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Female hormonal and reproductive factors and head and neck squamous cell carcinoma risk

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Abstract

Men are much more likely than women to develop head and neck squamous cell carcinoma (HNSCC), a discrepancy that is insufficiently explained by gender differences in smoking and alcohol consumption. It has been hypothesized that differential hormonal exposures may account for some of this risk but thus far the literature on female reproductive factors and HNSCC risk has been sparse. To address the association of HNSCC with female hormonal and reproductive factors, a case-control study was conducted on 149 women with head and neck cancer and 158 controls. After adjusting for potential confounding, postmenopausal women using female hormones for more than 5 years showed a borderline protective effect for HNSCC (adjusted OR = 0.47, 95% CI: 0.20-1.08), with a borderline trend across duration of use categories (P = 0.06). There was no association of HNSCC with age at menarche, hysterectomy/oophorectomy status, oral contraceptive use, history of fertility medication, or number of pregnancies, parity, or age at first pregnancy or live birth. The findings of this study do not support a link between HNSCC and reproductive factors, although the borderline association with HRT warrants further investigation.

Keywords

female hormones; hormone replacement; oral contraception; case-control study

1. INTRODUCTION

Cancers of the oral cavity, pharynx and larynx, collectively referred to as head and neck cancer, comprise the 7th most common malignancy amongst men in the United States but rank only 13th among women [1]. The overall risk of developing head and neck cancer for men is approximately 3 times as high as it is for women [2], and is as much as 7-fold when considering laryngeal cancer alone [3]. Nonetheless, it is estimated that 13,730 new cases of head and neck cancer and 3,180 deaths will occur among women in the United States in 2010 [1], the majority of which will be head and neck squamous cell carcinomas (HNSCC) [4].

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CONFLICTS OF INTEREST We have no conflicts of interest to declare.

Although there are gender disparities in terms of exposure to the primary known risk factors, tobacco and alcohol [2; 5], these differences alone are insufficient to explain the observed discrepancy in incidence. For example, the U.S. prevalence of smoking is 1.26 times higher [6] and the prevalence of heavy drinking is 1.48 times higher in men compared to women [7], which does not seem to fully account for the 3-fold higher male rates of HNSCC, albeit these estimates are ecological in nature. The possible involvement of hormonal factors has been postulated in an attempt to reconcile the differences. Various characteristics relating to female reproduction may impact cumulative levels of hormone exposure, as can exogenous hormone use, such as hormone replacement therapy (HRT), which describes a heterogeneous class of exogenous hormone-based treatment options for menopausal symptoms. Many of the HRT drugs contain estrogen, either alone or in combination with progesterone [8; 9]. Two recent epidemiologic studies seem to indicate that female reproductive risk factors related to estrogen exposure may exert a protective effect against HNSCC [10; 11]. It has also been observed that oral cancers in women develop more frequently during the postmenopausal period [11]. Moreover, sex hormone receptors have been identified in normal [12; 13; 14; 15] and malignant head and neck tissue [16; 17; 18].

Despite the aforementioned observations, a complete picture of the role of female reproductive factors in HNSCC risk remains unclear, as there is a paucity of literature on this subject with inconsistent results. This phenomenon is in part due to the small number of female HNSCC cases available at each Institution and in part to the fact that standardized reproductive information are not usually collected in women with HNSCC. This report includes the analysis of a case-control study of HNSCC among women to assess the association with reproductive and hormonal factors.

2. METHODS

Study Subjects

This study was conducted as a part of the University of Pittsburgh Head and Neck Cancer Specialized Program of Research Excellence (SPORE). The study population consisted of 149 women diagnosed with primary HNSCC at the University of Pittsburgh Medical Center (Pittsburgh, PA) from April 2006 through September 2010, with no prior history of non-cutaneous cancer. Female control subjects were selected from a pool of patients seeking treatment at the University of Pittsburgh ENT clinic for non-neoplastic conditions (n = 158), frequency-matched on age (+/− 5 years) at recruitment prior to exclusions. Reasons for exclusion of cases included subsequent determination that the tumor was not an initial primary tumor (n = 7) or occurred outside of the oral cavity, pharynx or larynx (n = 5). Institutional review board (IRB) approval was obtained under the University of Pittsburgh Head and Neck Cancer SPORE for collection and use of subject data. All subjects provided written informed consent for participation in this study.

Data Collection

Study subjects completed an epidemiologic questionnaire, providing detailed information on subject demographics, personal and family cancer history and health behaviors. Subjects also completed a supplemental questionnaire on female reproductive factors, which included questions on menstrual history, hysterectomy/oophorectomy status, exogenous female hormone use, oral contraceptive use, fertility medication use and history of pregnancy and childbirth. Clinical and pathologic data for HNSCC patients was abstracted from the medical records following diagnosis and was available through the University of Pittsburgh Head and Neck Oncology Registry.

Statistical Analysis

Descriptive statistics were generated according to case-control status. Normality of continuous covariates was evaluated using the Skewness-Kurtosis test [19]. T-tests were used to assess differences between normally distributed continuous variables; the Mann-Whitney U test was used in the case of non-normality. Fisher's exact test was used to assess differences between categorical variables. All tests were 2-sided and significance was considered where $P \leq 0.05$.

