VOLUME 30 · NUMBER 18 · JUNE 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Influence of Sex on the Survival of Patients With Esophageal Cancer

*Pierre Bohanes, Dongyun Yang, Ruchika S. Chhibar, Melissa J. Labonte, Thomas Winder, Yan Ning, Armin Gerger, Léonor Benhaim, David Paez, Takeru Wakatsuki, Fotios Loupakis, Rita El-Khoueiry, Wu Zhang, and Heinz-Josef Lenz*

All authors: The University of Southern California/Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA.

Submitted August 11, 2011; accepted February 28, 2012; published online ahead of print at www.jco.org on May 14, 2012.

Supported by the San Pedro Foundation, by Yvonne Bogdanovich, by Grant No. 5P30CA014089-27S1 from the National Institutes of Health P30CA, by Grant No. BIL KLS 02591-02-2010 from "Ligue Suisse contre le Cancer" (P.B.), and by grants from the Austrian Society of Hematology and Oncology, the Bank Austria Visiting Scientists Program, and the "Verein fuer Krebskranke" of the Medical University Graz (A.G.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Heinz-Josef Lenz, MD, USC/Norris Comprehensive Cancer Center, Keck School of Medicine, 1441 Eastlake Ave, Room 3456, Los Angeles, CA 90033; e-mail: lenz@usc.edu.



0732-183X/12/3018-2265/$20.00

DOI: 10.1200/JCO.2011.38.8751

## ABSTRACT

### Purpose
The prognostic value of sex for esophageal cancer survival is currently unclear, and growing data suggest that hormonal influences may account for incidence disparities between men and women. Therefore, moving from the hypothesis that hormones could affect the prognosis of patients with esophageal cancer, we investigated the primary hypothesis that sex is associated with survival and the secondary hypotheses that the relationship between sex and survival depends, at least in part, on age, histology, and race/ethnicity.

### Patients and Methods
By using the SEER databases from 1973 to 2007, we identified 13,603 patients (34%) with metastatic esophageal cancer (MEC) and 26,848 patients (66%) with locoregional esophageal cancer (LEC). Cox proportional hazards model for competing risks were used for analyses.

### Results
In the multivariate analysis, women had longer esophageal cancer-specific survival (ECSS) than men in both MEC (hazard ratio [HR], 0.949; 95% CI, 0.905 to 0.995; $P = .029$) and LEC (HR, 0.920; 95% CI, 0.886 to 0.955; $P < .001$) cohorts. When age and histology were accounted for, there was no difference for ECSS between men and women with adenocarcinoma. In contrast, women younger than age 55 years (HR, 0.896; 95% CI, 0.792 to 1.014; $P = .081$) and those age 55 years or older (HR, 0.905; 95% CI, 0.862 to 0.950; $P < .001$) with squamous cell LEC had longer ECSS than men. In the squamous cell MEC cohort, only women younger than age 55 years had longer ECSS (HR, 0.823; 95% CI, 0.708 to 0.957; $P = .011$) than men.

### Conclusion
Sex is an independent prognostic factor for patients with LEC or MEC. As secondary hypotheses, in comparison with men, women age 55 years or older with squamous cell LEC and women younger than age 55 years with squamous cell MEC have a significantly better outcome. These last two findings need further validation.

*J Clin Oncol 30:2265-2272. © 2012 by American Society of Clinical Oncology*

## INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, with 482,000 new cases (representing 3.8% of all new cancers) estimated in 2008, and the sixth most common cause of death from cancer with 407,000 deaths (representing 5.4% of all new cancers). Its incidence rates vary internationally more than 15-fold in men and almost 20-fold in women.[1] In the United States, it was estimated that 16,640 new cases of esophageal cancer were diagnosed in 2010 and 14,500 deaths occurred. Esophageal cancer is highly lethal with 11,650 (88.7%) estimated deaths among men and 2,850 (81.2%) among women.[2] Taken together with previous population studies,[3-9] the latter suggests a survival benefit for women when compared with men.

The prevalence of the two main histologic subtypes—adenocarcinoma and squamous cell carcinoma—differs depending on geographic location. Squamous cell carcinoma of the esophagus (SCCE) predominates in the Middle East, Africa, Asia, and parts of Europe. In contrast, adenocarcinoma of the esophagus (ACE) is prevalent in Western countries.[10] In the United States, the incidence of SCCE has steadily decreased in all ethnicities in the past three decades, with a concurrent increase in the incidence of ACE. In the white population, SCCE represents 27% of esophageal cancers. In contrast, SCCE remains a frequent malignancy in Hispanic, African American, and

Asian populations (41%, 81%, and 70% of esophageal cancers, respectively).[11]

In the United States, both ACE and SCCE are more frequent in men than in women, mirroring parts of the world where SCCE largely predominates.[1] Although this may represent various tumor-specific environmental exposures between sexes (eg, alcohol, tobacco), growing data suggest hormonal influences.[12-14] Sex differences affect esophageal cancer incidence, yet the significance of sex as an independent prognostic marker is unclear. A major limitation of previous studies that examined the prognostic value of sex is the lack of adequate adjustment for other relevant clinical prognostic factors. Therefore, we used the SEER database to assess the influence of sex on the esophageal cancer–specific survival (ECSS) in locoregional esophageal cancer (LEC) and metastatic esophageal cancer (MEC). We evaluated metastatic diseases separately from locoregional diseases, because clinicopathologic prognostic factors and treatments may not have the same influence throughout the evolution of the malignancy. On the basis of our previous data,[15] we hypothesized that hormonal status would influence survival in patients with esophageal cancer and that this influence might vary by histology and tumor stage.

