Research Article

Cancer Prevention Research

# Hormonal Factors and Risks of Esophageal Squamous Cell Carcinoma and Adenocarcinoma in Postmenopausal Women

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## Abstract

The incidences of esophageal adenocarcinoma and squamous cell carcinoma (SCC) are higher in males than in females. We investigated whether female-related hormonal factors are associated with risks of these two types of esophageal cancer. We examined the association between use of hormone therapy (HT) and the risks of esophageal adenocarcinoma and SCC in postmenopausal women enrolled in the Women's Health Initiative (WHI) clinical trials and observational studies. Twenty-three esophageal adenocarcinoma and 34 esophageal SCC cases were confirmed among the 161,080 participants, after a median of 11.82 years of follow-up. Risk of esophageal SCC was lower among HT users (past users: HR = 0.25, 95% CI: 0.06–1.10 in 2 cases; current users: HR = 0.41, 95% CI: 0.18–0.94 in 9 cases). A decreased esophageal SCC risk was observed for current users of estrogen plus progestin (E+P) therapy (HR = 0.25, 95% CI: 0.07–0.86 in 3 cases) but not for current users of estrogen-only therapy (HR = 0.96, 95% CI: 0.28–3.29 in 6 cases). No association was observed between the use of HT and the risk of esophageal adenocarcinoma. No other reproductive or hormonal factors were significantly associated with the risk of either SCC or adenocarcinoma. Current use of E+P therapy was found to be associated with a decreased risk of esophageal SCC, but no association was observed with esophageal adenocarcinoma. To provide more definitive evidence, a pooled analysis of all available studies or a much larger study would be needed. *Cancer Prev Res; 4(6); 840–50. ©2011 AACR.*

## Introduction

Esophageal adenocarcinoma has increased dramatically in incidence in many Western countries during the last 4 decades (1, 2) and is now the most common histologic type of esophageal cancer in the United States (3). Esophageal adenocarcinoma is about 7 times more common in males than females (4), for reasons that are largely unknown. This has led to speculation that sex hormones might play an important role in the disease. Support for this notion comes from studies which observed overexpression of estrogen receptors α and β in esophageal malignancies (5, 6).

Few epidemiologic studies have explored the association of hormonal related risk factors and esophageal adenocarcinoma (7–12) and results are conflicting. The most recent study conducted in a cohort of 201,506 women observed a 19% (HR = 0.81, 95% CI: 0.59–1.12) lower risk of gastric adenocarcinoma, which included esophageal adenocarcinoma, among subjects who used hormone therapy (HT), with a 48% (HR = 0.52, 95% CI: 0.26–1.07) lower risk in a subset of women with intact uterus who were users of estrogen plus progestin (E+P) HT (9). These findings contrast with others that have reported either an increased risk of esophageal adenocarcinoma (7) or no association with HT use (11, 12). In another study, breast-feeding was associated with a significant 59% (95% CI: 18%–80%) lower risk of esophageal adenocarcinoma (8).

Indirect supporting evidence of the relation between hormones and esophageal adenocarcinoma comes from studies of HT and the occurrence of symptomatic gastroesophageal reflux, which is a known risk factor for esophageal adenocarcinoma. In the Women's Health Initiative (WHI) HT trial, women randomized to estrogen (E), but not to E+P, had a higher incidence of reflux (13). Similar results were found in a study of twins, in which ever-users of estrogen therapy had significantly more reflux symptoms than nonusers (14). Finally, a Norwegian study reported that the link between obesity, which is also a strong risk factor for esophageal adenocarcinoma, and reflux was much stronger among women who used HT (15).

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**doi:** 10.1158/1940-6207.CAPR-10-0389

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Esophageal squamous cell carcinoma (SCC) differs from esophageal adenocarcinoma in its site of origin and etiology (16). Esophageal SCC occurs mainly in the middle and upper portion of the esophagus, as opposed to distally where most esophageal adenocarcinoma cases are found (17). During the last decades, there has been a slight decrease in incidence of esophageal SCC in the United States. This histologic type of esophageal cancer has a much smaller male-to-female ratio than that of esophageal adenocarcinoma (4). It has been hypothesized that this smaller ratio might partially be explained by the different patterns of smoking and alcohol drinking, the 2 strongest risk factors for esophageal SCC, between males and females. However, Freedman and colleagues reported that users of HT had a reduced risk of esophageal SCC compared with never-users (9). This inverse association was also observed in an analysis of 3 small case–control studies which, in addition, observed a significantly lowered risk of esophageal SCC among users of oral contraceptives (18).

From the foregoing discussion, it is clear that a better understanding of the role of hormones in esophageal cancer is needed. Using information from the WHI clinical trials (CT) and observational study (OS), we examined the association between hormonal factors and the risks of esophageal adenocarcinoma and SCC.

## Methods

Details of the WHI study design have been described previously (19, 20). Briefly, postmenopausal women, age 50 to 79, were recruited in 40 clinical centers in the United States between October 1, 1993 and December 31, 1998. The WHI included 4 randomized controlled CTs to test the effects of use of E-alone or E+P (HT trials), calcium plus vitamin D, and a low-fat dietary pattern on several outcomes. All women in the HT trials who were users of HT at the time of recruitment were required to have a 3-month washout period before enrollment in the trial. The WHI OS was designed to obtain detailed information on a full range of lifestyle and medical factors in postmenopausal women and observed the disease outcomes after a follow-up period for comparison with the CT results. Overall, there were 161,808 women enrolled in the WHI including 27,347 enrolled in the HT trials and 134,461 enrolled in the OS or non-HT trials.

