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The association of menstrual and reproductive factors with upper gastrointestinal tract cancers in the NIH-AARP cohort

Neal D. Freedman, PhD MPH[1], **James V. Lacey Jr., PhD**[1], **Albert R. Hollenbeck, PhD**[2], **Michael F. Leitzmann, MD DrPH**[3], **Arthur Schatzkin, MD DrPH**[1], and **Christian C. Abnet, PhD MPH**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

[2]AARP, Washington, DC, USA

[3]Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany

Abstract

Background—In most populations, incidence rates of upper gastrointestinal tract cancers (UGI: head and neck, esophagus, and stomach) are higher among men than among women. Established risk factors do not appear to explain these differences, suggesting a possible role for sex hormones.

Methods—201,506 women of the NIH-AARP Diet and Health cohort completed a questionnaire in 1995-1996. Hazard ratios and 95% confidence intervals were estimated from Cox proportional hazards models.

Results—During follow-up through 2003, 162 incident adenocarcinomas (ACs; esophagus (N=25) and stomach (N=137)) and 353 incident squamous cell carcinomas (SCCs; head and neck (n=297), and esophagus (N=56)) occurred. Among examined exposures, older age at menopause was associated inversely with SCC (p-trend across categories=0.013) but not AC (p-trend=0.501). Use of menopausal hormone therapy (MHT) was significantly associated with lower risk of SCC (HR=0.77, 0.62-0.96) and non-significantly associated with lower risk of AC (HR=0.81, 0.59-1.12). A subset (N=127,386) of the cohort completed a more detailed MHT questionnaire a year after baseline. In 74,372 women with intact uteri, ever use of estrogen-plus-progestin MHT conferred 0.47 (0.30-0.75) times the risk for SCC and 0.52 (0.26-1.07) times the risk for ACC. In 51,515 women with a hysterectomy before baseline, we found no associations between use of estrogen MHT and AC or SCC.

Conclusions—Higher estrogen and progesterone levels may be related inversely to UGI cancers and in this way help explain lower incidence rates in women compared to men.

Keywords

Head and Neck Neoplasms; stomach neoplasms; esophageal neoplasms; Estrogen Replacement Therapy

Correspondence: Neal Freedman PhD MPH, Division of Cancer Epidemiology and Genetics, Nutritional Epidemiology Branch, 6120 Executive Blvd, EPS/320, MSC 7232, Rockville, MD, 20852 USA Voice: +1 301 594-6119 Fax: +1 301 496-6829 freedmanne@mail.nih.gov.

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Introduction

Cancers of the head and neck (oral cavity, pharynx, and larynx), esophagus, and stomach, collectively called upper gastrointestinal tract cancers (UGI), have high worldwide incidence and mortality. Incidence rates are higher among men than women in most populations, with the male/female ratio ranging from 2:1 for adenocarinomas of the stomach to 7:1 for squamous cell carcinomas of the larynx and adenocarcinomas of the esophagus.1

Strong environmental risk factors have been identified,2–4 including alcohol use and tobacco smoking for the squamous sites and *Helicobacter pylori* and tobacco smoking for the adenocarcinomas. But, differential exposure to known risk factors in men and women does not seem to fully explain sex differences in incidence rates. For example, adiposity and reflux disease are strong risk factors for esophageal adenocarcinoma, yet the prevalence of these risk factors are similar in men and women.5 Alcohol drinking and tobacco smoking are two causes of head and neck cancer, yet recent data suggest that incidence rates in never-smoking never-drinking men are five times higher than in never-smoking never-drinking women.6,7

Hormonal differences between men and women may help explain these sex differences. Most previous studies of the association between menstrual and reproductive factors with gastric cancer8–17 and esophageal or head and neck cancer15,18–23 have been limited by small case numbers. Therefore, we examined the association of hormonal and menstrual factors with UGI cancer risk in the NIH-AARP Diet and Health Study.

Methods

The NIH-AARP Diet and Health Study is a large prospective cohort initiated in 1995 when a baseline questionnaire was mailed to 3.5 million members of AARP aged 50-71 years who resided in eight U.S. states (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania).24 Of those who returned the questionnaire, 566,402 respondents completed the survey in satisfactory detail and consented to be in the study. We excluded subjects with cancer or death at baseline (N=51,217), proxy respondents (N=15,760), and men (N=297,919). The resulting cohort included 201,506 women.

A second questionnaire, which collected detailed information on menopausal hormone therapy (MHT) and other covariates, was mailed in 1996-1997 to individuals who returned the baseline questionnaire. Of 337,074 completed questionnaires, we excluded participants who died (N = 1,619) or moved out of the study area (N = 547) before their completed second questionnaires were scanned, proxy respondents to the baseline questionnaire (N = 6959) or to the second questionnaire (N = 3,424), men (N=188,117), and those with a cancer at the time of the second questionnaire (N=9,022). The resulting cohort included 127,386 women, but we restricted analyses to 125,887 women who reported hysterectomy status at baseline.

The NIH-AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute (NCI). All participants provided informed consent.

Cohort follow-up

We ascertained vital status by annual linkage to the Social Security Administration Death Master File. Addresses of participants were updated annually using data from the National Change of Address database maintained by the U.S. Postal Service along with responses to mailings by study participants. Our total loss to follow-up, including both those who moved

out of the catchment area and those for whom we do not have a proper address was less than 5%.

Identification of cancer cases

Incident cancers were identified by linkage between the NIH-AARP cohort membership and 11 state cancer registry databases (8 states from baseline together with 3 most common states of relocation: Arizona, Nevada, and Texas). We estimate that 90% of cancers are detected in the cohort by this approach.25 Cancer sites were defined as previously described.[7,26]

Exposure Assessment

The baseline questionnaire asked about hysterectomy, oophorectomy, reproductive history, oral contraceptive use, menopausal status, MHT use, demographics, alcohol intake, tobacco smoking, physical activity, and diet. We lacked information on *Helicobacter pylori* infection and Gastroesophageal reflux disease.