## PATIENTS AND METHODS

### Study Design

The SEER public use database 1973 to 2007 (Version April 2010) was used for this analysis. The SEER Program, sponsored by the National Cancer Institute, collects information on cancer incidence and survival from 17 population-based cancer registries covering approximately 28% of the United States population.[16]

### Study Population

The criteria defined for inclusion in this study were primary histologically confirmed esophageal cancer and age at diagnosis of 18 years or older. We excluded a total of 14,169 patients (26%) from those diagnosed with esophageal cancer in the SEER database (n = 54,620) mainly because of unstaged or in situ tumors (n = 11,687), diagnosis not microscopically confirmed or unknown confirmation (n = 2,392), or no follow-up records (n = 1,547). A total of 40,451 patients with esophageal cancer matching the specified criteria were included in the final sample for this analysis (Appendix Figure A1, online only).

### Statistical Analysis

The primary end point in this study was ECSS, defined as the period from diagnosis to death from esophageal or gastric cancer. ECSS was censored at the last follow-up, December 31, 2007, or 5 years after diagnosis, whichever came first. Of 40,451 patients, 27,414 died from esophageal or gastric cancer, and 5,776 died from other causes within the first 5 years after diagnosis. The median follow-up time for patients (n = 7,261) who were censored was 39 months, and 39% of them had been observed for at least 5 years. Proportional hazards regression model for competing risks, according to the method of Fine and Gray,[17] was used to adjust for comorbidities that competed with death from esophageal cancer. The variables included in the model were sex, age, ethnicity, marital status, histology, tumor primary site, tumor grade, tumor stage, use of esophagectomy, use of radiation therapy, SEER registries, and year of diagnosis (Appendix Table A1, online only). Because detailed information on TNM staging in the early SEER database was not provided, stage was defined as locoregional (localized or regional in the SEER record description), or metastatic (distant). Because of differences in clinicopathologic factors and in treatments and the potentially different underlying hazard of (ECSS) failure, the analyses were conducted separately for patients with LEC or MEC. Pairwise interactions were examined by using stratified models and were tested by comparing corresponding likelihood ratio statistics between the baseline and nested Cox proportional hazards models, which included the multiplicative product terms. Departures of the proportional hazards assumption for the model were examined graphically by using smoothed plots of weighted Schoenfeld residuals. The primary hypothesis of this study was that sex was an independent prognostic factor for ECSS in both the LEC and MEC cohorts (ie, regardless of extent of disease). The secondary hypothesis tested was that the effect of sex on ECSS varied by age, histology, and/or race/ethnicity. All analyses were performed by using SAS software, version 9.2 (SAS Institute, Cary, NC) and library(cmprsk) in S-PLUS, version 3.3 (Statistical Sciences, Seattle, WA; S-PLUS 7.0 Enterprise Developer for Windows; S-PLUS, 1988, 2005, Insightful Corp.). Results were considered significant if a two-sided $P < .05$ was obtained. $P$ values were not adjusted for multiple testing of secondary hypotheses.[18]

## RESULTS

### LEC

*Patient characteristics.* This study included 26,848 patients with LEC diagnosed from 1973 to 2007. The proportion of patients diagnosed in 1973 to 1982, 1983 to 1995, and 1996 to 2007 was 12.2%, 25.4%, and 62.4%, respectively (Appendix Table A2, online only). ACE and SCCE were more commonly diagnosed in men than in women (ratio of men to women was 6.2:1 and 1.9:1, respectively).

*Sex and LEC.* The median age for men was 67 years (range, 19 to 103 years), and the median age for women was 70 years (range, 19 to 107 years). When comparing by histology, women were older than men in both ACE and SCCE cohorts (ACE: women, age 72 years [range, 19 to 103 years]; men, age 67 years [range, 19 to 99 years]; SCCE: women, age 69 years [range, 24 to 107 years]; men, age 66 years [range, 20 to 103 years]). The demographic and clinicopathologic characteristics of men and women with LEC are provided in Table 1.

*Sex, age, and survival for LEC.* In the multivariate model (Table 2 and Appendix Table A3, online only), women had significantly longer ECSS than men (4% absolute difference for 5-year ECSS rate).

**Table 1.** Demographic and Clinicopathologic Characteristics by Sex in Patients With LEC, SEER Data 1973-2007

| | LEC (N = 26,848) | | | | |
|---|---|---|---|---|---|
| | Males (n = 19,957) | | Females (n = 6,891) | | |
| Characteristic | No | % | No | % | *P* |
| Age, years | | | | | < .001 |
| 18-44 | 614 | 3.1 | 139 | 2 | |
| 45-54 | 2,573 | 12.9 | 626 | 9.1 | |
| 55-64 | 5,422 | 27.2 | 1,563 | 22.7 | |
| 65-74 | 6,430 | 32.2 | 2,129 | 30.9 | |
| ≥ 75 | 4,918 | 24.6 | 2,434 | 35.3 | |
| Race | | | | | < .001 |
| White | 15,026 | 75.3 | 5,196 | 75.4 | |
| African American | 2,811 | 14.1 | 1,094 | 15.9 | |
| Asian | 1,002 | 5 | 270 | 3.9 | |
| Hispanic | 1,040 | 5.2 | 301 | 4.4 | |
| Native American | 78 | 0.4 | 30 | 0.4 | |
| Histology | | | | | < .001 |
| Squamous | 9,066 | 45.4 | 4,869 | 70.7 | |
| Adenocarcinoma | 8,736 | 43.8 | 1,410 | 20.5 | |
| Other | 2,155 | 10.8 | 612 | 8.9 | |

Abbreviation: LEC, locoregional esophageal cancer.