### Data collection

All study participants completed baseline questionnaires with detailed information on demographic characteristics, lifestyle, and reproductive and medical history. Medication use was assessed by interviewer-administered questionnaire. Subjects had their weight, height, and waist and hip circumferences measured at baseline by study staff. One of our primary exposures of interest was HT use, which was defined relative to baseline in the OS and non-HT trials and randomization in the HT trial. Specifically, current users of HT were women using HT at baseline in the OS and non-HT trials or assigned to an active intervention arm in the HT trials. Past users of HT were women not using HT at baseline in the OS and non-HT trials but those who had done so before enrollment or assigned to the placebo arm in the HT trial but who were users of HT before randomization. Never-users of HT were women who had not used HT before baseline in the OS and the non-HT trials or women assigned to the placebo arm in the HT trial who had never used HT before randomization. The type of current HT use was defined as the one reported at baseline in the OS and the non-HT trials or the one assigned in the active intervention arm if in the HT trial. Duration of HT use was defined as the number of years using HT before baseline or randomization. All other exposures were analyzed as reported at baseline.

Original reports of clinical outcomes, including cancer, were obtained by self-administered questionnaires, annually in the OS and biannually in the CTs. All cases were confirmed by medical record and pathology report review and subsequently adjudicated at the clinical coordinating center according to SEER guidelines (21). Deaths were verified and cause of death was attributed following medical record review at the clinical coordinating center. In addition, the National Death Index (NDI) was run on participants at 2- to 3-year intervals.

Seven hundred twenty-two women had missing follow-up time and were excluded from the analysis, leaving 161,086 women (Fig. 1). As of August 14, 2009, a total of 63 esophageal cancer cases have been confirmed in the WHI data set. Thirty-four of them were classified according to the International Classification of Disease for Oncology (ICD-O) as SCC (ICD-O codes: 8070–8083), 23 as adenocarcinomas (ICD-O code: 8140), and 6 had an unspecified histology (ICD-O codes: 8000–8033; Fig. 1). The 6 cases with unspecified histology were removed from the analyses.

### Statistical analysis

Cox regression was used to compute HRs and corresponding 95% CI as a measure of association between potential risk factors and incidence of esophageal adenocarcinoma or SCC separately. Time to diagnosis was computed from randomization in the HT trial or from enrollment in the OS and non-HT trials to diagnosis, with censoring defined by last follow-up contact, death, or August 14, 2009, whichever came first. In analysis about esophageal adenocarcinoma risk, SCC cases were censored at the time of diagnosis and vice versa. Similarly, in analyses of mortality, time to death was computed from date of randomization in the HT trial or enrollment in the OS and non-HT trials, with censoring defined by date of loss to follow-up, or August 14, 2009, whichever came first. For some subjects who stopped follow-up, death information was obtained from the NDI search. Death after esophageal cancer diagnosis was assumed to be an esophageal cancer death. All other deaths were considered to be censored observations.

All analyses were adjusted for age at baseline, hysterectomy status, and study type (HT trials/OS or non-HT trials)

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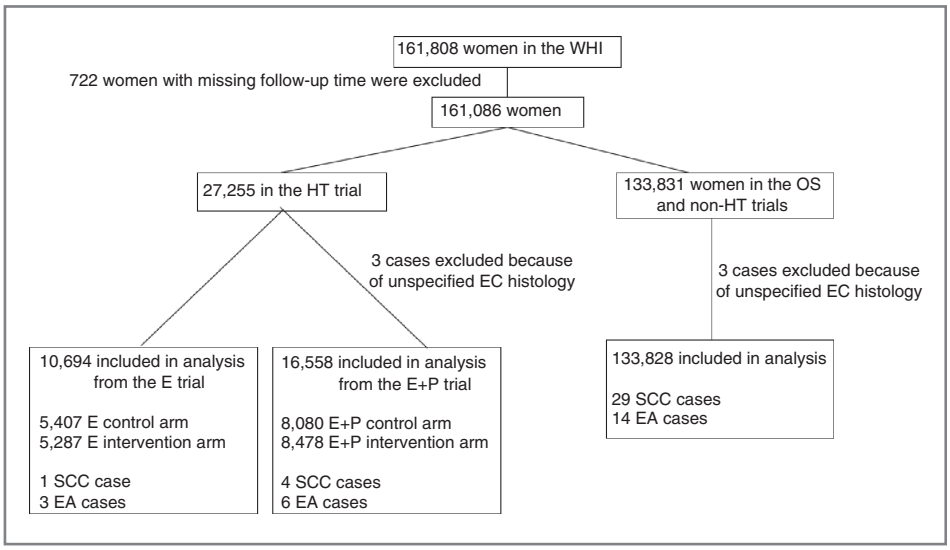


**Figure 1.** Flow diagram of study participants included in the analysis. EC, esophageal cancer; EA, esophageal adenocarcinoma.

by stratifying the baseline hazard function in the Cox model. Analyses regarding the risk of esophageal adenocarcinoma were also adjusted for body mass index (BMI), heartburn, and white race (white/nonwhite). Analyses of the risk of esophageal SCC were adjusted for pack-years of smoking and drinking. Age at menopause was defined as the age at which a woman had the last menstrual bleeding, a bilateral oophorectomy, or began using HT. Other potential confounders analyzed did not change the risk estimates by more than 10% and were not included in the models. Numbers presented in the tables are for women with no-missing values for the exposure of interest and corresponding adjusting variables. $P_{trend}$ values were obtained as the $P$ value associated with the corresponding continuous variable in the Cox model. All analyses were done by using STATA, version 10.1, software (StataCorp LP) for Macintosh.

## Results

A total of 161,080 women were included in this analysis with a median follow-up time of 11.82 years (interquartile range: 9.02–12.89 years) and person-years of 1,730,836.8. During the follow-up period, 23 women were diagnosed with esophageal adenocarcinoma and 34 with esophageal SCC.