The second questionnaire included detailed questions on MHT use, including dates of first and last use, regimen, usual dose, and specific medication names. As described previously, 27 participants were classified as users of estrogen-plus-progestin if their reported dates of first use were within 90 days of each other or if the reported durations of use were identical. Sequential regimens (N=13,018) included estrogen-plus-progestin used for 15 or fewer days per cycle; continuous regimens (N=19,110) included estrogen-plus-progestin used for 20 to 25 days per cycle (N=5,354) and every day of the cycle (N=13,756).

Statistical Methods

Analyses were performed with SAS version 9.1. A significance level of less than 0.05 was used and all tests were two-sided. Hazard ratios (HR) and 95% confidence intervals were calculated using Cox proportional hazards regression.28 Age was used as the underlying time metric.29 Follow-up time extended from the participants age on the date the questionnaire was returned until age at the end of follow-up (diagnosis of the first UGI cancer, death, end of study, or move out of registry ascertainment area). We tested for and found no deviations from the proportional hazards assumption. We also excluded the first two years of follow-up and the results did not change.

Multivariate models included adjustment for categorical variables of education and alcohol intake shown in Table 1, body mass index (BMI) in kg/m^2 (<18.5, ≤18.5-<25, ≤25-<30, ≤30-<35 and ≤35), smoking use (never cigarette smokers, quit ≤1 pack/day, quit >1 pack per day, currently smoking ≤1 pack/day, and currently smoking >1 pack/day), vigorous physical activity (never, rarely, 1-3 times/month, 1-2 times/week, 3-4 times/week, 5 or more times per week), and continuous variables for age at cohort entry and intakes of fruit, vegetables, and total energy. A separate indicator variable for missing was included in the models for subjects that were missing data on adjusting variables. The maximum amount of missing data for any covariate was 4%. As MHT is typically prescribed based on hysterectomy status, we stratified analyses of estrogen therapy (ET) or estrogen-plus-progestin therapy (EPT) by hysterectomy status. Regression models used women who reported not using MHT as the referent group. For analyses of duration and regimen, we included separate categories for unknown and those using other forms of hormone therapy.

To examine effect modification, we inspected risk estimates by stratum of tobacco smoking and alcohol intake. Multivariate models stratified by ever/never smoking use included adjustment for smoking dose and years since smoking cessation where appropriate as well as

the covariates used for the overall models including alcohol use; likewise, models stratified by alcohol use were adjusted for smoking and other covariates.

Results

Over the course of follow-up (median=7.5 years), 162 women were diagnosed with adenocarcinomas of the esophagus or stomach and 353 women were diagnosed with squamous cancers of the esophagus or head and neck. Participants developing both cancer types were more likely to smoke cigarettes than those in the cohort overall (Table 1). Relative to the cohort overall, participants with incident adenocarcinomas had higher BMI and total caloric intake, and less education. Participants with incident squamous cancers had higher alcohol consumption, lower BMI, lower fruit intake, and less education.

We first present risk estimates for the association of menstrual and reproductive factors with adenocarcinoma risk from multivariate adjusted models (Table 2). No associations were observed with age at menarche, age at menopause, oral contraceptive use, parity, hysterectomy, or bilateral oophorectomy. Ever use of MHT had a non-significant inverse association with adenocarcinoma risk (0.81, 95% CI: 0.59-1.12). We also found a borderline inverse association between older age at first birth and lower cancer risk (p-trend=0.145).

Analyses were also stratified by anatomic site (Table 2). Results for MHT appeared similar for both non-cardia gastric cancers (n=97; 0.76, 95% CI: 0.50-1.15) and adenocarcinomas of the gastric cardia and esophagus (n=65; 0.90, 95% CI: 0.54-1.49). Age at first birth had a borderline inverse association with adenocarcinomas of the gastric cardia and esophagus (p-trend=0.107), but not those of the non-cardia (p-trend=0.581). In contrast, we observed some evidence for an inverse association between older age at menopause and non-cardia gastric cancer risk (p-trend=0.189), but not adenocarcinomas of the gastric cardia and esophagus (p-trend=0.569).

Next, we investigated associations between menstrual and reproductive factors and UGI cancers with squamous histology (Table 3). No associations were observed with age at first birth, age at menarche, oral contraceptive use, parity, hysterectomy, or bilateral oophorectomy. A statistically significant association was observed for ever MHT use (HR: 0.77, 95% CI: 0.62-0.96). We also observed a statistically significant inverse association for age at menopause. Participants with an age at menopause of < 45 years had 1.42 (95% CI: 0.97-2.09) times the risk of participants with an age at menopause between 50-54 years; the p-trend across categories was 0.013.

We further stratified analyses of squamous tumors by anatomic site (Table 3). Similar to the results for the total squamous category, we found no associations between age at first birth, age at menarche, oral contraceptive use, parity, hysterectomy, or bilateral oophorectomy and cancer risk. Point estimates for ever-use of MHT were similar for both esophageal (HR: 0.74, 95% CI: 0.42-1.28) and head and neck (HR: 0.78, 95% CI: 0.61-0.99) tumors. Risk estimates for age at menopause also appeared similar for tumors of the esophagus (p-trend across increasing age at menopause= 0.019) and head and neck (p-trend=0.098) in multivariate adjusted models. Among sub-sites of the head and neck, associations were similar for the oral cavity, oro- and hypo-pharynx, and larynx (data not shown).