  

**Table 2.** Multivariate Analysis for ECSS in Patients With LEC, SEER Data 1973-2007

| Characteristic | LEC (N = 26,848) | | | | | |
|---|---|---|---|---|---|---|
| | No. of Patients | EC Death | 5-Year ECSS ± SE (%) | HR | 95% CI* | *P** |
| Sex | | | | | | < .001 |
| Male | 19,957 | 12,081 | 24 ± 0.3 | 1 (reference) | | |
| Female | 6,891 | 4,275 | 28 ± 0.5 | 0.920 | 0.886 to 0.955 | |
| Age, years | | | | | | < .001 |
| 18-44 | 753 | 438 | 31 ± 1.5 | 0.774 | 0.701 to 0.855 | |
| 45-54 | 3,199 | 1,889 | 29 ± 0.8 | 0.807 | 0.764 to 0.852 | |
| 55-64 | 6,985 | 4,124 | 29 ± 0.5 | 0.794 | 0.760 to 0.831 | |
| 65-74 | 8,559 | 5,169 | 26 ± 0.5 | 0.848 | 0.813 to 0.883 | |
| ≥ 75 | 7,352 | 4,736 | 19 ± 0.5 | 1 (reference) | | |
| Race | | | | | | .031 |
| White | 20,222 | 12,043 | 26 ± 0.3 | 1 (reference) | | |
| African American | 3,905 | 2,624 | 22 ± 0.6 | 1.068 | 1.016 to 1.123 | |
| Asian | 1,272 | 836 | 23 ± 1.0 | 1.089 | 0.999 to 1.186 | |
| Hispanic | 1,341 | 780 | 26 ± 1.1 | 0.989 | 0.916 to 1.067 | |
| Native American | 108 | 73 | 22 ± 3.3 | 1.133 | 0.838 to 1.533 | |
| Histology | | | | | | .003 |
| Squamous | 13,935 | 9,185 | 24 ± 0.4 | 1 (reference) | | |
| Adenocarcinoma | 10,146 | 5,506 | 27 ± 0.5 | 0.927 | 0.889 to 0.968 | |
| Other | 2,767 | 1,665 | 24 ± 0.7 | 0.965 | 0.911 to 1.022 | |

Abbreviations: EC, esophageal cancer; ECSS, esophageal cancer–specific survival; LEC, locoregional esophageal cancer; HR, hazard ratio.
*Based on ECSS in competing risks regression model, including all variables in the table and marital status, radiation sequence (no radiation/surgery, neoadjuvant radiation, adjuvant radiation, intraoperative radiation or unknown), stage (localized *v* regional), SEER registries, and year of diagnosis (1973-1982, 1983-1995, 1996-2007).

On the basis of our previous data in metastatic colorectal cancer, we examined the relationships between sex and ECSS by age, with patients being dichotomized below or above age 55 years for both men and women.[15] The ECSS was longer for women than for men and did not differ significantly between age groups ($P_{interaction}$ = 0.32; 4% absolute difference for 5-year ECSS rate in both age groups; Appendix Table A4, online only).

*Sex, age, histology, ethnicity, and survival for LEC.* We found a significant difference in ECSS between sexes in adenocarcinoma and squamous cell carcinoma ($p_{interaction}$ = 0.036, Appendix Table A4). ECSS was significantly longer for women when compared with men with squamous cell tumors (5% absolute difference for 5-year ECSS rate; Fig 1). In adenocarcinoma, this sex difference was not significant (Appendix Table A4).

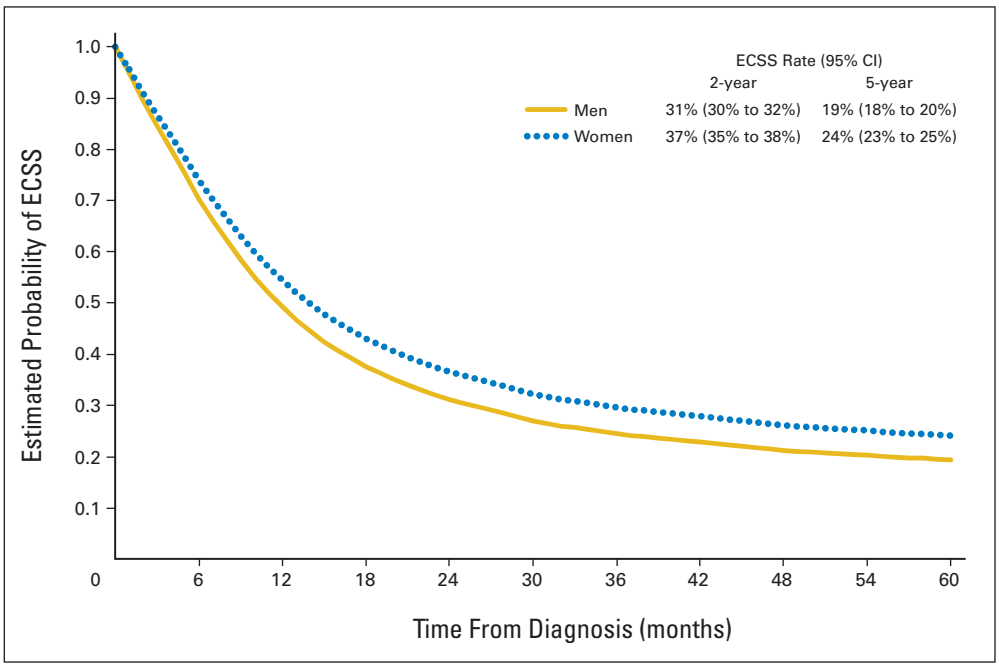


**Fig 1.** Adjusted survival curves of esophageal cancer–specific survival (ECSS) in patients with locoregional squamous cell carcinoma of the esophagus.

