were 1.57 (95% CI 1.14, 2.16) and 1.96 (95% CI 1.22, 3.17), respectively. Similarly, exposure to any acid-suppressive drugs (H_2 receptor antagonists and/or PPIs) and to PPIs only, as measured by the DDD exposure definition, was associated with the risk of developing other gastric adenocarcinomas. Finally, regarding the unspecified gastric adenocarcinomas, the associations with exposure to acid-suppressive drugs, as measured by the two exposure definitions, were very similar to those described in table II and table III for the association with gastric cancer.

Discussion

In this case-control study, exposure to acid-suppressive drugs within the past 5 years was significantly associated with the risk of gastric cancer in comparison to those who did not use these drugs during the same period. In the analyses stratified by the type of gastric cancer, exposure to acid-suppressive drugs was found to be associated with the unspecified gastric adenocarcinomas, inconsistently associated with the other gastric adenocarcinomas and unassociated with the adenocarcinomas of the cardia. Similar results were found for each of the two classes of acid-suppressive drugs (PPIs and H_2 receptor antagonists) when analysed separately.

Almost all the studies that have assessed the association between exposure to acid-suppressive drugs and risk of gastric cancer were restricted to the adenocarcinomas of the gastric cardia. In 2000, Farrow et al.[7] found no association between the use of

Table IV. Adjusted odds ratios (ORs)[a] for the association between the use of acid-suppressive drugs (any, histamine H_2 receptor antagonists only and proton pump inhibitors [PPIs] only) and the risk of gastric cancer (stratified by the classification of the gastric adenocarcinomas), as defined by the 'yes/no' and the defined daily dose exposure definitions

Prescriptions (number of tablets)	Gastric cardia adenocarcinoma [OR (95% CI)]	Other adenocarcinoma [OR (95% CI)]	Unspecified adenocarcinoma [OR (95% CI)]
H_2 receptor antagonists and/or PPIs			
None	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
At least one	0.86 (0.53, 1.40)	1.57 (1.14, 2.16)	1.39 (1.22, 1.57)
None	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q1 (0–42)	1.46 (0.74, 2.90)	1.63 (0.96, 2.75)	1.45 (1.19, 1.77)
Q2 (43–149)	0.54 (0.21, 1.40)	1.20 (0.70, 2.05)	1.42 (1.16, 1.73)
Q3 (150–516)	0.77 (0.33, 1.78)	1.89 (1.16, 3.08)	1.48 (1.22, 1.80)
Q4 (>517)	0.73 (0.31, 1.70)	1.66 (0.96, 2.86)	1.17 (0.93, 1.45)
H_2 receptor antagonists			
None	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
At least one	1.43 (0.74, 2.76)	1.37 (0.86, 2.17)	1.26 (1.05, 1.51)
None	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q1 (0–29)	0.74 (0.17, 3.34)	1.90 (0.92, 3.90)	1.07 (0.75, 1.52)
Q2 (30–86)	2.25 (0.87, 5.89)	0.89 (0.33, 2.44)	1.44 (1.07, 1.92)
Q3 (87–299)	1.57 (0.33, 7.49)	1.40 (0.62, 3.16)	1.23 (0.87, 1.73)
Q4 (>300)	1.18 (0.35, 3.96)	1.25 (0.53, 2.96)	1.28 (0.91, 1.80)
PPIs			
None	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
At least one	0.58 (0.26, 1.32)	1.96 (1.22, 3.17)	1.49 (1.23, 1.82)
None	*1.00 (referent)*	*1.00 (referent)*	*(1.00 referent)*
Q1 (0–41)	1.39 (0.44, 4.38)	1.98 (0.81, 4.82)	1.69 (1.22, 2.34)
Q2 (42–119)	0.24 (0.03, 1.89)	1.13 (0.41, 3.11)	1.53 (1.09, 2.16)
Q3 (120–479)	0.74 (0.20, 2.66)	2.48 (1.16, 5.31)	1.53 (1.10, 2.13)
Q4 (>580)	0.06 (0.00, 2.96)	2.48 (1.04, 5.95)	1.18 (0.80, 1.73)

a Adjustment was done for the following variables during the year prior to the diagnosis: number of prescriptions to any drug, total length of hospitalizations and number of visits to general practitioners, specialists and emergency rooms.

Q = quartile.

H_2 receptor antagonists and risk of gastro-oesophageal cancer (including adenocarcinoma of the gastric cardia and non-cardia gastric adenocarcinoma). Similarly, no association was reported between the frequency of using H_2 receptor antagonists and risk of adenocarcinoma of the gastric cardia in a study conducted by Chow et al.[3] The results of these studies are consistent with the findings of our study in which H_2 receptor antagonists use was not significantly associated with the risk of gastric cardia and other gastric adenocarcinomas (table IV).