More detailed information on MHT use was collected for a subset of 127,386 women who completed a follow-up questionnaire in 1996/1997. As usage patterns differed by hysterectomy status, we examined the association between estrogen therapy (ET) and cancer risk among women who reported having had a hysterectomy (N=51,515) and examined the association between estrogen-plus-progestin therapy (EPT) and cancer risk among women who reported an intact uterus (N=74,372). We found no evidence of an association between

ET and adenocarcinoma (Table 4) or squamous cancer risk (Table 5) but did observe an association between EPT and both histologic types (Table 4, Table 5). Ever-users of EPT had 0.52 times (95% CI: 0.26-1.07, 49 cases) the risk of non-users for adenocarcinomas and 0.47 times (95%CI: 0.30-0.75, 130 cases) the risk of non-users for squamous cancers and these associations varied by duration. The p-trend across increasing years of use was 0.068 for adenocarcinomas (Table 4) and 0.0004 for squamous cancers (Table 5). Among EPT users, risk estimates were similar for both sequential and continuous (15 + days per month) regimens (Table 4, Table 5). Results stratified by anatomic sub-site appeared similar to those for each histology overall, though case numbers were low. (Table 4, Table 5).

Because tobacco smoking and alcohol use are strong risk factors for squamous UGI cancers, we examined the association of EPT use in models stratified by these risk factors. Risk estimates for EPT use (versus never MHT use) were similar among never (HR: 0.22, 95%CI: 0.06-0.75) and ever tobacco smokers (HR: 0.55, 95%CI: 0.35-0.86; p-interaction= 0.202) and both alcohol drinkers (HR: 0.49, 95%CI: 0.30-0.78) and non-drinkers (HR: 0.54, 95%CI: 0.25-1.18; p-interaction=0.345).

Discussion

In this prospective cohort study, we found evidence for an inverse association between estrogen-plus-progestin MHT therapy and UGI cancers with squamous and adenocarcinoma histology. Older age at menopause was inversely associated with squamous, but not adenocarcinomas of the UGI tract. No significant associations were observed with age at first birth, age at menarche, oral contraceptive use, parity, hysterectomy, or bilateral oophorectomy for either histologic type.

In our study, we found evidence for an inverse association for MHT use with all tumor sites examined, though case numbers were low for specific anatomic and histologic sub-sites. The few previous studies of MHT use and UGI cancers have been limited by small case numbers and low prevalence of MHT use.[8,9,15,18-22] For squamous UGI tumors, possible inverse associations were observed with MHT use in European case-control studies of esophagus (odds ratio [OR]: 0.32, 95% CI: 0.09-1.13; 93 cases),[21] larynx (OR: 0.3, 95% CI 0.0-1.5; 68 cases),[22] oral cavity-pharynx (OR: 0.88, 95% CI: 0.45-1.72, 153 cases),[19] and oral cavity-pharynx-larynx-esophagus (OR: 0.7, 95% CI: 0.4-1.2; 253 cases).[20] Two other studies had risk estimates close to 1, one of the esophagus (relative risk [RR]: 0.93, 95% CI: 0.40-2.16; 74 cases)[15] and one of the oral cavity-pharynx (RR: 0.95, 95% CI: 0.33-2.72 for ≥ 25 months of MHT relative to 1-6 months of use; 153 cases).[18] For tumors with adenocarcinoma histology, two European studies showed possible inverse associations with MHT use (ever versus never: 0.7, 95% CI: 0.4-1.3, 258 cases;[20] 0.73, 95%CI: 0.37-1.45 for those with ≥ 25 months of MHT relative to 1-6 months of use,116 cases),[18] as did data from a Canadian study (ever versus never: 0.72, 95% CI: 0.72-1.40, 120 cases).[9] Results from a Chinese study showed little evidence for an association (0.94, 95% CI: 0.30-2.96, 153 cases);[8] though the prevalence of MHT in this population was only 2%. One previous United Kingdom study presented results for adenocarcinomas by anatomic site (esophageal adenocarcinoma: 1.17, 95% CI: 0.41-3.32, 53 cases; gastric cardia: 0.68, 95% CI: 0.23-2.01, 38 cases; gastric non-cardia: 0.34, 95%CI: 0.14-0.78, 109 cases).[15]

Similar to most previous reports, we observed no association with age at menarche, oral contraceptive use, or parity and UGI cancer.[8,17,19,21,22] We did find an inverse association with older age at menopause and squamous UGI cancers of the esophagus and head and neck. In three previous studies,[19,21,22] older age at menopause was inversely associated with squamous cancers of the esophagus (menopause ≥ 50 years relative to < 45 years, OR: 0.43, 95% CI: 0.22-0.83)[21] and oral cavity and pharynx (menopause ≥ 50 years

relative to < 50 years, OR: 0.46 (95%CI: 0.30-0.70),19 but not larynx.22 In contrast to several, but not all, previous studies,8-12,14,16,17 we found no association with age at menopause and adenocarcinoma risk. We found possible differences by anatomic sub-site. Risk estimates for an age at menopause >55 years relative to an age at menopause <45 years were 0.65 (95% CI: 0.22-1.86) for the non-cardia and 2.35 (95% CI: 0.56-9.9) for the esophagus and gastric cardia. Future studies are needed to determine whether risk estimates differ between gastric tumors of the cardia and non-cardia.

Confounding is a concern in all observational studies and it is possible that our estimates for MHT use and for older age at menopause are confounded by other risk factors, such as tobacco smoking or diet. In this analysis, we adjusted for education, body mass index, alcohol intake, tobacco smoking, physical activity, and fruit and vegetable intake. Because smoking and alcohol are strong risk factors for these cancer sites,6,7,26 residual confounding by smoking and alcohol are particular concerns for MHT use, particularly as MHT use was inversely associated with current cigarette smoking in our cohort (data not shown). But, in stratified models, the risk estimates for EPT persisted among non-users of tobacco and alcohol, suggesting that residual confounding by smoking or alcohol use does not explain our results.

