Estrogen and Risk of Gastric Cancer: A Protective Effect in a Nationwide Cohort Study of Patients with Prostate Cancer in Sweden

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Abstract

Background: The global pattern of male predominance in gastric cancer incidence remains unexplained. We tested the hypothesis that estrogen prevents gastric cancer in a cohort of men heavily exposed to estrogen.

Methods: We conducted a nationwide cohort study of men with a diagnosis of prostate cancer recorded in the Swedish Cancer Register in 1961-2000. Because estrogen therapy was the treatment of choice for prostate cancer in Sweden between 1950 and 1980, cohort members diagnosed earlier than 1980 were considered exposed to estrogen. Standardized incidence ratios (SIR) estimated relative risk. Complete follow-up was achieved through cross-linkages within the cancer register and the Swedish nationwide registers of emigration and causes of death.

Results: In 515,961 person-years of follow-up, we observed 304 gastric cancers as compared with 349 expected for the cohort members in the predefined "exposed" period 1961-1980, rendering a 13% decreased risk (SIR, 0.87; 95% confidence interval (95% CI), 0.78-0.98). Among patients with a latency of ≥15 years after a prostate cancer diagnosis in 1961-1980, SIR was 0.57 (95% CI, 0.30-0.97), suggesting a dose-response relation. Similarly, reduced risks were found for cardia cancer and noncardia gastric cancer. No decreased risk was found for the cohort members in 1981-2000, when estrogen treatment was less common (SIR, 0.99; 95% CI, 0.89-1.11).

Conclusions: Our study indicates a reduced risk of gastric cancer in a male cohort exposed to estrogen. These results support the hypothesis that estrogen may prevent gastric cancer, but additional studies are warranted. (Cancer Epidemiol Biomarkers Prev 2004;13(12):2203–7)

Introduction

Despite the generally decreasing incidence of gastric adenocarcinoma during the last decades, this cancer remains a major health hazard. Worldwide, gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths (1-3). The etiology of gastric cancer is multifactorial, and differences in the exposure to a range of environmental risk factors, such as infection with Helicobacter pylori, dietary exposures, and tobacco smoking, are believed to account for much of the marked variation seen in the incidence of gastric cancer over time and between populations (3, 4). Several issues about the etiology of gastric cancer remain unsolved, and recent reports on risk factor profiles and increasing incidence rates of gastric cardia adenocarcinoma indicate that noncardia and cardia gastric cancer are two separate entities (5-9). One of the most puzzling observations is the male predominance among patients with adenocarcinoma of all sites of the stomach (3, 8, 10). This feature is not clearly explained by sex differences in the distribution of known risk factors. The male-to-female ratio of gastric cancer has recently been studied in a worldwide perspective (11). A unique global pattern of the age-group-specific male-to-female ratio was seen for gastric adenocarcinoma, similar in populations with low and high incidence rates. This pattern has remained unchanged over decades, seemingly unaffected by the decreasing incidence rates of gastric cancer, and was not observed in any other gastrointestinal cancer (11). The authors suggested that this global phenomenon might be due to an apparent 10- to 15-year delay in onset of gastric cancer of the intestinal subtype in females compared with males. A hypothesis that might explain these findings is that the female sex hormone estrogen to some extent protects women against gastric cancer. Only a few epidemiologic studies have addressed the role of sex hormones in the etiology of gastric cancer; they have mainly investigated the association between menstrual or reproductive factors among women and the risk of gastric cancer, and the results have been contradictory (12-16).

To test the hypothesis that estrogen protects against the development of gastric cancer, we identified a large cohort of men exposed to therapy with high doses of estrogen, that is, men with prostate cancer diagnosed in Sweden during the period 1961 and 1980 (17). We assessed the risk of gastric cancer in this cohort compared with the entire comparable background population of Sweden.