**Table 3.** Demographic and Clinicopathologic Characteristics by Sex in Patients With MEC, SEER Data 1973-2007

| Characteristic | MEC (N= 13,603) Males (n = 10,752) No. | % | Females (n = 2,851) No. | % | *P* |
|---|---|---|---|---|---|
| Age, years | | | | | < .001 |
| 18-44 | 444 | 4.1 | 104 | 3.6 | |
| 45-54 | 1,776 | 16.5 | 377 | 13.2 | |
| 55-64 | 3,258 | 30.3 | 737 | 25.9 | |
| 65-74 | 3,202 | 29.8 | 889 | 31.2 | |
| ≥ 75 | 2,072 | 19.3 | 744 | 26.1 | |
| Race | | | | | < .001 |
| White | 7,996 | 74.4 | 2,012 | 70.6 | |
| African American | 1,521 | 14.1 | 550 | 19.3 | |
| Asian | 555 | 5.2 | 128 | 4.5 | |
| Hispanic | 628 | 5.8 | 140 | 4.9 | |
| Native American | 52 | 0.5 | 21 | 0.7 | |
| Histology | | | | | < .001 |
| Squamous | 4,162 | 38.7 | 1,660 | 58.2 | |
| Adenocarcinoma | 5,171 | 48.1 | 841 | 29.5 | |
| Other | 1,419 | 13.2 | 350 | 12.3 | |

Abbreviation: MEC, metastatic esophageal cancer.

Finally, the relationship between sex, histology, and age was analyzed. In patients with adenocarcinoma, there was no significant difference in ECSS between men and women in patients younger than age 55 years or age 55 years or older. In contrast, women (n = 4,300) with squamous cell LEC age ≥ 55 years old had significantly longer ECSS than men (n = 7,660) of similar age (HR, 0.905; 95% CI, 0.862 to 0.950; $P < .001$; 5% absolute difference for 5-year ECSS rate). There was a trend in the association between sex (1,406 men and 569 women) and ECSS in squamous cell LEC for those younger than age 55 years (HR, 0.896; 95% CI, 0.792 to 1.014; $P = .081$; 4% absolute difference for 5-year ECSS rate). The effect of sex on ECSS was consistent across all ethnicities ($P_{interaction} > .05$; Appendix Table A4).

## MEC

*Patient characteristics.* This study included 13,603 patients with MEC diagnosed from 1973 to 2007. The proportion of patients with MEC diagnosed in 1973 to 1982, 1983 to 1995, and 1996 to 2007 was 12.1%, 23.1%, and 64.8%, respectively (Appendix Table A2). ACE and SCCE were more commonly diagnosed in men than in women (ratio of men to women was 6.1:1 and 3.6:1, respectively).

*Sex and MEC.* The median age for men was 64 years (range, 22 to 97 years), and the median age for women was 67 years (range, 21 to 95 years). When analyzing by histology, women were older in both ACE and SCCE cohorts (ACE: women, age 69 years [range, 21 to 95 years]; men, age 64 years [range, 22 to 97 years]; SCCE: women, age 66 years [range, 26 to 95 years]; men, age 64 years [range, 23 to 95 years]). The demographic and clinicopathologic characteristics of men and women with MEC are provided in Table 3.

*Sex, age, and survival for MEC.* In the multivariate model (Table 4 and Appendix Table A3), women had significantly longer ECSS than men (2% absolute difference for 2-year ECSS rate). The difference in ECSS between sexes varied significantly by age in patients with metastatic disease ($P_{interaction} = .048$; Appendix Table A4). Women with MEC younger than age 55 years had an ECSS better than men of similar age (5% absolute difference for 2-year ECSS rate). In contrast, this sex difference did not persist in patients ≥ 55 years old (2% absolute difference for 2-year ECSS rate).

**Table 4.** Multivariate Analysis for ECSS in Patients With MEC, SEER Data 1973-2007

| Characteristic | MEC (N = 13,603) No. | EC Death | 2-Year ECSS ± SE (%) | HR | 95% CI* | *P** |
|---|---|---|---|---|---|---|
| Sex | | | | | | .029 |
| Male | 10,752 | 8,769 | 9 ± 0.3 | 1 (reference) | | |
| Female | 2,851 | 2,289 | 11 ± 0.5 | 0.949 | 0.905 to 0.995 | |
| Age, years | | | | | | < .001 |
| 18-44 | 548 | 439 | 14 ± 1.3 | 0.816 | 0.742 to 0.898 | |
| 45-54 | 2,153 | 1,771 | 11 ± 0.6 | 0.910 | 0.856 to 0.968 | |
| 55-64 | 3,995 | 3,274 | 11 ± 0.4 | 0.921 | 0.872 to 0.973 | |
| 65-74 | 4,091 | 3,297 | 10 ± 0.4 | 0.907 | 0.858 to 0.958 | |
| ≥ 75 | 2,816 | 2,277 | 7 ± 0.4 | 1 (reference) | | |
| Race | | | | | | .20 |
| White | 10,008 | 8,166 | 10 ± 0.3 | 1 (reference) | | |
| African American | 2,071 | 1,683 | 9 ± 0.5 | 1.035 | 0.974 to 1.101 | |
| Asian | 683 | 551 | 11 ± 1.0 | 0.942 | 0.854 to 1.039 | |
| Hispanic | 768 | 597 | 11 ± 0.9 | 0.929 | 0.854 to 1.010 | |
| Native American | 73 | 61 | 7 ± 2.0 | 1.087 | 0.788 to 1.499 | |
| Histology | | | | | | .027 |
| Squamous | 5,822 | 4,695 | 10 ± 0.4 | 1 (reference) | | |
| Adenocarcinoma | 6,012 | 4,929 | 10 ± 0.4 | 1.071 | 1.019 to 1.125 | |
| Other | 1,769 | 1,434 | 9 ± 0.5 | 1.051 | 0.985 to 1.121 | |