Our results imply a role for exogenous sex hormones in the etiology of UGI cancer, with a significant association for EPT therapy, but not ET therapy. Previous studies have not investigated the association of MHT type with UGI cancer risk and this result could be due to chance. Yet, distinct associations between EPT and ET therapy have been observed for other cancer types, particularly for breast and endometrial cancer.27,30-32 In addition, EPT, but not ET, was inversely associated with colorectal cancer in the Women's Health Initiative randomized clinical trial.33,34

Our study had several strengths, including its prospective design and ability to investigate specific contemporary formulations and regimens of MHT use. Our study was limited by lack of information on *Helicobacter pylori* (Hp) infection, an important gastric cancer risk factor. In one previous study in a population with higher Hp infection rates than in the United States, Hp infection did not confound the observed association between menstrual and reproductive factors and gastric cancer risk.8 We also lacked information on hormone use after the second questionnaire, could not identify which women had a hysterectomy after baseline, and lacked assessment of gastroesophageal reflux disease. Finally, although our cohort was large, we still had modest case numbers, limiting our ability to detect moderate associations. As we investigated multiple exposures and endpoints, significant results may be due to chance. Future studies are needed to replicate these findings.

In conclusion, in this United States prospective cohort study, we observed significant inverse associations between squamous UGI cancer risk and older age at menopause, and use of estrogen-plus-progestin menopausal hormone therapy. We also found suggestive associations between estrogen-plus-progestin MHT and adenocarcinomas of the UGI tract. These results add further evidence for a possible role of sex hormones in the etiology of UGI tract cancers.

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Table 1

Cohort Characteristics

Characteristics*	Cohort (201,506)	Adenocarcinomas of the esophagus and stomach (162)	Squamous cancers of the esophagus and head and neck (353)
Age at entry into the cohort (Median, IQR)	62.3 (57.5-66.4)	65.6 (61.9-68.6)	63.7 (59.6-67.5)
Body Mass Index (Median, IQR)	25.7 (22.9-29.6)	26.1 (22.9-30.5)	23.8 (21.3-27.6)
Total daily energy intake (kcal; Median, IQR)	1,461 (1,117-1,901)	1,520 (1,157-1,984)	1,457 (1,094-2,019)
Fruit intake (Servings per 1000 kcal/day; Median, IQR)	1.7 (1.0-2.5)	1.7 (0.9-2.7)	1.3 (0.7-2.1)
Vegetable intake (Servings per 1000 kcal/day; Median, IQR)	2.2 (1.6-3.1)	2.1 (1.6-2.7)	2.0 (1.4-2.8)
Alcohol intake, No. (%)			
0 drinks/day	59,054 (29.5)	55 (34.4)	95 (27.1)
≤ - < 1 drinks/day	115,481 (57.6)	83 (51.9)	153 (43.6)
1 - ≤ 3 drinks/day	20,356 (10.2)	17 (10.6)	62 (17.7)
> 3 drinks/day	5,518 (2.8)	5 (3.1)	41 (11.7)
Cigarette Smoking Status, No. (%)			
Never	88,540 (45.6)	50 (33.1)	56 (16.8)
Former	73,032 (37.6)	69 (45.7)	102 (30.5)
Current	32,560 (16.8)	32 (21.2)	176 (52.7)
Education, No. (%)			
Less than high school	12,635 (6.5)	14 (8.9)	28 (8.2)
12 years (completed high school)	51,189 (26.3)	51 (32.5)	101 (29.5)
Some post-high school training	71,116 (36.5)	54 (34.4)	124 (36.3)
Completed college	29,534 (15.2)	16 (10.2)	45 (13.2)
Completed graduate school	30,156 (15.5)	22 (14.0)	44 (12.9)
Ethnicity, No. (%)			
Non-Hispanic white	179,494 (90.6)	139 (88.0)	319 (91.7)
Non-Hispanic black	11,648 (5.9)	14 (8.9)	25 (7.2)
Hispanic	3,865 (2.0)	5 (3.2)	1 (0.3)
Asian/ Pacific Islander/ Native American	3,214 (1.6)	0	3 (0.9)

*Numbers may not add up to 201,506 due to missing data.

Table 2

Baseline questionnaire menstrual and reproductive factors with risk of adenocarcinomas in the esophagus and stomach in the NIH-AARP cohort