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Materials and Methods

Design. The methods used in this cohort study have been described elsewhere (18). In brief, we conducted a population-based, nationwide, historical cohort study covering January 1, 1961, through December 31, 2000, in Sweden. The cohort consisted of all Swedish residents who received a diagnosis of prostate cancer (International Classification of Diseases, Seventh Revision [ICD-7] = 177) and were included in the national Swedish Cancer Register during the period 1961-2000. The Swedish Cancer Register was founded in 1958 but did not encompass the entire country until 1960; therefore, we started the study period in 1961. The Swedish Cancer Register has a completeness rate of 98% for gastric cancer according to validation studies (19, 20). The National Registration Numbers, 10-digit unique personal identifiers assigned to all Swedish residents, were used to allow complete follow-up in nationwide Swedish registers. We did cross-linkage within the cancer register as well as the registers of emigration and causes of death throughout the study period. The cohort members were followed up until the earliest occurring event of any of the following end points: (a) primary gastric cancer (ICD-7 151), (b) emigration, (c) death, or (d) end of study period (December 31, 2000). Person-years were calculated from the date of prostate cancer diagnosis to the date of the first end point. We excluded the first year of follow-up after the prostate cancer diagnosis in the main analyses to limit the effect of surveillance bias, that is, patients with a newly diagnosed prostate cancer could be more likely to have another cancer detected due to the diagnostic evaluation of their prostate cancer.

Statistical Analyses. The standardized incidence ratio (SIR; the ratio of the observed to the expected number of newly diagnosed gastric cancers) was used as a measure of relative risk. The expected number of cases was calculated by multiplying the observed number of person-years by age- and calendar year-specific incidence rates derived from the entire Swedish male population, using 5-year intervals. The 95% confidence interval (95% CI) of the SIR was calculated under the assumption that the number of cases followed a Poisson distribution (21). The methods of treating prostate cancer differed considerably between the decades preceding the year 1980 compared with the years after, that is, estrogen therapy was the predominant treatment strategy before 1980 (17). Therefore, we decided a priori to stratify the analyses into the “exposed” period 1961-1980 and the “less exposed” period 1981-2000 to evaluate any differences in the risk of a gastric cancer. These results were further stratified with regard to latency interval between prostate cancer diagnosis and gastric cancer diagnosis to assess any dose-response relation. We also did separate analyses for the two main anatomic subsites of the stomach [i.e., in the gastric cardia (ICD-7 151)] and distal to the gastric cardia. Because complete specific recordings of the gastric subsite cardia in the Swedish Cancer Register did not start until the year 1970, we stratified into the period 1970-1980 and 1981-2000 for this specific subsite analysis.

Results

Study Participants. A total of 148,238 patients constituted the final cohort of Swedish men with a diagnosis of prostate cancer, together contributing with 515,961 person-years at risk. The cohort members were followed up for a median of 3.0 years. The mean age at entry (i.e., age at prostate cancer diagnosis) was 74 years. The prostate cancer was histologically verified in 92% of the patients.

Risk of Gastric Cancer. After the predetermined exclusion of the first year of follow-up, we observed 612 gastric cancers in the cohort during the study period compared with 658 expected (SIR, 0.93; 95% CI, 0.86-1.01). After stratification into periods, a statistically significant 13% reduced risk of a gastric cancer was revealed among patients receiving a prostate cancer diagnosis in the exposed period 1961-1980 (SIR, 0.87; 95% CI, 0.78-0.98), whereas no association was found among the group diagnosed during the less exposed period 1981-2000 (SIR, 0.99; 95% CI, 0.89-1.11; Table 1). The difference between the two periods almost reached the level of statistical significance (P = 0.10). Analysis by latency interval after diagnosis of prostate cancer revealed increasing protective effects with longer latency before initiation of estrogen therapy.

Table 1. SIR with 95% CI of gastric adenocarcinoma in a cohort of Swedish men with a diagnosis of prostate cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Period</th>
<th>No. of person-years at risk</th>
<th>Median follow-up time (y)</th>
<th>No. of expected cases of gastric cancer</th>
<th>No. of observed cases of gastric cancer</th>
<th>SIR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total gastric cancer</td>
<td>1961-1980 (estrogen exposed)</td>
<td>211,099</td>
<td>2.9</td>
<td>348.83</td>
<td>304</td>
<td>0.87 (0.78-0.98)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>1981-2000 (estrogen less exposed)</td>
<td>304,862</td>
<td>3.1</td>
<td>309.72</td>
<td>308</td>
<td>0.99 (0.89-1.11)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>1961-2000</td>
<td>515,961</td>
<td>3.0</td>
<td>658.56</td>
<td>612</td>
<td>0.93 (0.86-1.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cardia</td>
<td>1970-1980 (estrogen exposed)</td>
<td>144,289</td>
<td>3.3</td>
<td>18.55</td>
<td>13</td>
<td>0.70 (0.57-1.20)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>1981-2000 (estrogen less exposed)</td>
<td>305,215</td>
<td>3.3</td>
<td>50.73</td>
<td>58</td>
<td>1.14 (0.87-1.48)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>1970-1981 (estrogen exposed)</td>
<td>144,008</td>
<td>3.3</td>
<td>190.93</td>
<td>165</td>
<td>0.86 (0.74-1.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>Noncardia</td>
<td>1981-2000 (estrogen less exposed)</td>
<td>304,933</td>
<td>3.1</td>
<td>259.28</td>
<td>250</td>
<td>0.96 (0.85-1.09)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

NOTE: Data stratified into two periods. The predominant treatment for prostate cancer in the years before 1980 was estrogen therapy. First year of follow-up was excluded.

