Do Sex Hormones Play a Role in the Etiology of Esophageal Adenocarcinoma? A New Hypothesis Tested in a Population-based Cohort of Prostate Cancer Patients

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Abstract

The striking male predominance in patients with adenocarcinoma of the esophagus (male:female ratio = 6:1) is not explained by known risk factors. We hypothesized that sex hormones could be responsible for this sex imbalance. If the hypothesis is correct, treatment that increases the estrogen level and/or decreases the testosterone level in males might reduce the risk of developing esophageal adenocarcinoma. To test our hypothesis, we performed a population-based, retrospective cohort study among all patients given a diagnosis of prostate cancer in Sweden between 1958 and 1992. The vast majority had received prolonged antiandrogenic treatment, typically with estrogens. A total of 100,215 patients were followed up for an average of 4 years. The standardized incidence ratio, the ratio of the observed to the expected number of incident cancers, was used as a measure of relative risk, with the expected number derived from the entire Swedish population. We observed 14 adenocarcinomas of the esophagus during follow-up in the cohort, compared to the 16 expected, yielding a relative risk close to unity (standardized incidence ratio = 0.9; 95% confidence interval = 0.5–1.5). Analysis by latency intervals after prostate cancer diagnosis revealed no clear trend toward increasing or decreasing risk over time. In conclusion, our Swedish data did not provide any support for our hypothesis of a role of sex hormones in the etiology of esophageal adenocarcinoma.

Introduction

The incidence of adenocarcinoma of the esophagus is rising at an epidemic rate, especially among white men in the United States and western Europe, including Sweden (1–3), and there is a clear need to unveil the etiological factors. One intriguing and probably important observation is the strong male predominance (male:female ratio of 6:1 or higher), which is similar in all studied populations (1–3). Whereas the 3:1 male predominance among patients with squamous cell carcinoma of the esophagus has been attributed almost entirely to sex differences in the prevalence of exposure to alcohol and tobacco (4), the sex imbalance among patients with adenocarcinoma of the esophagus is not likely to be explained by such exposure because alcohol and tobacco are only moderately strong risk factors for the latter type of cancer (5).

In the absence of other known environmental risk factors with a sex distribution that is sufficiently skewed to explain the imbalance in the risk of adenocarcinoma, we hypothesized that the male predominance might be explained by hormonal factors. The apparent protection in women could then be ascribed to either high estrogen or low testosterone levels or a combination of the two. If this hypothesis is correct, treatment that increases the estrogen level and/or decreases the testosterone level in males would reduce their risk of developing adenocarcinoma of the esophagus. To test this hypothesis, we studied this risk in a cohort of men with cancer of the prostate. In this cohort, the vast majority had received antiandrogenic treatment (6).

Subjects and Methods

We carried out a population-based, retrospective cohort study among all 100,215 patients recorded as having received a diagnosis of prostate cancer (International Classification of Diseases 7 = 177) between 1958 and 1992 in the ~98% complete Swedish Cancer Register (7). Follow-up for tracing of subsequent cancers was accomplished through cross-linkage within the register. Information required for correct censoring was obtained by record linkages with the nationwide registers of Emigration and Causes of Death. The National Registration Numbers, unique personal identifiers assigned to all Swedish residents, were used to ensure correct matching in these linkages. Each prostate cancer patient was followed up until the time of diagnosis of an adenocarcinoma of the esophagus (International Classification of Diseases 7 = 150, histological code = 096), death, emigration, or end of follow-up (December 31, 1992), whichever occurred first.

The mean age at entry was 74 years. The prostate cancers were verified histologically in 92% of the patients. The cohort members were followed up for an average of 4 years (the median follow-up time was 2.8 years), and a total of 406,275 person-years at risk were examined in this study.

The SIR,[2] *i.e.*, the ratio of the observed to the expected number of incident adenocarcinomas of the esophagus, was used as a measure of relative risk. The expected number of adenocarcinomas of the esophagus was calculated by multiply-

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[2] The abbreviations used are: SIR, standardized incidence ratio; CI, confidence interval.

Table 1 SIR and 95% CI for adenocarcinoma of the esophagus among Swedish men prostate cancer, by latency interval

	Latency interval after prostate cancer diagnosis (yr)				
	<1	1–4	5–9	10–34	0–34
No. of patients remaining in the cohort	100,215	77,752	36,913	11,460	100,215
No. of person-years at risk	88,002	164,059	108,814	45,401	406,275
No. of observed adenocarcinomas of the esophagus	3	5	4	2	14
No. of expected adenocarcinomas of the esophagus	3.1	6.2	4.6	2.2	16.1
SIR	1.0	0.8	0.9	0.9	0.9
95% CI	0.2–2.8	0.3–1.9	0.2–2.2	0.1–3.3	0.5–1.5

ing the observed number of person-years by age- and calendar year-specific incidence rates derived from the entire Swedish male population. We did not count esophageal cancers detected incidentally at autopsy, either in the cohort or when calculating the expected rates. The 95% CI of the SIR was calculated under the assumption that the number of observed cancers followed a Poisson distribution (8).