Variable*	Cohort (n=201,506)	Adenocarcinomas of the esophagus and stomach (n=162)		Esophageal adenocinarma + Gastric Cardia (n=65)		Non-cardia gastric cancer (n=97)	
	No. (%)	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI
OC use							
Never	119,237 (60.1)	111 (69.8)	1.00 (ref)	41 (63.1)	1.00 (ref)	70 (74.5)	0.90 (0.53-1.52)
1-10 years	59,901 (30.2)	35 (22.0)	0.94 (0.63-1.39)	16 (24.6)	1.00 (0.55-1.83)	19 (20.2)	0.71 (0.29-1.79)
10 + years	19,115 (9.6)	13 (8.2)	1.05 (0.59-1.89)	8 (12.3)	1.50 (0.69-3.28)	5 (5.3)	1.16 (0.33-4.11)
			p trend=0.969		p trend=0.422		p trend=0.442
Parity							
0	30,169(15.2)	28 (18.0)	1.00 (ref)	12 (19.1)	1.00 (ref)	16 (17.2)	1.00 (ref)
1	20,921 (10.5)	12 (7.7)	0.59 (0.30-1.17)	7 (11.1)	0.83 (0.32-2.12)	5 (5.4)	0.43 (0.16-1.16)
2	51,874 (26.1)	37 (23.7)	0.76 (0.47-1.25)	15 (23.8)	0.76 (0.35-1.63)	22 (23.7)	0.78 (0.41-1.49)
3+	96,144 (48.3)	79 (50.6)	0.78 (0.50-1.21)	29 (46.0)	0.71 (0.36-1.42)	50 (53.8)	0.83 (0.47-1.47)
			p trend= 0.519		p trend = 0.337		p trend= 0.996
Age at menarche							
< 12	97,561 (49.0)	83 (52.2)	1.00 (ref))	38 (58.5)	1.00 (ref)	45 (47.9)	1.00 (ref)
13-14	82,884 (41.6)	59 (37.1)	0.81 (0.58-1.13)	23 (35.4)	0.72 (0.43-1.21)	36 (38.3)	0.88 (0.57-1.36)
>=15	18,807 (9.4)	17 (10.7)	0.98 (0.58-1.65)	4 (6.2)	0.53 (0.19-1.51)	13 (13.8)	1.31 (0.71-2.44)
			p trend= 0.478		p trend= 0.116		p trend= 0.711
Age at menopause							
Pre-menopause	7,294 (3.6)	2 (1.2)	--	2 (3.1)	2.62 (0.51-13.40)	0 (0)	--
< 45	13,534 (6.7)	13 (8.0)	1.11 (0.59-2.08)	3 (4.6)	0.69 (0.20-2.40)	10 (10.3)	1.37 (0.66-2.87)
45-49	31,167 (15.5)	30 (18.5)	1.25 (0.78-2.02)	13 (20.0)	1.42 (0.67-3.04)	17 (17.5)	1.15 (0.62-2.13)
50-54	53,526 (26.6)	39 (24.1)	1.00 (ref)	14 (21.5)	1.00 (ref)	25 (25.8)	1.00 (ref)
55 +	11,988 (6.0)	9 (5.6)	0.97 (0.47-2.00)	5 (7.7)	1.62 (0.58-4.50)	4 (4.1)	0.65 (0.22-1.86)
Surgical menopause	76,833 (38.1)	63 (38.9)	1.12 (0.75-1.68)	26 (40.0)	1.29 (0.67-2.47)	37 (38.1)	1.04 (0.62-1.73)
			p trend‡= 0.501		p trend‡= 0.569		p trend‡= 0.189
Type of Surgery							
None	108,466 (55.2)	89 (57.1)	1.00 (ref)	31 (48.4)	1.00 (ref)	58 (63.0)	1.00 (ref)
Hysterectomy only	31,404 (16.0)	19 (12.2)	0.73 (0.45-1.20)	7 (10.9)	0.79 (0.35-1.80)	12 (13.0)	0.70 (0.41-1.20)

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Variable*	Cohort (n=201,506)	Adenocarcinomas of the esophagus and stomach (n=162)		Esophageal adenocinarma + Gastric Cardia (n=65)		Non-cardia gastric cancer (n=97)	
	No. (%)	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI
+ Bilateral Oophorectomy	42,833 (21.8)	35 (22.4)	0.94 (0.64-1.39)	16 (25.0)	1.27 (0.70-2.34)	19 (20.7)	0.77 (0.3701.30)
+ Other ovarian surgery	6,206 (3.2)	6 (3.9)	1.16 (0.51-2.65)	3 (4.7)	1.64 (0.50-5.38)	3 (3.3)	0.89 (0.28-2.85)
Bilateral oophorectomy only	1,048 (0.5)	1 (0.6)	0.93 (0.13-6.68)	1 (1.6)	2.80 (0.38-20.60)	0 (0)	--
Other ovarian surgery only	6,424 (3.3)	6 (3.9)	1.10 (0.48-2.51)	6 (9.4)	2.98 (1.24-7.15)	0 (0)	--
Age at first birth							
Never	28,623 (14.5)	27 (17.0)	1.00 (ref)	11 (17.2)	1.00 (ref)	16 (16.8)	1.00 (ref)
< 24	122,386 (61.8)	102 (64.2)	0.82 (0.53-1.26)	44 (68.8)	0.93 (0.47-1.84)	58 (61.1)	0.76 (0.43-1.34)
25-29	35,355 (17.9)	20 (12.6)	0.56 (0.31-0.99)	7 (10.9)	0.53 (0.20-1.37)	13 (13.7)	0.58 (0.28-1.20)
>=30	11,676 (5.9)	10 (6.3)	0.82 (0.40-1.70)	2 (3.1)	0.44 (0.10-2.01)	8 (8.4)	1.05 (0.47-2.45)
			p trend= 0.145		p trend = 0.107		p trend= 0.581
Ever use of MHT No	89,099 (45.4)	87 (55.8)	1.00 (ref)	33 (52.4)	1.00	54 (58.1)	1.00 (ref)
Yes	106,934 (54.6)	69 (44.2)	0.81 (0.59-1.12)	30 (47.6)	0.90 (0.54-1.49)	39 (41.9)	0.76 (0.50-1.16)
Years of MHT use							
Never	89,099 (45.4)	87 (56.1)	1.00 (ref)	33 (52.4)	1.00 (ref)	54 (58.7)	1.00 (ref)
< 10	65,654 (33.5)	36 (23.2)	0.76 (0.51-1.14)	15 (23.8)	0.79 (0.42-1.48)	21 (22.8)	0.75 (0.45-1.26)
>= 10	41,110 (21.0)	32 (20.7)	0.84 (0.56-1.27)	15 (23.8)	1.04 (0.56-1.93)	17 (18.5)	0.72 (0.42-1.26)
			p trend= 0.293		p trend= 0.954		p trend= 0.192

Abbreviations: MHT, menopausal hormone therapy

*Numbers may not add up to 201,506 due to missing data.

†Multivariate adjusted models, adjusted for age, body mass index, fruit and vegetable consumption, smoking use, alcohol intake, physical activity, and total energy intake.

‡p-trend for age at natural menopause.