The association between the use of PPIs and the risk of gastro-oesophageal cancers has been assessed among patients with Barrett's oesophagus.[19,20] The reason for this emphasis is the fact that exposure of the oesophagus to an acid or an acid and pancreatobiliary refluxate is important in the pathogenesis of Barrett's oesophagus, and possibly in the progression of Barrett's oesophagus to dysplasia and carcinoma.[19,20] Garcia Rodriguez et al.[10] found an increased risk of gastric non-cardia adenocarcinoma with >3 years of use of both classes of acid-suppressive drugs, which is consistent with our reported results.

One of the strengths of this study is that the potential for recall bias in terms of exposure to acid-suppressive drugs was eliminated because pre-recorded exposure histories maintained by the RAMQ prescription claims database were used. This database has been found to be both accurate

and reliable.[14] In addition, the large sample size allowed for reasonably precise estimates for the effects of using acid-suppressive drugs on the risk of gastric cancer.

There were several limitations to this study. Misclassification of the adenocarcinomas of the lower oesophagus and the gastric cardia may have occurred. This was related to the difficulty of determining the exact site of origin for tumours arising near the gastro-oesophageal junction.[21] Nevertheless, this misclassification is expected to be non-differential in terms of exposure to acid-suppressive drugs. Although exposure to acid-suppressive drugs was characterized using classes of drugs rather than individual drugs, the assumption that all the drugs in each class would have similar effects on the risk of gastric cancer was considered.[22] Exposure misclassification may have occurred because outpatient-dispensed prescription data were used without knowledge of whether the patients actually consumed the dispensed medications. Nevertheless, such an exposure misclassification is expected to be non-differential in terms of the disease status (cases and controls). No information on acid-suppressive drugs dispensed during hospitalizations or as samples in physicians' offices was available; however, the amounts were probably small relative to the amounts used in calculating exposure. Moreover, patients who received acid-suppressive drugs in hospitals or as samples in physicians' offices are very likely to continue treatment, and thus be identified as 'exposed'. Another limitation is the possibility of protopathic bias; cancer symptoms may have resulted in an acid-suppressive drug prescription. However, excluding all dispensed prescriptions in the 6 months prior to the index date was shown to control adequately for this type of bias (separate analyses were carried out to identify the best lag-time to be applied for the purpose of controlling for protopathic bias).[17] Finally, the results could have been affected by the lack of control for some potentially confounding factors (such as smoking, alcohol consumption and infection with *H. pylori*) due to their absence from the RAMQ databases.[23]

The results of this study raise an important question which needs to be addressed: does exposure to acid-suppressive drugs (H_2 receptor antagonists or PPIs) cause gastric cancer in the 5-year period following exposure? The answer to such a question should be addressed in light of some criteria that are usually used to establish causation.[24] Restriction in our study to the 5-year period prior to the date of diagnosis, especially with a long latency period of gastric cancer (may be 20 years or more), makes it difficult establish causation. Moreover, the weak association between acid-suppressive drugs and risk of gastric cancer, and the lack of a dose-response trend are not suggestive of a cause-effect relationship. Finding similar effects for receiving dispensed prescriptions of either type of acid-suppressive drug (H_2 receptor antagonists or PPIs) in association with the risk of gastric cancer also supports a non-causal association. If the observed effect was due to the carcinogenicity of the acid-suppressive drugs, the pattern of the effect of the two classes of acid-suppressive drugs on the risk of gastric cancer would have been different because it is unlikely that the two classes (with different molecules) have a similar carcinogenic effect. An alternative plausible explanation of the findings would be a distortion in the observed risk estimates due to confounding by indication, a bias frequently encountered in observational epidemiological studies of drug effects. For the indication to a certain treatment to be a confounding variable, it must be associated with the risk of the outcome, as well as with the allocation of the treatment. Acid-suppressive drugs are prescribed for the relief of ARD symptoms (i.e. indication), which in turn have been reported to be associated with the risk of gastric cancer.[3-5] Thus, subjects who suffer from ARD symptoms are more likely to be prescribed acid-suppressive drugs, and thus would be found to be at an increased risk of gastric cancer, which might be the effect of the ARD rather than the drugs prescribed to treat the symptoms of ARD.