Characteristics of the study participants are shown in Table 1. Compared with never-users, current users of HT were younger, of white race, more likely to have a college degree, and lower BMI. These 2 groups of women were similar in symptomatic heartburn and cigarette and alcohol use. Past users were more likely to be white and have lower BMI than never-users.

There was no evidence that HT use or other reproductive factors were associated with altered risk of esophageal adenocarcinoma (Table 2), with the exception of breastfeeding that was associated with a nonsignificant reduction of risk (HR = 0.44, 95% CI: 0.18–1.07). In contrast with esophageal adenocarcinoma, women who had ever used HT were at a lower risk of esophageal SCC compared with never-users. Specifically, past use of HT was associated with a 75% lower risk in 2 cases (HR = 0.25, 95% CI: 0.06–1.10) and current use of HT was associated with a significant 59% lower risk in 9 cases (HR = 0.41, 95% CI: 0.18–0.94). The reduced risk seems to be concentrated among baseline E+P users (HR = 0.25, 95% CI: 0.07–0.86 in 3 cases) as no association was observed for E-alone (HR = 0.96, 95% CI: 0.28–3.29 in 6 cases). A nonsignificant reduction of risk of esophageal SCC was also observed with the duration of use of E-alone and E+P (data not shown). No statistically significant evidence of effects on SCC risk was observed for other hormonal/reproductive factors (Table 2).

For esophageal adenocarcinoma, each of the available measures of obesity was strongly associated with incidence (Table 3). Of the 23 cases of esophageal adenocarcinoma, 21 (91.3%) were in the top half of the distribution of the entire WHI cohort with regard to waist-to-hip ratio and waist circumference. Compared with those in the highest quartile, those in the lowest quartile of waist circumference experienced a 92% (95% CI: 37%–99%) lower incidence of esophageal adenocarcinoma ($P_{trend} < 0.001$). A similar trend was seen with BMI. Having mild, moderate, or severe symptoms of heartburn were associated with approximately 2-, 3-, and 6-fold increased risk of esophageal adenocarcinoma, respectively ($P_{trend} = 0.009$). Compared with never smokers, women who smoked more than 40 pack-years were at a significantly increased esophageal adenocarcinoma risk ($P_{trend} = 0.023$).

For esophageal SCC, as expected, a history of cigarette use was strongly associated with increased risk, particularly among current smokers (Table 3). In contrast, in this population, drinking was not associated with risk of esophageal SCC. Increasing income was also associated with decreasing SCC risk ($P_{trend} = 0.013$).

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**Table 1.** Distribution of characteristics of subjects by use of HT

| Characteristics | Never-users ($N = 61,473$) *n* (%) | Past users only ($N = 23,482$) *n* (%) | Current users ($N = 75,986$) *n* (%) |
|---|---|---|---|
| Age, y | | | |
| 50–59 | 17,084 (27.8) | 6,348 (27.0) | 29,783 (39.2) |
| 60–69 | 28,185 (45.9) | 10,376 (44.2) | 33,670 (44.3) |
| 70–79 | 16,204 (26.4) | 6,758 (28.8) | 12,533 (16.5) |
| Race | | | |
| White | 48,373 (78.7) | 19,680 (83.8) | 64,975 (85.5) |
| Black | 7,736 (12.6) | 1,994 (8.5) | 4,744 (6.2) |
| Other | 5,200 (8.5) | 1,733 (7.4) | 6,098 (8.0) |
| Missing | 164 (0.3) | 75 (0.3) | 169 (0.2) |
| Education | | | |
| High school or less | 15,672 (25.5) | 5,416 (23.1) | 14,896 (19.6) |
| Some college/vocational | 22,269 (36.2) | 9,476 (40.4) | 28,866 (38.0) |
| College graduate or more | 23,025 (37.5) | 8,417 (35.8) | 31,703 (41.7) |
| Missing | 507 (0.8) | 173 (0.7) | 521 (0.7) |
| Income | | | |
| <$19,999 | 12,070 (19.6) | 4,075 (17.4) | 9,049 (11.9) |
| $20,000–$34,999 | 14,804 (24.1) | 5,867 (25.0) | 15,820 (20.8) |
| $35,000–$49,999 | 11,419 (18.6) | 4,439 (18.9) | 14,940 (19.7) |
| ≥$50,000 | 18,364 (29.9) | 7,518 (32.0) | 31,817 (41.9) |
| Missing | 4,816 (7.8) | 1,583 (6.7) | 4,360 (5.7) |
| BMI, kg/m$^2$ | | | |
| <18.5 | 582 (1.0) | 203 (0.9) | 608 (0.8) |
| 18.5–24.9 | 18,439 (30.0) | 7,754 (33.0) | 28,514 (37.5) |
| 25.0–29.9 | 20,722 (33.7) | 8,360 (35.6) | 26,342 (34.7) |
| 30.0–34.9 | 12,343 (20.1) | 4,329 (18.4) | 12,884 (17.0) |
| ≥35.0 | 8,755 (14.2) | 2,633 (11.2) | 7,093 (9.3) |
| Missing | 632 (1.0) | 203 (0.9) | 545 (0.7) |
| Symptoms of heartburn | | | |
| Did not occur | 39,937 (65.0) | 14,395 (61.3) | 48,417 (63.7) |
| Mild | 15,558 (25.3) | 6,401 (27.3) | 19,957 (26.3) |
| Moderate | 4,177 (6.8) | 1,961 (8.4) | 5,622 (7.4) |
| Severe | 1,150 (1.9) | 528 (2.3) | 1,458 (1.9) |
| Missing | 651 (1.1) | 197 (0.8) | 532 (0.7) |
| Pack-years of cigarette use | | | |
| Never | 31,838 (51.8) | 11,483 (48.9) | 37,680 (49.6) |
| <4.9 | 8,226 (13.4) | 3,291 (14.0) | 11,296 (14.9) |
| 5–19.9 | 8,194 (13.3) | 3,350 (14.3) | 10,822 (14.2) |
| 20–39.9 | 6,342 (10.3) | 2,643 (11.3) | 8,225 (10.8) |
| ≥40 | 4,859 (7.9) | 1,979 (8.4) | 5,497 (7.2) |
| Missing | 2,014 (3.3) | 736 (3.1) | 2,466 (3.3) |
| Alcohol use | | | |
| Non-drinker | 7,647 (12.4) | 2,519 (10.7) | 7,343 (9.7) |
| Past drinker | 12,467 (20.3) | 4,684 (20.0) | 12,769 (16.8) |
| <1 drink/wk | 19,999 (32.5) | 7,537 (32.1) | 25,067 (33.0) |
| 1–7 drinks/wk | 14,293 (23.3) | 5,784 (24.6) | 20,934 (27.6) |
| >7 drinks/wk | 6,533 (10.6) | 2,782 (11.9) | 9,378 (12.3) |
| Missing | 534 (0.9) | 176 (0.8) | 495 (0.7) |