Table 3

Baseline questionnaire menstrual and reproductive factors with risk of squamous carcinomas of the esophagus and head and neck in the NIH-AARP cohort

Variable *	Cohort (n=201,506)	Squamous cancers of the head & neck and esophagus (n=353)		Esophageal Squamous Cell Carcinoma (n=56)		Squamous cancers of the head and neck (n=297)	
	No. (%)	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI
OC use							
Never	119,237 (60.1)	216 (62.8)	1.00 (ref)	31 (57.4)	1.00 (ref)	185 (63.8)	1.00 (ref)
1-10 years	59,901 (30.2)	98 (28.5)	1.02 (0.79-1.31)	16 (29.6)	1.20 (0.64-2.28)	82 (28.3)	0.99 (0.75-1.30)
10 + years	19,115 (9.6)	30 (8.7)	0.92 (0.62-1.36)	7 (13.0)	1.49 (0.64-3.48)	23 (7.9)	0.83 (0.53-1.29)
			p trend= 0.797		p trend= 0.330		p trend=0.479
Parity							
0	30,169(15.2)	59 (17.1)	1.00 (ref)	13 (24.1)	1.00 (ref)	46 (15.8)	1.00 (ref)
1	20,921 (10.5)	43 (12.5)	1.01 (0.68-1.51)	7 (13.0)	0.84 (0.33-2.13)	36 (12.4)	1.07 (0.69-1.65)
2	51,874 (26.1)	92 (26.7)	0.97 (0.69-1.34)	15 (27.8)	0.78 (0.37-1.65)	77 (26.5)	1.02 (0.70-1.47)
3+	96,144 (48.3)	151 (43.8)	0.82 (0.61-1.12)	19 (35.2)	0.55 (0.27-1.14)	132 (45.4)	0.89 (0.63-1.26)
			p trend= 0.140		p trend= 0.100		p trend= 0.374
Age at menarche							
< 12	97,561 (49.0)	165(47.7)	1.00 (ref)	23 (42.6)	1.00 (ref)	142 (48.6)	1.00 (ref)
13-14	82,884 (41.6)	146 (42.2)	0.99 (0.79-1.24)	26 (48.2)	1.23 (0.70-2.16)	120 (41.1)	0.95 (0.75-1.22)
>=15	18,807 (9.4)	35 (10.1)	0.98 (0.68-1.42)	5 (9.3)	0.98 (0.37-2.58)	30 (10.3)	0.99 (0.66-1.47)
			p trend= 0.912		p trend= 0.747		p trend= 0.801
Age at menopause							
Pre-menopause	7,294 (3.6)	9 (2.6)	1.26 (0.60-2.63)	0 (0)	--	9 (3.0)	1.60 (0.75-3.39)
< 45	13,534 (6.7)	39 (11.1)	1.42 (0.97-2.09)	9 (16.1)	1.84 (0.80-4.25)	30 (10.1)	1.34 (0.86-2.06)
45-49	31,167 (15.5)	72 (20.4)	1.29 (0.94-1.78)	14 (25.0)	1.38 (0.67-2.87)	58 (19.5)	1.27 (0.89-1.82)
50-54	53,526 (26.6)	80 (22.7)	1.00 (ref)	15 (26.8)	1.00 (ref)	65 (21.9)	1.00 (ref)
55 +	11,988 (6.0)	12 (3.4)	0.75 (0.41-1.38)	0 (0)	--	12 (4.0)	0.92 (0.50-1.71)
Surgical menopause	76,833 (38.1)	123 (34.8)	1.07 (0.80-1.42)	14 (25.0)	0.72 (0.35-1.50)	109 (36.7)	1.14 (0.84-1.56)
			p trend‡= 0.013		p trend‡= 0.019		p trend‡= 0.098
Type of Surgery							
None	108,466 (55.2)	193 (57.1)	1.00 (ref)	39 (72.2)	1.00 (ref)	154 (54.2)	1.00 (ref)

Variable *	Cohort (n=201,506)	Squamous cancers of the head & neck and esophagus (n=353)		Esophageal Squamous Cell Carcinoma (n=56)		Squamous cancers of the head and neck (n=297)	
	No. (%)	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI	No. (%)	HR,† 95% CI
Hysterectomy only	31,404 (16.0)	59 (17.5)	1.13 (0.85-1.52)	7 (13.0)	0.72 (0.32-1.60)	52 (18.3)	1.24 (0.90-1.70)
+ Bilateral Oophorectomy	42,833 (21.8)	65 (19.2)	0.89 (0.67-1.18)	6 (11.1)	0.43 (0.18-1.02)	59 (20.8)	1.00 (0.74-1.35)
+ Other ovarian surgery	6,206 (3.2)	9 (2.7)	0.82 (0.42-1.61)	2 (3.7)	1.01 (0.24-4.20)	7 (2.5)	0.79 (0.37-1.68)
Bilateral oophorectomy only	1,048 (0.5)	3 (0.9)	1.35 (0.43-4.21)	0 (0)	--	3 (1.1)	1.68 (0.54-5.27)
Other ovarian surgery only	6,424 (3.3)	9 (2.7)	0.69 (0.36-1.35)	0 (0)	--	9 (3.2)	0.87 (0.44-1.70)
Age at first birth							
Never	28,623 (14.5)	57 (16.5)	1.00 (ref)	13 (24.1)	1.00 (ref)	44 (15.1)	1.00 (ref)
< 24	122,386 (61.8)	220 (63.6)	0.92 (0.68-1.24)	30 (55.6)	0.66 (0.34-1.31)	190 (65.1)	0.99 (0.71-1.39)
25-29	35,355 (17.9)	55 (15.9)	0.85 (0.59-1.24)	8 (14.8)	0.55 (0.22-1.32)	47 (16.1)	0.95 (0.63-1.43)
>=30	11,676 (5.9)	14 (4.1)	0.67 (0.37-1.20)	3 (5.6)	0.62 (0.17-2.17)	11 (3.8)	0.68 (0.35-1.33)
			p trend= 0.165		p trend= 0.221		p trend= 0.341
Ever use of MHT No	89,099 (45.4)	191 (55.8)	1.00 (ref))	30 (55.6)	1.00 (ref)	161 (55.9)	1.00 (ref)
Yes	106,934 (54.6)	151 (44.2)	0.77 (0.62-0.96)	24 (44.4)	0.74 (0.42-1.28)	127 (44.1)	0.78 (0.61-0.99)
Years of MHT use							
Never	89,099 (45.4)	191 (55.9)	1.00 (ref)	30 (55.6)	1.00 (ref)	161 (55.9)	1.00 (ref)
< 10	65,654 (33.5)	91 (26.6)	0.80 (0.62-1.04)	15 (27.8)	0.80 (0.42-1.53)	76 (26.4)	0.80 (0.61-1.06)
>= 10	41,110 (21.0)	60 (17.5)	0.73 (0.54-0.98)	9 (16.7)	0.66 (0.31-1.40)	51 (17.7)	0.74 (0.54-1.02)
			p trend= 0.020		p trend= 0.249		p trend= 0.043