Results

Fourteen histologically confirmed adenocarcinomas of the esophagus were observed during follow-up in the cohort, compared to 16 expected (SIR = 0.9; 95% CI = 0.5–1.5; Table 1). Analysis by latency interval after diagnosis of prostate cancer revealed no clear trend toward an increasing or decreasing risk over time (Table 1). For comparison, we analyzed the risk for total esophageal cancers (both squamous cell carcinoma and adenocarcinoma) in the same cohort, and found 82 observed cases *versus* 104 expected (SIR = 0.8; 95% CI = 0.6–1.0).

Discussion

Our population-based cohort study, which was designed to detect possible effects of estrogen and testosterone in the etiology of adenocarcinoma of the esophagus, yielded an essentially negative result.

In our study, the rarity of esophageal adenocarcinoma limited the power to detect a moderately protective effect. Despite more than 400,000 observed person-years at risk, the CI shows that we were unable to rule out a 50% reduced risk overall, and there were only six cases of esophageal adenocarcinoma that occurred more than 5 years after the diagnosis of prostate cancer.

Clearly, it would have been preferable to determine the exposure to antiandrogenic therapy in each individual cohort member, but no such information was available in the registers. However, the treatment of choice in Sweden during 1950–1980 was estrogen therapy, given either p.o. or parenterally. During these decades, virtually all patients given a diagnosis of prostate cancer, regardless of tumor stage, received such treatment for long periods, typically until death (6). If the treatment failed, the common strategy was to switch to another estrogen drug. Orchidectomy, the main alternative to estrogen treatment, gained little popularity in Sweden during the main part of the study period (6). Currently, antiandrogenic treatment is reserved mainly for patients with advanced prostate cancer, and thus, at present, 50–60% of the patients with prostate cancer receive such treatment from the time of diagnosis (9, 10). Thus, the vast majority of the patients in our cohort received antiandrogenic therapy, mainly estrogens.

A potential problem is that the patients may not have survived long enough after the prostate cancer diagnosis for a protective effect to become clinically evident. If it is at all effective, the mode of action and latency time of estrogen treatment remain to be established. The effects of sex hormones in hormone-dependent cancers appear to be short-lived, indicating an impact mainly in the late stages of the carcinogenic process. For example, the increased risk of developing breast cancer after estrogen treatment in women seems to disappear within 5 years of termination of the treatment (11). We, therefore, postulated that changes in esophageal adenocarcinoma risk attributed to modification of hormone levels should be discernible within a decade after exposure, if they exist at all.

Although the mechanisms are not well understood, sex hormones seem to play a role in the development of prostate cancer (12). However, there is no strong association between serum levels of androgens and risk of prostate cancer (13). Nonetheless, if the hormone-tissue interactions (of whatever kind) that lead to prostate cancer are also responsible for the development of esophageal adenocarcinoma, prostate cancer patients may have a higher baseline risk of esophageal adenocarcinoma compared with the general population of men. We, therefore, expected a possibly elevated risk in the first years after the prostate cancer diagnosis, with a subsequent decrease over time, discernible within the maximum follow-up time in our study. We did not find any indications supporting either of these assumptions.

The completeness of the cancer register (7) should minimize both selection and ascertainment biases. Although, on average, prostate cancer patients are likely to be under closer medical surveillance than the general population, which served for comparison, the alarming local symptoms of esophageal cancer usually lead to a prompt diagnosis whether the patients are under medical surveillance or not. Misclassification of esophageal adenocarcinoma as squamous cell carcinoma should be of minor quantitative importance because the vast majority of all esophageal cancers in Sweden are histologically confirmed; this proportion increased from 82% in 1958 to 91% in 1978 and 99% in 1992 (14–16). Bias might have arisen if the esophageal carcinomas were misclassified as secondary manifestations of the preceding prostate cancer. Esophageal metastases are, however, rare, and the high frequency of histological confirmation of tumors in Sweden should minimize such bias. With the assumption that any biases would affect the risks of esophageal adenocarcinoma and squamous cell carcinoma to a similar extent, we analyzed the risk for total esophageal cancers in the cohort, *i.e.*, both adenocarcinomas and squamous cell carcinoma, to see if the findings for adenocarcinomas deviated from those for total esophageal cancer. Our results did not point to any important differences between the risk for esophageal adenocarcinomas and that for all esophageal cancers. One other study, using case-control methods, found a risk of prostate cancer that was similar for those with esophageal adenocarcinomas and squamous cell carcinomas (17).

In conclusion, our data did not provide any support for our

hypothesis of a protective effect of antiandrogenic therapy against the development of esophageal adenocarcinoma or for an increased baseline risk among prostate cancer patients. A weakness of this study is the lack of precision in our relative risk estimates. We are, therefore, unable to strongly refute the possibility that estrogens and/or testosterones may play some role for the marked sex difference in the risk. Although its incidence is rapidly increasing, esophageal adenocarcinoma is still a rare disease, and any epidemiological research on the etiology of this cancer, regardless of the study design, will suffer from this fact. Here, we studied all 100,215 prostate cancer patients across Sweden diagnosed during a 35-year period and found 14 observed esophageal adenocarcinomas. With this constraint in mind, it is clearly of importance not to overinterpret but also not to discard all pieces of evidence that might lead to a further understanding of the etiology of esophageal adenocarcinoma.

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