Abbreviations: EC, esophageal cancer; ECSS, esophageal cancer–specific survival; HR, hazard ratio; MEC, metastatic esophageal cancer.
*Based on ECSS in competing risks regression model, including all variables in the table and marital status, radiation sequence (no radiation/surgery, neoadjuvant radiation, adjuvant radiation, intraoperative radiation or unknown), SEER registries, and year of diagnosis (1973-1982, 1983-1995, 1996-2007).

  

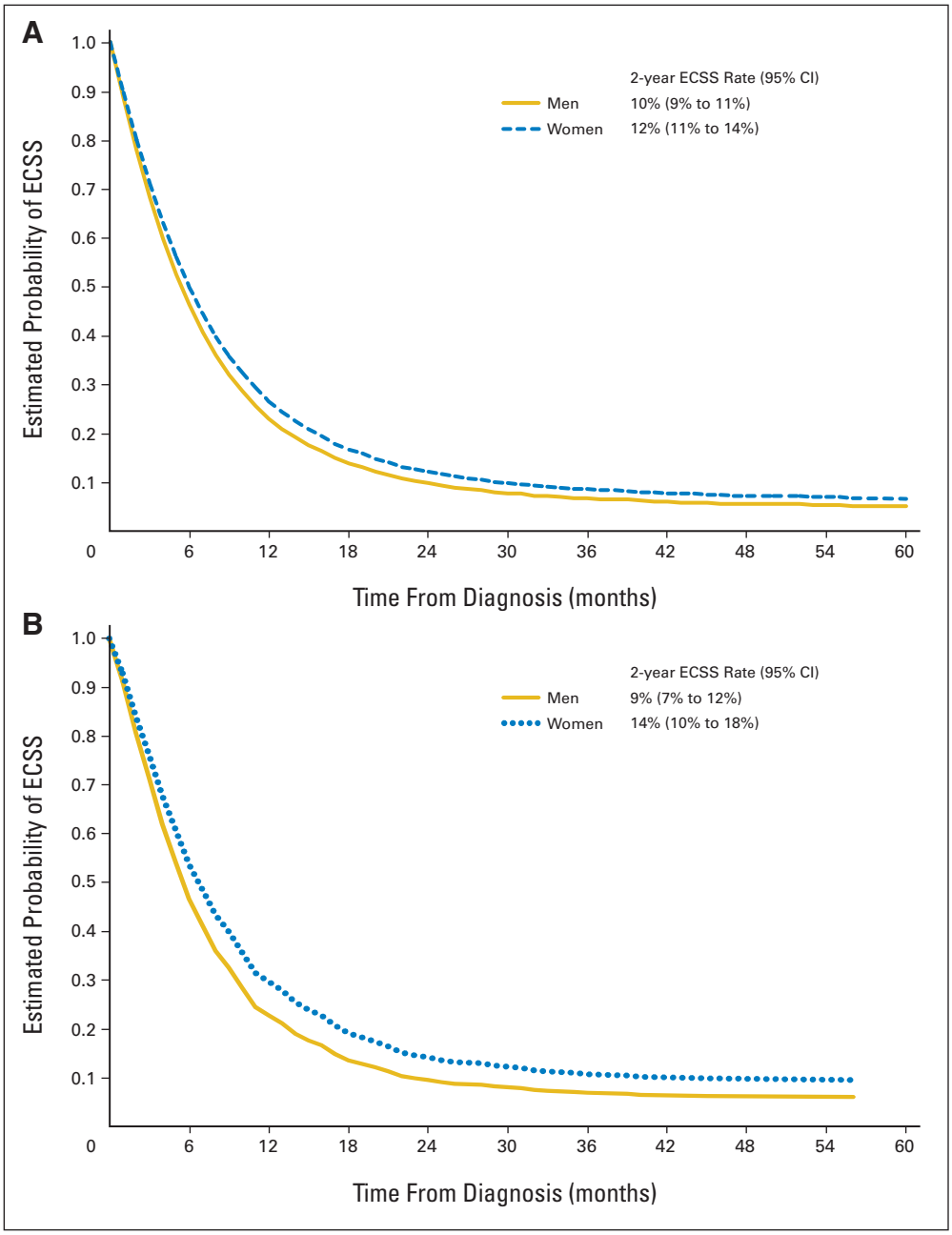


**Fig 2.** Adjusted survival curves of esophageal cancer-specific survival (ECSS) in (A) all patients with metastatic squamous cell carcinoma of the esophagus and (B) in patients with metastatic squamous cell carcinoma of the esophagus younger than age 55 years.

*Sex, age, histology, ethnicity, and survival for MEC.* There was no significant difference for ECSS between women and men in both ACE and SCCE (Fig 2A and Appendix Table A4). However, when the relationship between sex, histology, and age was analyzed, women younger than age 55 years (n = 284) had significantly longer ECSS than men of the same age (n = 791; HR, 0.823; 95% CI, 0.708 to 0.957; $P = .011$; Fig 2B; 5% absolute difference for 2-year ECSS rate). In contrast, women with SCCE age ≥ 55 years (n = 1,376) had no significantly different ECSS than men of same age (n = 3,371; HR, 0.967; 95% CI, 0.902 to 1.037; $P = .35$). In patients with ACE, there was no significant difference in ECSS between men and women in age groups younger than age 55 years or age 55 years or older. The effect of sex on ECSS was consistent across all ethnicities ($P_{interaction} > .05$; Appendix Table A4).