Abbreviations: MHT, menopausal hormone therapy

*Numbers may not add up to 201,506 due to missing data.

†Multivariate adjusted models, adjusted for age, body mass index, fruit and vegetable consumption, smoking use, alcohol intake, physical activity, and total energy intake.

‡p-trend for age at natural menopause.

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Table 4

Type of menopausal hormone therapy with adenocarcinoma cancer risk.

Variable	Cohort	Adenocarcinomas of the esophagus and stomach		Esophageal adenocinarma + Gastric Cardia		Non-cardia gastric cancer	
	No. (%)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)
Among women with a hysterectomy	**51,515 (100)**	**38 (100)**		**19 (100)**		**19 (100)**	
No MHT †	10,522 (20.4)	6 (15.8)	1.00 (ref)	3 (15.8)	1.00 (ref)	3 (15.8)	1.00 (ref)
Ever used ET	29,645 (57.6)	23 (60.5)	1.78 (0.71-4.44)	11 (57.9)	1.78 (0.48-6.56)	12 (63.2)	1.68 (0.46-6.10)
Recency							
Former (% of ET users)	6,275 (21.4)	7 (30.4)	2.25 (0.75-6.75)	4 (36.4)	2.59 (0.57-11.77)	3 (25.0)	1.80 (0.36-9.02)
Current (% of ET users)	23,109 (78.6)	16 (69.6)	1.65 (0.63-4.31)	7 (64.6)	1.53 (0.38-6.13)	9 (75.0)	1.68 (0.44-6.38)
		p trend = 0.392		p trend = 0.662		p trend = 0.484	
Total duration of use							
< 10 years (% of ET users)	12,729 (43.6)	11 (47.8)	2.20 (0.80-6.05)	5 (45.5)	2.04 (0.48-8.74)	6 (50.0)	2.21 (0.54-9.06)
10+ years (% of ET users)	16,458 (56.4)	12 (52.2)	1.57 (0.58-4.27)	6 (55.5)	1.65 (0.40-6.83)	6 (50.0)	1.42 (0.35-5.83)
		p trend = 0.479		p trend = 0.548		p trend = 0.739	
Ever used EPT	8,075 (15.7)	6 (15.8)	2.01 (0.63-6.44)	4 (21.1)	2.72 (0.57-12.87)	2 (10.5)	1.24 (0.20-7.70)
Ever used other or unknown type	3242 (6.3)	3 (7.9)	1.92 (0.48-7.75)	1 (5.3)	1.35 (0.14-13.24)	2 (10.5)	2.12 (0.35-12.95)
Among women with an intact uterus	**74,372 (100)**	**49 (100)**		**19 (100)**		**30 (100)**	
No MHT †	38,404 (51.7)	34 (69.4)	1.00 (ref)	11 (57.9)	1.00 (ref)	23 (76.7)	1.00 (ref)
Ever used EPT	28,060 (37.8)	11 (22.5)	0.52 (0.26-1.07)	6 (31.6)	0.73 (0.26-2.06)	5 (16.7)	0.40 (0.15-1.09)
Recency							
Former (% of EPT users)	6,291 (22.7)	2 (18.2)	0.41 (0.10-1.71)	1 (16.7)	0.54 (0.07-4.26)	1 (20.0)	0.34 (0.05-2.51)
Current (% of EPT users)	21,376 (77.3)	9 (81.8)	0.57 (0.27-1.24)	5 (83.3)	0.81 (0.27-2.44)	4 (80.0)	0.43 (0.14-1.30)
		p for trend = 0.122		p trend = 0.669		p trend = 0.105	
Total duration of use							
< 5 years (% of EPT users)	12,277 (44.8)	4 (40.0)	0.51 (0.18-1.46)	2 (40.0)	0.61 (0.13-2.85)	2 (40.0)	0.46 (0.11-1.99)
5+ years (% of EPT users)	15,152 (55.2)	6 (60.0)	0.47 (0.19-1.16)	3 (60.0)	0.62 (0.17-2.31)	3 (60.0)	0.39 (0.11-1.34)
		p for trend = 0.068		p trend = 0.421		p trend = 0.098	
Regimen of use							
Sequential (< 15 days/month)	10,029 (38.6)	3 (27.3)	0.41 (0.12-1.36)	1 (16.7)	0.35 (0.04-2.81)	2 (40.0)	0.46 (0.10-2.00)

Variable	Cohort	Adenocarcinomas of the esophagus and stomach		Esophageal adenocinarma + Gastric Cardia		Non-cardia gastric cancer	
	No. (%)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)
Continuous (15 + days/month)	15,927 (61.4)	8 (72.7)	0.67 (0.30-1.49)	5 (83.3)	1.06 (0.35-3.15)	3 (60.0)	0.43 (0.13-1.48)
Ever used ET	5,276 (7.1)	3 (6.1)	0.60 (0.18-1.96)	2 (10.5)	1.22 (0.27-5.52)	1 (3.3)	0.30 (0.04-2.22)
Ever used other or unknown type	2,569 (3.5)	1 (2.0)	0.43 (0.06-3.18)	0 (0)	--	1 (3.3)	0.59 (0.08-4.42)

*Multivariate adjusted models, adjusted for age, body mass index, fruit and vegetable consumption, smoking use, alcohol intake, physical activity, and total energy intake.