In 1996, Hansson et al.[25] demonstrated in a large cohort study, that gastric ulcer disease and gastric cancer had common aetiological factors, probably atrophic gastritis induced by *H. pylori*. They also

proposed factors associated with duodenal ulcer disease that appeared to be protective against gastric cancer.[25] However, La Vecchia et al.[26] later confirmed, by a case-control study, that the risk of gastric cancer is increased after gastric ulcer. They did not support, however, a reduced risk after duodenal ulcer. This could be due to variable baseline characteristics of the populations studied, or to the different role and impact of *H. pylori* and other determinants of duodenal ulcer and gastric cancer in various countries.[26] This might further support our findings that the minor increase in the risk of gastric cancer with exposure to either H_2 receptor antagonists or PPIs occurred within the past 5 years was most likely due to confounding by indication.

Conclusion

Although the rates of adenocarcinomas of the stomach have remained stable or have decreased during the past few decades, the rates of adenocarcinomas of the gastric cardia have risen steeply during this time period.[27-30] Acid-suppressive drugs are prescribed for different reasons: GORD, peptic ulcer and control of *H. pylori*. Moreover, these drugs are also prescribed to relieve the dyspepsia symptoms caused by NSAIDs commonly taken for conditions such as arthritis. In conclusion, a slight elevation in the risk of gastric cancer was found if exposure to either H_2 receptor antagonists or PPIs occurred within the past 5 years, in comparison to those who did not use these drugs during the same period. However, this association is probably not causal since it is most likely due to confounding by indication. Further research is required to clarify this important public health issue.

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References

1. Roder D. The epidemiology of gastric cancer. Gastric Cancer 2002; 5 (1): 5-11
2. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003; 53: 5-26
3. Chow W, Finkle W, McLaughlin J, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 1995; 274 (6): 474-7
4. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340 (11): 825-31
5. Engel L, Chow W, Vaughan T, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003; 95: 1404-13
6. Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. J Am Pharm Assoc 2000; 40: 52-62
7. Farrow D, Vaughan T, Sweeney C, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control 2000; 11: 231-8
8. Enzinger P, Mayer R. Esophageal Cancer. N Engl J Med 2003; 349: 2241-52
9. Chang J, Katzka D. Gastroesophageal reflux diseases, Barrett esophagus, and esophageal adenocarcinoma. Arch Intern Med 2004; 164: 1482-8
10. Garcia Rodriquez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. Gut 2006; 55 (11): 1538-44
11. Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. Gastroenterology 2000; 118: 661-9
12. Uemura N, Okamoto S, Yamamoto S. *H. pylori* infection and the development of gastric cancer. Keio J Med 2002; 51: 63-8
13. Carter M, Katz DL, Haque S, et al. Does acid suppression by antacids and H2 receptor antagonists increase the incidence of atrophic gastritis in patients with or without *H. pylori* gastritis. J Clin Gastroenterol 1999; 29: 183-7
14. Tamblyn R, Lavoie G, Petrella L, et al. The use of prescription claims databases in pharmaco-epidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995; 48: 999-1009
15. Régie de l'Assurance Maladie du Québec. Statistiques annuelles 2003. Quebec City: Quebec Government, 2003
16. WHO. International classification of diseases. 9th rev (ICD-9). Geneva: WHO, 1977
17. Tamim H, Tahami A, LeLorier J. Application of lag-time into exposure definitions to control protopathic bias. Pharmacoepidemiol Drug Saf 2007; 16 (3): 250-8
18. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2001 [online]. Available from URL: http://www.whocc.no/atcddd [Accessed 2008 May 1]
19. Hillman L, Chiragakis L, Shadbolt B, et al. Proton pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004; 180: 387-91

20. El-Serag H, Aguirre T, Davis S, et al. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol 2004; 99: 1877-83
21. Corley D, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. J Natl Cancer Inst 2004; 96 (18): 1383-71
22. Vanderhoff B, Tahboub R. Proton pump inhibitors: an update. Am Fam Physician 2002; 66 (2): 273-80
23. Alberts SR, Cervantes A, van de Velde CJ. Gastric cancer: epidemiology, pathology and treatment. Ann Oncol 2003; 14 Suppl. 2: 31-6
24. Bradford-Hill A. The environment and disease: association or causation? Proc R Soc Med 1965; 58: 295-30
25. Hansson LE, Nyren O, Hsing AW, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. N Engl J Med 1996; 335: 242-9
26. La Vecchia C, Braga C, Negri E, et al. Risk of stomach cancer in patients with gastric or duodenal ulcer. Eur J Cancer Prev 1997; 6: 20-3
27. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265 (10): 1287-9
28. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J Cancer Prev 1992; 1 (3): 265-9
29. Morales TG. Adenocarcinoma of the gastric cardia. Dig Dis 1997; 15 (6): 346-56
30. Roder D. The epidemiology of gastric cancer. Gastric Cancer 2002; 5 (1): 5-11

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