## DISCUSSION

The important burden of esophageal cancer in the United Stated is linked with its poor outcome (eighth position for cancer deaths), with both squamous cell and adenocarcinoma histology having poor prognosis.[2] In the last 25 years, there has been a shift in esophageal histology with a decrease of SCCE and an increase in ACE. This shift has been attributed to the change in commonly reported risk factors.[19-21] Although women experienced a shift in esophageal cancer histology similar to that of men, their rates of SCCE decrease and ACE increase were lower.[22] Importantly, despite this gradual shift, SCCE remains a frequent malignancy representing 35% of all carcinomas of the esophagus.[11]

We demonstrate in one of the largest cohorts of patients with esophageal cancer that sex is an independent prognostic marker for patients with either LEC or MEC. Furthermore, our data suggest that sex may be prognostic only in squamous cell esophageal tumors. Previous studies have reported a prognostic value for sex in Asian patients with stage I to III SCCE.[7,23,24] We hypothesized that hormonal influences, and thus menopause, could explain this prognostic difference. Age is commonly considered as a surrogate for menopause. On the basis of our previous study,[15] we selected age 55 years as a surrogate for menopause. This predetermined cutoff was chosen because menopause occurs in only 5% of women after age 55 years.[25] We found that in metastatic SCCE, only women younger than age 55 years had a lower risk of dying of esophageal cancer when compared with men of similar age. In contrast, women younger than or older than age 55 years with locoregional SCCE had a better prognosis, with the latter being statistically significant.

Estrogen receptors (ERs) are expressed in SCCE, and early preclinical studies[26,27] have demonstrated that estrogens could inhibit squamous cell tumor growth. The influence of sex hormones was further demonstrated in in vivo studies.[26,28] These antiproliferative functions are likely to occur through ER beta (ER$\beta$), which is the predominant ER expressed in SCCE.[29] In contrast to ER alpha (ER$\alpha$), ER$\beta$ has antiproliferative functions.[30] Unfortunately, the link between ER and esophageal cancer is currently poorly understood, mostly because of the confounding role of circulating estrogen and the concomitant expression of tumor androgen receptors (ARs). Current literature supports a biologic role of estrogens in early SCCE.[12,31] These data contrast with our study, showing no survival difference between women younger than age 55 years and those age 55 years or older with localized SCCE. This apparent contradiction may be reconciled by taking into account the prosurvival signals induced by androgens. ARs are expressed in SCCE and have been shown to enhance tumor growth.[26,27,32] Therefore, it is not surprising in our study that men with localized SCCE have an overall worse outcome. Our data show that the impact of age is different in localized and metastatic SCCE, suggesting that ER$\beta$ pathway signaling may be dynamic. Metastatic squamous cell tumors may lose their inhibitory ER$\beta$ capacity, which would reduce the survival benefit for women, particularly in postmenopausal women with low levels of ER$\beta$ ligand. Further studies are needed to clarify the mechanism and interaction of sex steroids in esophageal squamous cell tumors.

Although hormonal influences are strong candidates for explaining this sex difference in outcome, other prognostic factors should be considered. One candidate is the human papilloma virus (HPV). Oncogenic types of HPV have been reported to play a significant role in SCCE carcinogenesis in high-risk geographic areas (eg, East Asia). In contrast, its role in the United States is less clear, with low detection rates being reported.[33,34] Moreover, in contrast to head and neck cancer in which HPV infection predominates in males and is correlated with better prognosis,[35] no sex imbalance or prognostic value has been shown in SCCE.[36,37] Other potential prognostic factors are alcohol or smoking status. Because the SEER database provides no information on smoking status or alcohol consumption, we could not investigate their potential prognostic influence.

In agreement with a recent SEER-based study,[38] women with LEC or MEC and adenocarcinoma histology did not have a different outcome from men, irrespective of their menopausal status. ER$\beta$ and AR protein expression have been documented in adenocarcinoma of the esophagus.[29,39,40] However to date, convincing preclinical data showing a direct influence of sex hormones on adenocarcinoma cells or xenografts are lacking. Altogether, although hormonal influences may play a role in the carcinogenesis of esophageal adenocarcinoma,[14,41,42] ER or AR pathways may drive established adenocarcinoma of the esophagus only marginally, if at all.

Our study has several limitations related to the lack of details provided by the SEER database on the TNM tumor stage (only recently reported), on treatment information for the sequence of radiation therapy, on systemic treatment (no information), and on socioeconomic status. Despite these limitations, our results remained significant in the LEC cohort after adjusting for localized or regional stage. Our analyses also remained significant after adjusting for the year of diagnosis as a surrogate for type of therapy as follows: the study population was divided into three subsets based on year of diagnosis (1973 to 1982, 1983 to 1995, and 1996 to 2007). These cutoffs were selected on the basis of relevant publications likely to have driven a change of practice.[43-45] Adjustment for the year of diagnosis also allowed controlling for the quality of the elder SEER database. Although details on socioeconomic status are not provided, our results remain significant after adjusting for marital status, previously shown to be prognostic in colorectal cancer.[46]

Because of the lack of details on comorbidities in the SEER database, we restricted our analyses to ECSS, which is influenced to a lesser degree than overall survival. However, we cannot exclude that our data reflect an imbalance between comorbidities between sexes. It is possible that misclassification of cardia adenocarcinoma might have obscured the prognostic influence of sex steroids in ACE.[47] Finally, our findings derived from our secondary hypotheses have not been adjusted for multiple testing and therefore should be confirmed in futures studies. Despite these limitations, studies performed in population-based registries provide unique opportunities to evaluate a large number of patients. This approach is particularly useful in diseases such as esophageal cancer for which few large prospective studies are available.