†Never users of menopausal hormone therapy (MHT) serve as the reference group for all categories. All models include indicator variables for use of estrogen therapy (ET), estrogen-plus-progestin (EPT), ever used other or unknown type of MHT, and missing data.

Table 5

Type of menopausal hormone therapy with squamous cancer risk.

Variable	Cohort	Squamous cancers of the head & neck and esophagus		Esophageal Squamous Cell Carcinoma		Squamous cancers of the head and neck	
	No. (%)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)
Among women with a hysterectomy	**51,515 (100)**	**80 (100)**		**14 (100)**		**66 (100)**	
No MHT †	10,522 (20.4)	19 (23.8)	1.00 (ref)	2 (14.3)	1.00 (ref)	17 (25.8)	1.00 (ref)
Ever used ET	29,645 (57.6)	51 (63.8)	1.03 (0.60-1.77)	9 (64.3)	1.72 (0.36-8.20)	42 (63.6)	0.96 (0.54-1.71)
Recency							
Former (% of ET users)	6,275 (21.4)	9 (18.0)	0.79 (0.36-1.74)	2 (25.0)	1.72 (0.24-12.49)	7 (16.7)	0.69 (0.28-1.67)
Current (% of ET users)	23,109 (78.6)	41 (82.0)	1.10 (0.63-1.92)	6 (75.0)	1.44 (0.28-7.44)	35 (83.3)	1.07 (0.59-1.95)
		p for trend = 0.653		p for trend = 0.694		p for trend = 0.715	
Total duration of use							
< 10 years (% of ET users)	12,729 (43.6)	18 (36.0)	0.92 (0.47-1.77)	2 (25.0)	0.98 (0.13-7.18)	16 (38.1)	0.92 (0.46-1.85)
10+ years (% of ET users)	16,458 (56.4)	32 (64.0)	1.10 (0.61-1.97)	6 (75.0)	1.82 (0.35-9.32)	26 (61.9)	1.03 (0.55-1.92)
		p for trend = 0.696		p for trend = 0.389		p for trend = 0.911	
Ever used EPT	8,075 (15.7)	8 (10.0)	0.61 (0.26-1.43)	3 (21.4)	1.92 (0.30-12.21)	5 (7.6)	0.44 (0.16-1.22)
Ever used other or unknown type	3242 (6.3)	2 (2.5)	0.39 (0.09-1.67)	0 (0)	--	2 (3.0)	0.42 (0.10-1.84)
Among women with an intact uterus	**74,372 (100)**	**130 (100)**		**25 (100)**		**105 (100)**	
No MHT †	38,404 (51.7)	83 (63.9)	1.00 (ref)	18 (72.0)	1.00 (ref)	65 (61.9)	1.00 (ref)
Ever used EPT	28,060 (37.8)	25 (19.2)	0.47 (0.30-0.75)	5 (20.0)	0.41 (0.15-1.14)	20 (19.1)	0.49 (0.29-0.82)
Recency							
Former (% of EPT users)	6,291 (22.7)	10 (40.0)	0.80 (0.41-1.54)	1 (20.0)	0.36 (0.05-2.74)	9 (45.0)	0.91 (0.45-1.84)
Current (% of EPT users)	21,376 (77.3)	15 (60.0)	0.37 (0.21-0.66)	4 (80.0)	0.43 (0.14-1.31)	11 (55.0)	0.36 (0.19-0.68)
		p for trend = 0.0006		p for trend = 0.113		p for trend = 0.0024	
Total duration of use							
< 5 years (% of EPT users)	12,277 (44.8)	17 (68.0)	0.74 (0.43-1.27)	2 (40.0)	0.42 (0.10-1.86)	15 (75.0)	0.83 (0.46-1.48)
5+ years (% of EPT users)	15,152 (55.2)	8 (32.0)	0.28 (0.13-0.58)	3 (60.0)	0.41 (0.12-1.45)	5 (25.0)	0.23 (0.09-0.57)
		p for trend = 0.0004		p for trend = 0.121		p for trend = 0.0015	
Regimen of use							
Sequential (< 15 days/month)	10,029 (38.6)	5 (26.3)	0.26 (0.11-0.65)	1 (20.0)	0.23 (0.03-1.73)	4 (28.6)	0.27 (0.10-0.75)

Variable	Cohort	Squamous cancers of the head & neck and esophagus		Esophageal Squamous Cell Carcinoma		Squamous cancers of the head and neck	
	No. (%)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)	No. (%)	HR* (95% CI)
Continuous (15 + days/month)	15,927 (61.4)	14 (73.7)	0.47 (0.26-0.83)	4 (80.0)	0.58 (0.19-1.76)	10 (71.4)	0.43 (0.22-0.84)
Ever used ET	5,276 (7.1)	12 (9.2)	0.91 (0.49-1.67)	1 (4.0)	0.35 (0.05-2.60)	11 (10.5)	1.06 (0.56-2.02)
Ever used other or unknown type	2,569 (3.5)	10 (7.7)	2.01 (1.04-3.88)	1 (4.0)	0.92 (0.12-6.90)	9 (8.6)	2.31 (1.15-4.65)

*Multivariate adjusted models, adjusted for age, body mass index, fruit and vegetable consumption, smoking use, alcohol intake, physical activity, and total energy intake.

†Never users of menopausal hormone therapy (MHT) serve as the reference group for all categories. All models include indicator variables for use of estrogen therapy (ET), estrogen-plus-progestin (EPT), ever used other or unknown type of MHT, and missing data.