NOTE: Data might not add up to 100% because of rounding. One hundred thirty-nine women had missing information on the use of HT and they were excluded from this table.

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**Table 2.** Adjusted HRs of hormonal related risk factors by outcome

| Risk factor | Esophageal adenocarcinoma | | | | Esophageal SCC | | | |
|---|---|---|---|---|---|---|---|---|
| | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 23$) | HR[a] | 95% CI | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 34$) | HR[b] | 95% CI |
| HT use | | | | | | | | |
| Never-users | 60,031 (38.1) | 9 (39.1) | 1.00 | ref. | 59,091 (38.2) | 21 (65.6) | 1.00 | ref. |
| Past users only | 22,998 (14.6) | 3 (13.0) | 0.74 | 0.20–2.82 | 22,622 (14.6) | 2 (6.3) | 0.25 | 0.06–1.10 |
| Current users | 74,704 (47.4) | 11 (47.8) | 0.87 | 0.35–2.17 | 73,132 (47.2) | 9 (28.1) | **0.41** | **0.18–0.94** |
| Type of HT (in current users) | | | | | | | | |
| Never-users | 60,031 (44.6) | 9 (45.0) | 1.00 | ref. | 59,109 (38.2) | 21 (70.0) | 1.00 | ref. |
| E-alone | 39,630 (29.4) | 5 (25.0) | 0.57 | 0.15–2.13 | 38,846 (29.4) | 6 (20.0) | 0.96 | 0.28–3.29 |
| E+P | 35,068 (26.0) | 6 (30.0) | 1.12 | 0.35–3.59 | 34,280 (25.9) | 3 (10.0) | **0.25** | **0.07–0.86** |
| Duration of HT use, y | | | | | | | | |
| Never-users | 60,031 (40.3) | 9 (45.0) | 1.00 | ref. | 59,091 (40.4) | 21 (67.7) | 1.00 | ref. |
| <10 | 54,215 (36.4) | 7 (35.0) | 0.94 | 0.34–2.62 | 53,133 (36.4) | 3 (9.7) | **0.19** | **0.06–0.64** |
| ≥10 | 34,623 (23.3) | 4 (20.0) | 0.72 | 0.20–2.57 | 33,950 (23.3) | 7 (22.6) | 0.62 | 0.24–1.56 |
| | | | | $P_{trend} = 0.632$ | | | | $P_{trend} = 0.093$ |
| Use of oral contraceptives | | | | | | | | |
| No | 92,222 (58.4) | 15 (65.2) | 1.00 | ref. | 90,630 (58.5) | 25 (78.1) | 1.00 | ref. |
| Yes | 65,641 (41.6) | 8 (34.8) | 0.92 | 0.37–2.28 | 64,345 (41.5) | 7 (21.9) | 0.47 | 0.19–1.15 |
| Number of term pregnancies | | | | | | | | |
| None | 18,638 (11.9) | 2 (8.7) | 0.91 | 0.17–5.02 | 18,351 (11.9) | 5 (15.6) | 0.65 | 0.22–1.97 |
| 1–2 | 53,250 (33.9) | 9 (39.1) | 1.39 | 0.42–4.59 | 52,160 (33.8) | 7 (21.9) | **0.34** | **0.12–0.92** |
| 3–4 | 61,984 (39.5) | 8 (34.8) | 0.87 | 0.26–2.90 | 60,889 (39.5) | 11 (34.4) | 0.46 | 0.19–1.10 |
| ≥5 | 23,094 (14.7) | 4 (17.4) | 1.00 | ref. | 22,754 (14.8) | 9 (28.1) | 1.00 | ref. |
| | | | | $P_{trend} = 0.681$ | | | | $P_{trend} = 0.239$ |
| Ever breast-fed[f] | | | | | | | | |
| No | 57,194 (41.8) | 13 (61.9) | 1.00 | ref. | 56,018 (41.7) | 10 (37.0) | 1.00 | ref. |
| Yes | 79,709 (58.2) | 8 (38.1) | 0.44 | 0.18–1.07 | 78,444 (58.3) | 17 (63.0) | 1.32 | 0.60–2.89 |
| Number of months breast-fed[f] | | | | | | | | |
| Never breast-fed | 57,194 (41.9) | 13 (61.9) | 1.00 | ref. | 56,018 (41.8) | 10 (37.0) | 1.00 | ref. |
| 1–6 | 40,174 (29.4) | 3 (14.3) | 0.32 | 0.09–1.13 | 39,483 (29.5) | 12 (44.4) | 1.73 | 0.75–4.02 |
| ≥7 | 39,102 (28.7) | 5 (23.8) | 0.57 | 0.21–1.60 | 38,539 (28.8) | 5 (18.5) | 0.84 | 0.29–2.48 |
| | | | | $P_{trend} = 0.183$ | | | | $P_{trend} = 0.960$ |
| Age at menopause, y | | | | | | | | |
| <45 | 43,060 (29.0) | 4 (20.0) | 1.00 | ref. | 42,343 (29.0) | 8 (28.6) | 1.00 | ref. |
| 45—49 | 36,185 (24.4) | 7 (35.0) | 2.55 | 0.70–9.30 | 35,552 (24.4) | 4 (14.3) | 0.51 | 0.14–1.79 |
| 50—54 | 51,502 (34.7) | 5 (25.0) | 1.33 | 0.31–5.78 | 50,652 (34.7) | 10 (35.7) | 0.86 | 0.29–2.53 |
| ≥55 | 17,670 (11.9) | 4 (20.0) | 2.63 | 0.54–12.77 | 17,328 (11.9) | 6 (21.4) | 1.36 | 0.40–4.62 |
| | | | | $P_{trend} = 0.450$ | | | | $P_{trend} = 0.527$ |