Despite aggressive multimodality treatment strategies for localized SCCE, the expected 2-year survival rate remains between 20% and 50%.[48] To set a benchmark, it has been estimated that adding concomitant chemotherapy to radiotherapy in localized SCCE provides a 7% reduction to 2-year mortality.[49] Therefore, although the magnitude of the effect of sex in localized SCCE can be seen as small (5% absolute difference for 5-year ECSS), this may translate to the development of clinically meaningful treatment strategies in a disease in which there are a limited number of active agents. Similarly, in the metastatic setting in which no phase III trials have ever been reported, our data showing a 5% absolute difference for 2-year ECSS rate between men and women younger than age 55 years is intriguing. Nevertheless, when considering the relatively low prevalence of ECSS, the latter may have a modest impact in the United States. These data may be of critical importance for other parts of the world with a higher prevalence of SCCE.

In summary, this study shows that sex is an independent prognostic factor regardless of the extent of the disease. Several findings

  

derived from our secondary hypotheses should be confirmed in another independent cohort: the better outcome seen in women with squamous cell MEC may be restricted to women younger than age 55 years; women younger than or older than age 55 years with squamous cell LEC have a better prognosis, with the latter being statistically significant; sex is not a significant prognostic factor in established esophageal adenocarcinoma. We suggest that these associations are possibly related to both estrogen and androgen exposition. Taken together, these data are important because SCCE remains an important burden despite the shift in histology occurring in the Western world. Moreover, in areas of the world where the SCCE incidence is high, this shift has yet not been observed with relatively stable SCCE incidences.[50] If our secondary hypotheses are validated in other databases, future correlative studies in SCCE should focus on the pathways of sex steroids to elucidate the molecular mechanisms linked with poor outcome. With better understanding, the activation of these pathways may be modified, creating new approaches in SCCE treatment.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Pierre Bohanes, Dongyun Yang, Ruchika S. Chhibar, Melissa J. Labonte, Thomas Winder, Yan Ning, Wu Zhang, Heinz-Josef Lenz
**Financial support:** Heinz-Josef Lenz
**Administrative support:** Rita El-Khoueiry
**Collection and assembly of data:** Dongyun Yang, Ruchika S. Chhibar, David Paez, Rita El-Khoueiry
**Data analysis and interpretation:** Pierre Bohanes, Dongyun Yang, Ruchika S. Chhibar, Melissa J. Labonte, Armin Gerger, Léonor Benhaim, Takeru Wakatsuki, Fotios Loupakis, Wu Zhang, Heinz-Josef Lenz
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