*P* within groups of gastric cancer for evaluating difference in SIR between periods.

† For definition of exposed and less exposed see Materials and Methods.

‡ Registration of the gastric subsite cardia became complete in the year 1970 in the Swedish Cancer Register.

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Table 2. SIR and 95% CI for gastric adenocarcinoma among men with prostate cancer by period and latency interval

<table>
<thead>
<tr>
<th>Latency interval after prostate cancer diagnosis (y)</th>
<th>1961-1980 (estrogen exposed)*</th>
<th>1981-2000 (estrogen less exposed)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed SIR (95% CI)</td>
<td>Observed SIR (95% CI)</td>
</tr>
<tr>
<td>1-4</td>
<td>160</td>
<td>0.87 (0.74-1.01)</td>
</tr>
<tr>
<td>5-9</td>
<td>95</td>
<td>0.94 (0.76-1.15)</td>
</tr>
<tr>
<td>10-14</td>
<td>36</td>
<td>0.89 (0.62-1.23)</td>
</tr>
<tr>
<td>15+</td>
<td>13</td>
<td>0.56 (0.30-0.96)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Prostate cancer was predominantly treated with estrogen in the years before 1980. Number of observed cases presented for each latency interval.
*For definition of exposed and less exposed see Materials and Methods.

interval during the exposed period but not in the less exposed period (Table 2). This could indicate a dose-response relation between duration of estrogen exposure and reduced risk of gastric cancer, but the trend was not statistically significant (Table 2). In the analysis of anatomic subsite, reduced risks were found among patients in the exposed stratum of 1970-1980 of both gastric cardia cancer (SIR, 0.70; 95% CI, 0.37-1.20) and noncardia cancer (SIR, 0.86; 95% CI, 0.74-1.01). No decreased risks were found during the later less exposed period (Table 1).

Discussion

Our population-based Swedish cohort study, designed to detect possible effects of estrogen in the etiology of gastric cancer, revealed a reduced risk of gastric cancer among a cohort of patients with prostate cancer of whom most had received estrogen treatment.

Some methodologic aspects of our study deserve attention. Because the Swedish Cancer Register is nationwide and virtually complete since the early 1960s, we could use the entire male population of Sweden during a long period as the base for our cohort, rendering a follow-up of a substantial number of person-years at risk, which reduces the risk of bias or chance errors. Loss to follow-up is the main source of error in many large cohort studies. However, our ability to do precise record linkages to the well-functioning and continuously updated registries of causes of death and emigration vouch for a virtually complete follow-up in our study.

A potential shortcoming of our study is that information about the specific estrogen exposure of an individual cohort member was not available, which introduces risk of misclassification of the exposure. Our assumption of high exposure to estrogen in the early part of our cohort with prostate cancer has a scientific foundation, however. Estrogen therapy or bilateral orchietomy was the available standard treatment for prostate cancer during the period 1950-1980 in many countries, including Sweden (17, 22-24), but orchietomy gained little popularity in Sweden during these years (17). Hence, most patients diagnosed with a prostate cancer in Sweden during the decades before 1980 received estrogen treatment for long periods, usually until death, regardless of the tumor stage (17). In the years following 1980, the treatment of prostate cancer in Sweden became more heterogeneous: radical prostatectomy, radiation therapy, and cytotoxic drugs were added to the therapeutic alternatives (17). Therefore, patients diagnosed after 1980 received estrogen to a lesser extent than those diagnosed in earlier years. Based on this information we decided, a priori, to stratify our analyses into two separate periods rather than a continuum to improve the precision of our estimates of the cohort’s exposure to estrogen. It is important to stress that this decision was made well ahead of the start of the analyses, and no other cutoff points in time were considered. The remaining exposure misclassification would only dilute the relative risk estimates toward the null (25).