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**Table 2.** Adjusted HRs of hormonal related risk factors by outcome (cont'd)

| | Esophageal adenocarcinoma | | | | Esophageal SCC | | | |
|---|---|---|---|---|---|---|---|---|
| **Risk factor** | **Number (%) of women ($N = 161,080$)** | **Number (%) of cases ($N = 23$)** | **HR[a]** | **95% CI** | **Number (%) of women ($N = 161,080$)** | **Number (%) of cases ($N = 34$)** | **HR[b]** | **95% CI** |
| Age at menarche, y | | | | | | | | |
| <12 | 18,428 (14.0) | 4 (19.1) | 1.00 | ref. | 18,187 (14.0) | 6 (20.7) | 1.00 | ref. |
| 12 | 27,470 (20.8) | 6 (28.6) | 1.07 | 0.30–3.79 | 27,003 (20.8) | 9 (31.0) | 0.99 | 0.35–2.80 |
| 13 | 34,365 (26.0) | 4 (19.1) | 0.59 | 0.15–2.36 | 33,824 (26.0) | 4 (13.8) | 0.35 | 0.10–1.24 |
| 14 | 22,826 (17.3) | 3 (14.3) | 0.70 | 0.15–3.15 | 22,474 (17.3) | 5 (17.2) | 0.65 | 0.20–2.14 |
| ≥15 | 29,041 (22.0) | 4 (19.1) | 0.72 | 0.18–2.91 | 28,532 (21.9) | 5 (17.2) | 0.51 | 0.16–1.69 |
| | | | | $P_{trend} = 0.482$ | | | | $P_{trend} = 0.169$ |
| Age at first term pregnancy, y | | | | | | | | |
| <20 | 20,112 (16.1) | 4 (21.1) | 1.43 | 0.42–4.85 | 19,779 (16.1) | 2 (8.0) | 0.44 | 0.10–1.96 |
| 20–24 | 59,431 (47.7) | 8 (42.1) | 1.00 | ref. | 58,455 (47.7) | 13 (52.0) | 1.00 | ref. |
| 25–29 | 33,407 (26.8) | 5 (36.3) | 1.26 | 0.41–3.87 | 32,833 (26.8) | 5 (20.0) | 0.67 | 0.24–1.90 |
| ≥30 | 11,751 (9.4) | 2 (10.5) | 1.52 | 0.32–7.22 | 11,501 (9.4) | 5 (20.0) | 1.91 | 0.67–5.45 |
| | | | | $P_{trend} = 0.883$ | | | | $P_{trend} = 0.195$ |

NOTE: Numbers only for women with no-missing values for the exposure of interest and corresponding adjusting variables.

[a]Adjusted for BMI (continuous), heartburn (did not occur/mild/moderate/severe), white race (white/nonwhite) and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).

[b]Adjusted for pack-years of smoking (never/<5/5–19.9/20–39.9/≥40), drinking (non-drinker/past drinker/<1 drink per week/1–7 drinks per week/>7 drinks per week), and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).

[c]Adjusted for past use of HT (defined as non–current users relative to baseline in the OS and non-HT trials but reported use of HT before baseline; and users of HT before randomization in the HT trial but assigned to the placebo arm).

[d]Adjsuted for past use of E (similar definitio`n to past use of HT).

[e]Adjusted for past use of E+P (similar definition to past use of HT).

[f]Only women with at least one live birth.





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**Table 3.** Adjusted hazard ratios of other risk factors by outcome

