

Gastric cardia adenocarcinoma in Taiwanese men: Positive associations due to selection bias

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Abstract

The factors associated with an increase in gastric cardia adenocarcinoma are poorly understood. Environmental factors such as *Helicobacter pylori* (*H. pylori*) infection and diet have been hypothesized to play a role in the recently increased risk of this disease, but additional studies are needed. In conducting studies to establish the relationship between potential risk factors and gastric cardia adenocarcinoma, it is necessary to carefully consider the role of bias. In a recently published study, the reported associations between *H. pylori* as well as post-meal physical exertion and gastric cardia adenocarcinoma may have been greatly influenced by selection bias.

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Key words: *Helicobacter pylori*; Gastric cardia adenocarcinoma; Gastric cancer; Selection bias

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TO THE EDITOR

The positive association between *Helicobacter pylori* (*H. pylori*) infection and development of non-cardia gastric cancers is well established^[1,2]. Although various observational studies have been conducted to elucidate the roles of *H. pylori* and other environmental factors in the development of cancer in the gastric cardia^[3], these roles are still not well defined and therefore additional studies are needed.

A recent hospital based case-control study conducted by Chen *et al*^[4] attempted to address these roles, reporting a positive association between gastric cardia adenocarcinoma and *H. pylori* infection. Specifically, the study found that men with gastric cardia adenocarcinoma are almost three times more likely to have antibodies against *H. pylori* and also three times more likely to have conducted work or exercise after meals^[4]. While the authors did recognize that their conclusion may have been distorted by differential misclassification due to recall bias, the reported associations could also be explained by selection bias called exclusion bias.

Controls were cancer-free, inpatients from family medicine departments including inpatients reporting to the hospital for a general check-up^[4]. Furthermore, controls with "stomach-related" diseases were excluded from participating in the study^[4]. In order to prevent selection bias, controls should be selected so that they have a distribution of exposures similar to the population from which

cases arise^[5]. Rothman *et al*^[5] indicate that the exclusion of controls presenting with illness relating to and after the exposure “reduces the prevalence of the exposure in the controls ... hence biases the effect estimates upward”. Although the authors did not specify which stomach-related diseases were excluded, *H. pylori* infection has been identified as a major risk factor in the development of many stomach-related issues such as chronic gastritis, peptic ulcer disease and gastric adenocarcinoma^[6]. Furthermore, the development of precancerous lesions is preceded by a variety of stomach-related symptoms and factors including *H. pylori* infection possibly 20 years prior to the event^[1]. Hence, if control subjects with any of the aforementioned stomach-related diseases were excluded from the present study, fewer controls with antibodies against *H. pylori* would be identified compared to the study cases (men with gastric cardia adenocarcinoma). By excluding control subjects with stomach-related diseases, the authors inadvertently created an under representation of *H. pylori* in the control series compared to the population from which cases arose, which could explain the observed positive association between *H. pylori* infection and gastric cardia adenocarcinoma^[5].

Case-control studies have the potential to be internally valid and provide an efficient and cost effective means to estimate exposure-outcome associations, especially

for rare outcomes such as those in the present study. Of utmost importance in this and all studies, utilizing the case-control design, however, is the requirement to carefully select control subjects to avoid distorted estimates of effect for which post-study statistical analyses cannot ameliorate.

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