## REFERENCES


1. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010
2. Jemal A, Siegel R, Xu J, et al: Cancer Statistics, 2010. CA Cancer J Clin 60:277-300, 2010
3. Schreiber D, Rineer J, Vongtama D, et al: Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol 5:244-250, 2010
4. Salek R, Bezenjani SE, Saedi HS, et al: A geographic area with better outcome of esophageal carcinoma: Is there an effect of ethnicity and etiologic factors? Oncology 77:172-177, 2009
5. Schwer AL, Ballonoff A, McCammon R, et al: Survival effect of neoadjuvant radiotherapy before esophagectomy for patients with esophageal cancer: A Surveillance, Epidemiology, and End Results study. Int J Radiat Oncol Biol Phys 73:449-455, 2009
6. Paulson EC, Ra J, Armstrong K, et al: Underuse of esophagectomy as treatment for resectable esophageal cancer. Arch Surg 143:1198-1203, 2008
7. Morita M, Yoshida R, Ikeda K, et al: Advances in esophageal cancer surgery in Japan: An analysis of 1000 consecutive patients treated at a single institute. Surgery 143:499-508, 2008
8. Badwe RA, Patil PK, Bhansali MS, et al: Impact of age and sex on survival after curative resection for carcinoma of the esophagus. Cancer 74:2425-2429, 1994
9. Sugimachi K, Matsuoka H, Matsufuji H, et al: Survival rates of women with carcinoma of the esophagus exceed those of men. Surg Gynecol Obstet 164:541-544, 1987
10. Kamangar F, Dores GM, Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137-2150, 2006
11. Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2008. National Cancer Institute, Bethesda, MD. http://seer.cancer.gov/csr/1975_2008/
12. Wang QM, Qi YJ, Jiang Q, et al: Relevance of serum estradiol and estrogen receptor beta expression from a high-incidence area for esophageal squamous cell carcinoma in China. Med Oncol 28:188-193, 2011
13. Derakhshan MH, Liptrot S, Paul J, et al: Oesophageal and gastric intestinal-type adenocarcinomas show the same male predominance due to a 17 year delayed development in females. Gut 58:16-23, 2009
14. Marmo R, Rotondano G, Piscopo R, et al: Combination of age and sex improves the ability to predict upper gastrointestinal malignancy in patients with uncomplicated dyspepsia: A prospective multicentre database study. Am J Gastroenterol 100:784-791, 2005
15. Hendifar A, Yang D, Lenz F, et al: Gender disparities in metastatic colorectal cancer survival. Clin Cancer Res 15:6391-6397, 2009
16. National Cancer Institute: Surveillance, Epidemiology , and End Results, Overview of the SEER program. http://seer.cancer.gov/about/overview.html
17. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999
18. Rothman KJ: No adjustments are needed for multiple comparisons. Epidemiology 1:43-46, 1990
19. Engel LS, Chow WH, Vaughan TL, et al: Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 95:1404-1413, 2003
20. Corley DA, Kubo A, Levin TR, et al: Helicobacter pylori infection and the risk of Barrett's oesophagus: A community-based study. Gut 57:727-733, 2008
21. Pohl H, Welch HG: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 97:142-146, 2005
22. Brown LM, Devesa SS, Chow WH: Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. J Natl Cancer Inst 100:1184-1187, 2008
23. Wang BY, Goan YG, Hsu PK, et al: Tumor length as a prognostic factor in esophageal squamous cell carcinoma. Ann Thorac Surg 91:887-893, 2011
24. Tong DK, Law S, Kwong DL, et al: Histological regression of squamous esophageal carcinoma assessed by percentage of residual viable cells after neoadjuvant chemoradiation is an important prognostic factor. Ann Surg Oncol 17:2184-2192, 2010
25. McKinlay SM, Brambilla DJ, Posner JG: The normal menopause transition. Maturitas 14:103-115, 1992
26. Ueo H, Matsuoka H, Sugimachi K, et al: Inhibitory effects of estrogen on the growth of a human esophageal carcinoma cell line. Cancer Res 50:7212-7215, 1990
27. Matsuoka H, Sugimachi K, Ueo H, et al: Sex hormone response of a newly established squamous cell line derived from clinical esophageal carcinoma. Cancer Res 47:4134-4140, 1987
28. Utsumi Y, Nakamura T, Nagasue N, et al: Role of estrogen receptors in the growth of human esophageal carcinoma. Cancer 64:88-93, 1989
29. Kalayarasan R, Ananthakrishnan N, Kate V, et al: Estrogen and progesterone receptors in esophageal carcinoma. Dis Esophagus 21:298-303, 2008
30. Hartman J, Ström A, Gustafsson JA: Estrogen receptor beta in breast cancer: Diagnostic and therapeutic implications. Steroids 74:635-641, 2009
31. Nozoe T, Oyama T, Takenoyama M, et al: Significance of immunohistochemical expression of estrogen receptors alpha and beta in squamous cell carcinoma of the esophagus. Clin Cancer Res 13:4046-4050, 2007
32. Yamashita Y, Hirai T, Mukaida H, et al: Detection of androgen receptors in human esophageal cancer. Jpn J Surg 19:195-202, 1989
33. Malik SM, Nevin DT, Cohen S, et al: Assessment of immunohistochemistry for p16INK4 and high-risk HPV DNA by in situ hybridization in esophageal squamous cell carcinoma. Int J Surg Pathol 19:31-34, 2011
34. Syrjänen KJ: HPV infections and oesophageal cancer. J Clin Pathol 55:721-728, 2002
35. Tribius S, Ihloff AS, Rieckmann T, et al: Impact of HPV status on treatment of squamous cell cancer of the oropharynx: What we know and what we need to know. Cancer Lett 304:71-79, 2011
36. Antonsson A, Nancarrow DJ, Brown IS, et al: High-risk human papillomavirus in esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 19:2080-2087, 2010
37. Dreilich M, Bergqvist M, Moberg M, et al: High-risk human papilloma virus (HPV) and survival in patients with esophageal carcinoma: A pilot study. BMC Cancer 6:94, 2006

**38.** Solomon N, Zhuge Y, Cheung M, et al: The roles of neoadjuvant radiotherapy and lymphadenectomy in the treatment of esophageal adenocarcinoma. Ann Surg Oncol 17:791-803, 2010

**39.** Akgun H, Lechago J, Younes M: Estrogen receptor-beta is expressed in Barrett's metaplasia and associated adenocarcinoma of the esophagus. Anticancer Res 22:1459-1461, 2002

**40.** Tihan T, Harmon JW, Wan X, et al: Evidence of androgen receptor expression in squamous and adenocarcinoma of the esophagus. Anticancer Res 21:3107-3114, 2001

**41.** van Soest EM, Siersema PD, Dieleman JP, et al: Age and sex distribution of the incidence of Barrett's esophagus found in a Dutch primary care population. Am J Gastroenterol 100:2599-2600, 2005

**42.** van Blankenstein M, Looman CW, Johnston BJ, et al: Age and sex distribution of the prevalence of Barrett's esophagus found in a primary referral endoscopy center. Am J Gastroenterol 100:568-576, 2005

**43.** Walsh TN, Noonan N, Hollywood D, et al: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335: 462-467, 1996

**44.** Advani SH, Saikia TK, Swaroop S, et al: Anterior chemotherapy in esophageal cancer. Cancer 56:1502-1506, 1985

**45.** Ezdinli EZ, Gelber R, Desai DV, et al: Chemotherapy of advanced esophageal carcinoma: Eastern Cooperative Oncology Group experience. Cancer 46:2149-2153, 1980

**46.** Wang L, Wilson SE, Stewart DB, et al: Marital status and colon cancer outcomes in US Surveillance, Epidemiology and End Results registries: Does marriage affect cancer survival by gender and stage? Cancer Epidemiol 35:417-422, 2011

**47.** Souza RF, Spechler SJ: Concepts in the prevention of adenocarcinoma of the distal esophagus and proximal stomach. CA Cancer J Clin 55:334-351, 2005

**48.** Gebski V, Burmeister B, Smithers BM, et al: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. Lancet Oncol 8:226-234, 2007

**49.** Rebecca WO, Richard MA: Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. Cochrane Database Syst Rev 1:CD002092, 2003

**50.** Hongo M, Nagasaki Y, Shoji T: Epidemiology of esophageal cancer: Orient to Occident—Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 24:729-735, 2009



  