| Risk factor | Esophageal adenocarcinoma | | | | Esophageal SCC | | | |
|---|---|---|---|---|---|---|---|---|
| | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 23$) | HR[a] | 95% CI | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 34$) | HR[b] | 95% CI |
| BMI,[c] kg/m$^2$ | | | | | | | | |
| <24.9 | 55,559 (35.2) | 2 (8.7) | 0.12 | 0.02–0.64 | 54,120 (35.2) | 11 (34.4) | 1.00 | ref. |
| 25.0–29.9 | 54,810 (34.7) | 8 (34.8) | 0.42 | 0.14–1.24 | 53,394 (34.8) | 14 (43.8) | 1.23 | 0.56–2.72 |
| 30.0–34.9 | 29,227 (18.5) | 7 (30.4) | 0.66 | 0.22–1.98 | 28,389 (18.5) | 5 (15.6) | 0.86 | 0.30–2.50 |
| ≥35.0 | 18,270 (11.6) | 6 (26.1) | 1.00 | ref. | 17,762 (11.6) | 2 (6.3) | 0.59 | 0.13–2.72 |
| | | | | $P_{trend} = 0.005$ | | | | $P_{trend} = 0.529$ |
| Waist-to-hip ratio[c] | | | | | | | | |
| Quartile 1 ($x \leq 0.76$) | 39,750 (25.1) | 1 (4.4) | 0.11 | 0.01–0.83 | 38,730 (25.1) | 4 (12.9) | 0.50 | 0.16–1.59 |
| Quartile 2 ($0.76 < x \leq 0.80$) | 39,653 (25.0) | 1 (4.4) | 0.09 | 0.01–0.73 | 38,611 (25.0) | 6 (19.4) | 0.64 | 0.23–1.75 |
| Quartile 3 ($0.80 < x \leq 0.86$) | 39,717 (25.1) | 9 (39.1) | 0.78 | 0.33–1.87 | 38,627 (25.0) | 10 (32.3) | 0.99 | 0.42–2.35 |
| Quartile 4 ($x > 0.86$) | 39,399 (24.9) | 12 (52.2) | 1.00 | ref. | 38,330 (24.8) | 11 (35.5) | 1.00 | ref. |
| | | | | $P_{trend} = 0.002$ | | | | $P_{trend} = 0.173$ |
| Waist circumference[c] | | | | | | | | |
| Quartile 1 ($x \leq 76$) | 40,043 (25.2) | 1 (4.4) | 0.08 | 0.01–0.63 | 39,014 (25.3) | 6 (18.8) | 0.65 | 0.23–1.84 |
| Quartile 2 ($76 < x \leq 84.5$) | 39,700 (25.0) | 1 (4.4) | 0.07 | 0.01–0.55 | 38,681 (25.0) | 9 (28.1) | 0.90 | 0.36–2.26 |
| Quartile 3 ($84.5 < x \leq 95$) | 40,787 (25.7) | 6 (26.1) | 0.38 | 0.15–0.98 | 39,675 (25.7) | 7 (21.9) | 0.65 | 0.25–1.73 |
| Quartile 4 ($x > 95$) | 38,150 (24.0) | 15 (65.2) | 1.00 | ref. | 37,086 (24.0) | 10 (31.3) | 1.00 | ref. |
| | | | | $P_{trend} < 0.001$ | | | | $P_{trend} = 0.564$ |
| Symptoms of heartburn[d] | | | | | | | | |
| Did not occur | 101,628 (64.4) | 9 (39.1) | 1.00 | ref. | 99,110 (64.4) | 23 (71.9) | 1.00 | ref. |
| Mild | 41,517 (26.3) | 8 (34.8) | 1.89 | 0.73–4.90 | 40,459 (26.3) | 7 (21.9) | 0.71 | 0.31–1.66 |
| Moderate | 11,623 (7.4) | 4 (17.4) | 3.13 | 0.95–10.26 | 11,273 (7.3) | 2 (6.3) | 0.70 | 0.16–2.97 |
| Severe | 3,098 (2.0) | 2 (8.7) | 5.63 | 1.19–26.59 | 3,026 (2.0) | – | – | – |
| | | | | $P_{trend} = 0.009$ | | | | $P_{trend} = 0.268$ |
| Cigarette use[e] | | | | | | | | |
| Never smoker | 79,517 (51.0) | 8 (34.8) | 1.00 | ref. | 80,514 (50.9) | 7 (21.2) | 1.00 | ref. |
| Past smoker | 65,641 (42.1) | 13 (56.5) | 1.92 | 0.79–4.65 | 66,551 (42.1) | 17 (51.5) | 2.93 | 1.18–7.32 |
| Current smoker | 10,860 (7.0) | 2 (8.7) | 2.49 | 0.52–11.98 | 11,014 (7.0) | 9 (27.3) | 12.67 | 4.55–35.28 |
| Pack-years of cigarette use[e] | | | | | | | | |
| Never smoker | 79,517 (51.9) | 8 (36.4) | 1.00 | ref. | 80,514 (51.9) | 7 (21.9) | 1.00 | ref. |
| <20 | 44,519 (29.1) | 6 (27.3) | 1.42 | 0.49–4.12 | 45,147 (29.1) | 7 (21.9) | 1.89 | 0.64–5.56 |
| 20–39.9 | 16,924 (11.1) | 2 (9.1) | 1.16 | 0.25–5.48 | 17,136 (11.1) | 10 (31.3) | 7.27 | 2.67–19.83 |
| ≥40 | 12,124 (7.9) | 6 (27.3) | 4.12 | 1.42–11.99 | 12,299 (7.9) | 8 (25.0) | 7.98 | 2.79–22.85 |
| | | | | $P_{trend} = 0.023$ | | | | $P_{trend} < 0.001$ |

*(Continued on the following page)*

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**Table 3.** Adjusted hazard ratios of other risk factors by outcome (cont'd)