Similarly, although misclassification of the diagnosis of gastric cancer should be unusual due to the high quality of the Swedish Cancer Register (19), any misclassification of the diagnosis of gastric cancer should be nondifferential with regard to the exposure and, at the most, introduce bias that dilutes the association toward the null. Therefore, the reduced risk of gastric cancer found in our study is rather likely to have been underestimated and could not be explained by misclassification of the exposure or the outcome.

A potential limitation of our study is the lack of adjustment for some potential confounding factors, including tobacco smoking, H. pylori infection, and dietary habits. To evaluate the effect of tobacco smoking on the results we estimated the cohort members’ relative risk of lung cancer, which is strongly linked to exposure to tobacco smoking. We found reduced risks of lung cancer (ICD-7 162) among men in the period 1961-1980 (SIR, 0.75; 95% CI, 0.66-0.84) as well as in the period 1981-2000 (SIR, 0.78; 95% CI, 0.71-0.86). This could indicate that tobacco smoking was underrepresented in the cohort, similarly in the two periods compared with the background population, with no statistically significant difference between the two periods (P = 0.55). There is no reason to believe that estrogen exposure is strongly associated with any of these potentially confounding factors. Moreover, any negative confounding is very unlikely to have influenced the association only during the period 1961-1980 and not during 1981-2000. In theory, there is a possibility that prostate cancer patients might have received different dietary advice (e.g., increased intake of fruit and fresh vegetables) that might affect the risk of gastric cancer more before 1980 compared with later. However, the role of dietary habits in carcinogenesis has not received major attention until the years after
and change in dietary habits was not an established treatment option of patients with prostate cancer (17). Thus, it is unlikely that confounding by dietary factors could explain the inverse association found in our study.

Our findings are in agreement with some previous studies of various estrogen exposures and risk of gastric cancer. A recent study found a global age-specific pattern of the male-to-female ratio of gastric cancer that suggests basic biological differences between the sexes (e.g., a preventive effect of estrogen) that could explain the worldwide male predominance in the incidence of gastric cancer (11). Three case-control studies (13, 14, 16) and one cohort study (15) of postmenopausal women all indicated a negative association between longer fertility (i.e., longer exposure to estrogen) and gastric cancer. However, this was contradicted in a Norwegian cohort study that found an inverse association between age at menarche and gastric cancer (12). We have used parts of the present cohort in a previous study to test whether estrogen therapy may prevent adenocarcinoma of the esophagus, but we did not identify any decreased risk (18). Lack of negative association between estrogen exposure and esophageal adenocarcinoma does not contradict the negative association with gastric adenocarcinoma, however, because the reported global pattern of sex differences has been found to be unique for gastric cancer and was not found for other gastrointestinal cancers (11). Animal experiments have reported a suppressive action of female hormone on gastric carcinogenesis (26, 27). Furthermore, in a placebo-controlled randomized study of adjuvant treatment of breast cancer, there was an increased risk of gastric cancer among women who received the drug tamoxifen, used mainly for its antiestrogen effect on estrogen receptor–positive breast cancer (28). Hormone replacement therapy has been associated with a reduced risk of colorectal cancer in several studies (29, 30), but to our knowledge no such study has been conducted evaluating risk of gastric cancer.

The mechanism behind a potential role for estrogens in the etiology of gastric cancer is uncertain. Estrogens regulate cell growth and differentiation in numerous tissues in both females and males and have critical roles in breast and uterine carcinogenesis (31). Furthermore, estrogens act on cells through intracellular estrogen receptors that regulate target gene expression (31), and estrogen receptors have been identified in human gastric mucosa and gastric cancer cells (32, 33). There are reports that estrogen increases apoptosis in human gastric cancer cells (34), and recently, estrogen has been found to stimulate the expression of trefoil peptides in the stomach (35). Trefoil peptides play key roles in mucosal protection through mucous-barrier formation and in mucosal repair through promotion of restitution after injury, and their genes may act as tumor suppressors (35). Thus, there are some possible mechanisms for the potentially protective effects of estrogen in gastric carcinogenesis.

In conclusion, our nationwide, population-based cohort study indicates that treatment with estrogen might reduce the risk of gastric cancer, hence adding support to the hypothesis that estrogen plays a protective role in the etiology of gastric cancer. This finding warrants additional studies about the association, as well as experimen-mental studies that can shed light on the mechanism underlying this potentially protective action. If there is indeed a preventive effect, it might in the future open the way for a new set of specific estrogen-related therapies for the prevention of gastric cancer in high-risk persons.

Acknowledgments

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References

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