| Risk factor | Esophageal adenocarcinoma | | | | Esophageal SCC | | | |
|---|---|---|---|---|---|---|---|---|
| | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 23$) | HR[a] | 95% CI | Number (%) of women ($N = 161,080$) | Number (%) of cases ($N = 34$) | HR[b] | 95% CI |
| Alcohol use[f] | | | | | | | | |
| Non-drinker | 17,091 (10.9) | 1 (4.4) | 0.38 | 0.05–2.87 | 17,291 (11.2) | 2 (6.3) | 1.28 | 0.28–5.82 |
| Past drinker | 29,318 (18.7) | 5 (21.7) | 1.01 | 0.36–2.77 | 29,016 (18.7) | 10 (31.3) | 1.96 | 0.92–4.20 |
| Current drinker | 110,422 (70.4) | 17 (73.9) | 1.00 | ref. | 108,670 (70.1) | 20 (62.5) | 1.00 | ref. |
| Alcohol use[f] | | | | | | | | |
| Non–current drinker | 46,409 (29.6) | 6 (26.1) | 1.00 | ref. | 46,307 (29.9) | 12 (37.5) | 1.00 | ref. |
| <1 drink/wk | 51,721 (33.0) | 8 (34.8) | 1.18 | 0.41–3.42 | 51,124 (33.0) | 6 (18.8) | 0.41 | 0.15–1.10 |
| 1–7 drinks/wk | 40,331 (25.7) | 7 (30.4) | 1.53 | 0.50–4.64 | 39,579 (25.5) | 11 (34.4) | 0.83 | 0.36–1.90 |
| >7 drinks/wk | 18,370 (11.7) | 2 (8.7) | 1.00 | 0.20–5.06 | 17,967 (11.6) | 3 (9.4) | 0.36 | 0.10–1.29 |
| | | | | $P_{trend} = 0.687$ | | | | $P_{trend} = 0.247$ |
| Education | | | | | | | | |
| High school or less | 35,112 (22.4) | 8 (23.5) | 1.00 | ref. | 34,586 (22.5) | 7 (21.9) | 1.00 | ref. |
| Some college/vocational | 59,541 (38.0) | 10 (29.4) | 1.01 | 0.39–2.62 | 58,360 (37.9) | 10 (31.3) | 0.85 | 0.32–2.24 |
| College graduate or more | 62,019 (39.6) | 16 (47.1) | 0.55 | 0.17–1.78 | 60,889 (39.6) | 15 (46.9) | 1.32 | 0.53–3.33 |
| | | | | $P_{trend} = 0.324$ | | | | $P_{trend} = 0.445$ |
| Income | | | | | | | | |
| <$19,999 | 24,473 (16.6) | 10 (30.3) | 1.00 | ref. | 24,160 (16.7) | 10 (32.2) | 1.00 | ref. |
| $20,000–$34,999 | 35,833 (24.3) | 13 (39.4) | 0.66 | 0.23–1.88 | 35,192 (24.3) | 11 (35.5) | 0.76 | 0.32–1.80 |
| $35,000–$49,999 | 30,254 (20.5) | 4 (12.1) | 0.25 | 0.05–1.22 | 29,715 (20.5) | 4 (12.9) | 0.34 | 0.10–1.11 |
| ≥$50,000 | 56,832 (38.6) | 6 (18.2) | 0.60 | 0.20–1.83 | 55,674 (38.5) | 6 (19.4) | 0.30 | 0.10–0.88 |
| | | | | $P_{trend} = 0.282$ | | | | $P_{trend} = 0.013$ |

NOTE: Numbers only for women with no-missing values for the exposure of interest and corresponding adjusting variables.

[a]Adjusted for BMI (continuous), heartburn (did not occur/mild/moderate/severe), white race (white/nonwhite) and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).

[b]Adjusted for pack-years of smoking (never/<5/5–19.9/20–39.9/≥40), drinking (non-drinker/past drinker/<1 drink per week/1–7 drinks per week/>7 drinks per week) and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).

[c]Not adjusted for BMI.

[d]Not adjusted for heartburn.

[e]Not adjusted for smoking.

[f]Not adjusted for drinking.





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**Table 4.** Esophageal cancer mortality, assuming deaths after diagnosis of esophageal cancer to be esophageal cancer deaths

| | Esophageal adenocarcinoma | | | | Esophageal SCC | | | |
|---|---|---|---|---|---|---|---|---|
| Risk factor | Number (%) of women ($N = 161,080$) | Number (%) of deaths ($N = 17$) | HR[a] | 95% CI | Number (%) of women ($N = 161,080$) | Number (%) of deaths ($N = 28$) | HR[b] | 95% CI |
| HT use | | | | | | | | |
| Never-users | 60,031 (38.1) | 6 (35.3) | 1.00 | ref. | 59,091 (38.2) | 16 (59.3) | 1.00 | ref. |
| Past users only | 22,998 (14.6) | 3 (17.7) | 1.03 | 0.25–4.28 | 22,622 (14.6) | 2 (7.4) | 0.33 | 0.07–1.43 |
| Current users | 74,704 (47.4) | 8 (47.1) | 0.89 | 0.29–2.68 | 73,132 (47.2) | 9 (33.3) | 0.55 | 0.23–1.31 |
| Type of HT (in current users) | | | | | | | | |
| Never-users | 60,031 (44.6) | 6 (42.9) | 1.00 | ref. | 59,091 (44.7) | 16 (64.0) | 1.00 | ref. |
| E-alone | 39,630 (29.4) | 5 (35.7) | 0.72 | 0.17–3.02 | 38,846 (29.4) | 6 (24.0) | 1.07 | 0.30–3.88 |
| E+P | 38,068 (26.0) | 3 (21.4) | 0.98 | 0.21–4.64 | 34,280 (25.9) | 3 (12.0) | 0.38 | 0.11–1.35 |

NOTE: Numbers only for women with no-missing values for the exposure of interest and corresponding adjusting variables.
[a]Adjusted for BMI (continuous), heartburn (did not occur/mild/moderate/severe), white race (white/nonwhite) and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).
[b]Adjusted for pack-years of smoking (never/<5/5–19.9/20–39.9/≥40), drinking (non-drinker/past drinker/<1 drink per week/1–7 drinks per week/>7 drinks per week) and stratified by age (50–59/60–69/70–79), hysterectomy status, and study type (HT trial/OS or non-HT trials).

We examined the relationship between HT use and type of HT use and esophageal cancer mortality. Of the 23 cases of esophageal adenocarcinoma, 17 (74%) died during the study period with a median time from diagnosis to death of 1.02 years (interquartile range: 0.67–1.83 years). Use of HT was not associated with the risk of dying from esophageal adenocarcinoma (Table 4). Of the 34 cases of esophageal SCC, 28 (82%) died during the study period with a median time from diagnosis to death of 1.22 years (interquartile range: 0.60–2.20 years). Esophageal SCC mortality was inversely related with use of E+P, although nonsignificantly, consistent with the relationship observed with incidence of esophageal SCC.

## Discussion

No association was observed between use of HT and risk of esophageal adenocarcinoma. In contrast, the use of HT was associated with a lower risk of esophageal SCC in postmenopausal women. This association was observed in current users of E+P but not in current users of E-alone. No other hormonal or reproductive factors were significantly related to risk of either esophageal SCC or adenocarcinoma. Esophageal cancer mortality exhibited a similar pattern of hormone effects but these were not statistically significant.

Our findings of no association between HT use and risk of esophageal adenocarcinoma are similar to the results of 2 other studies (11, 12). One study examined the risk of esophageal adenocarcinoma after initiation of estrogen therapy among prostate cancer patients and thus is not directly comparable to our study (22). A second study examined the short-term risk of esophageal adenocarcinoma among breast cancer survivors treated with tamoxifen, a selective estrogen receptor modulator, reporting a 1.6-fold increase in esophageal adenocarcinoma risk (95% CI = 0.8–3.1; ref. 7). However, their study did not provide information on whether these women had also been treated with radiation, which may increase esophageal risk in breast cancer patients (23–25). A more recent study did not find an association between the risk of gastric adenocarcinoma, which included esophageal adenocarcinoma, and the use of HT when the most distal cases of stomach cancer were removed from the analysis (HR = 0.90, 95% CI: 0.54–1.49; ref. 9). Interestingly, we found that breast-feeding was associated with a nonsignificant 54% reduction of risk of esophageal adenocarcinoma (HR = 0.44, 95% CI: 0.18–1.07), similar to the 59% reduction (95% CI: 18%–80%) found in a case–control study from the United Kingdom (8).

Some of our findings about the risk of esophageal SCC are consistent with results reported previously (9, 18). In a pooled analysis of 3 case–control studies in Italy and Switzerland, ever use of HT was associated with a reduction in risk of esophageal SCC (OR = 0.32, 95% CI: 0.09–1.13; ref. 18). Results from Freedman and colleagues also suggest that users of HT were at slightly lower risk of esophageal SCC (HR = 0.74, 95% CI: 0.42–1.28; ref. 9). This study found that use of E+P among women with intact uterus was associated with a decreased risk (HR = 0.41, 95% CI: 0.15–1.14; ref. 9). Our findings are consistent with the notion that an inverse association may be limited to users of E+P. It could be that those women not taking HT have less access to health care because of low socioeconomic status. Although socioeconomic status is a

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risk factor for esophageal SCC (26, 27), our results were qualitatively similar after adjustment for education and income.

Most relative risk estimates associated with the established risk factors for esophageal adenocarcinoma and SCC, such as obesity, symptomatic reflux smoking, and drinking, have been studied in populations of men only (28, 29) or predominantly men (30, 31). In our cohort of women, we found that smoking, symptomatic reflux, and BMI were associated with esophageal adenocarcinoma in similar patterns to other studies (30–33). For esophageal SCC, smoking was associated with a large increase in risk, as previously reported (18, 29). In contrast, we did not observe alcohol use to be associated with the risk of esophageal SCC, but it is worth noting that these women were not heavy drinkers; more than 88% of women reported having 7 or fewer drinks per week. In other studies, associations with drinking were found in much heavier drinkers (18, 29).

Several limitations should be noted. The major one is the small number of esophageal cancer cases observed. This is a problem that most studies of esophageal cancer in women suffer, particularly prospective studies, because of the low incidence of this disease among women (7–12, 18). The small number of events observed in the HT trials did not allow for a reliable estimate of HT effects using only clinical trial information so these data were pooled with the larger observational study to increase study power. These analyses used the randomized assignment for the trial participants as well as the baseline use status in the remaining WHI participants, in a manner related to Prentice and colleagues (34). Even in the pooled data set, the numbers of cases were small and might have precluded us from observing statistically significant associations, especially with the risk of esophageal adenocarcinoma. Another limitation of our study was that our estimates rely on information collected at study enrollment for the exposures of interest and did not take into account changes that might have occurred during the follow-up period. We also tested for multiple variables, which might have increased the likelihood of finding a false association by chance. Finally, we attempted to control for known confounders, but it is possible that unknown or unmeasured variables might have influenced our results.

Our study has several notable strengths such as a prospective design, high quality assessment of HT use as well as other reproductive variables, and high-quality assessment of endpoints. We were also able to adjust for a majority of the known risk factors for the 2 types of cancer.

In summary, the use of HT was found to be associated with a decreased risk of esophageal SCC, but no association was observed with esophageal adenocarcinoma. Because of the small numbers of cases, a pooled analysis of all available studies or a much larger study would be needed to provide more definitive and reliable evidence of the use of HT, reproductive factors, and the risks of esophageal adenocarcinoma and SCC.

## Disclosure of Potential Conflict of interest

No potential conflicts of interest were disclosed.

## Grant Support

C. Bodelon and T.L. Vaughan were supported by grant numbers T32 CA009168 and K05CA124911, respectively, from the NIH. The WHI program is funded by the National Heart, Lung, and Blood Institute, NIH, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

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Received December 19, 2010; revised March 11, 2011; accepted April 8, 2011; published OnlineFirst April 19, 2011.

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