Separate multivariable unconditional logistic regression models were employed to evaluate the association of HNSCC with reproductive and hormonal factors while adjusting for potential risk factors; both crude and adjusted models included age, the frequency-matched factor [20]. Multivariable models were fit based on biological and statistical considerations. All adjusted models also included highest level of education (*high school or less*, *some college or technical school* and *college or more*) and smoking (*never*, *≤ 10 pack-years* and *>10 pack-years*); the model testing the association between HNSCC and oral contraceptive use was additionally adjusted for number of pregnancies and family history of cancer in a first degree relative (*yes*/*no*); the models assessing HNSCC risk and age at menarche, hysterectomy/oophorectomy status, use of fertility medication, number of pregnancies, age at first pregnancy and age at first live birth were also adjusted for family history of cancer in a first degree relative (*yes*/*no*). Due to sparse use among non-menopausal women, the model examining the role of hormone replacement therapy (HRT) on HNSCC risk was restricted to post-menopausal women. The models evaluating HNSCC risk and age at first pregnancy and age at first live birth were restricted to women reporting ever having a pregnancy and live birth, respectively. Responses were missing for HRT use from 2.0% of subjects (3 cases and 3 controls) and fertility medication use was missing for 0.7% of subjects (1 case and 1 control); data was complete for all other covariates. Global fit of each model was assessed using the Hosmer and Lemeshow goodness-of-fit test [21], considered a poor-fit if $P \leq 0.10$. All statistical analyses were conducted using Stata 11 (College Station, TX).

3. RESULTS

A description of the demographics and health behaviors of the study population according to case-control status is provided in Table I. Female HNSCC patients had significantly less educational attainment relative to control subjects ($P < 0.001$); and were more often smokers ($P < 0.001$) and heavier drinkers ($P = 0.002$).

Prior to adjusting for potential confounding, several differences in hormonal and reproductive characteristics were observed between HNSCC patients and control women (Table II**)**. Relative to women who were 18 years or younger at their first pregnancy, there was a protective effect for women having their first pregnancy between the age of 19 and 29 years of age (crude OR = 0.45, 95% CI: 0.24-0.88); and having 3 or more live births was associated with HNSCC (crude OR = 1.96, 95% CI: 1.04-3.68). Additionally, there was a crude inverse association between HRT use among postmenopausal women and HNSCC (crude OR = 0.41, 95% CI: 0.24-0.70), with an inverse trend with increasing duration of use ($P_{trend} = 0.001$).

After adjusting for potential confounding in the multivariable analysis (Table II), HNSCC was no longer significantly associated with parity or age of first pregnancy or live birth. There was a borderline protective effect for postmenopausal women using HRT for more than 5 years (adjusted OR = 0.47, 95% CI: 0.20-1.08), with a borderline trend across duration of use categories ($P = 0.06$). The models testing the association between HNSCC and HRT use were further stratified by smoking status and by tumor site (for cases), but no difference in estimates was observed between strata (Table III).

4. DISCUSSION

The risk of developing HNSCC is much higher for men than for women, a gap which is incompletely explained by gender discrepancies in exposure to alcohol and tobacco. This has led some to theorize that hormonal differences may, in part, account for this disparity in disease. However, there is a paucity of research reports surrounding female-specific risk factors of HNSCC. In this report, we enhance the sparse literature with an analysis of female reproductive factors and hormone use stemming from a case-control on female HNSCC.

We report no significant associations of female reproductive factors with HNSCC. Very few studies have addressed the topic of reproductive history and HNSCC, with inconsistent results. To our knowledge, ours is the only study to evaluate the association of fertility medication use and HNSCC and to assess number of pregnancies, independent of parity. In agreement with our results, in a large cohort study of 297 female HNSCC patients, Freedman et al [10] observed no significant associations between HNSCC and age at menarche, hysterectomy/oophorectomy status, oral contraceptive use, parity or age at first live birth. Others have reported on the role of female reproductive factors and HNSCC with conflicting results. A case-control study involving 195 women with oral or pharyngeal cancer [22] showed no association with several reproductive factors, but identified a protective effect of late menopause and lower parity; a small study from the same group on 68 women with laryngeal cancer [23] report an association with late menarche (≥ 15 years). In a large case-control study (530 cases and 530 controls), Suba et al [11] found associations between cancer of the oral cavity and early age at menopause and hysterectomy and/or oophorectomy. The results of these three studies are incongruent, and collectively there is no clear evidence in the literature for involvement of any single female reproductive characteristic with HNSCC.

Our study presents marginal evidence that the use of hormone replacement therapy (HRT) may confer a protective effect against HNSCC, with a borderline inverse dose-response across categories of increasing duration. These findings are in-line with those of Freeman and colleagues [8] who report a relative risk of 0.78 (95% CI: 0.61-0.99), although several others found no association [11; 23; 24; 25]. Part of the inconsistency may be attributed to heterogeneity among studies, which reflects the diversity of the populations and of the type of exposure; all of the studies but one (Freedman) were conducted in various parts of Europe. Exogenous hormonal exposures, such as HRT and oral contraception, vary between Europe and US. For example, a study based on pharmaceutical sales data from the 1990s, prior to the decline in use of HRT, reports substantial differences in use of HRT between the United States and Europe [26]. HRT is available in many different forms, with varying doses depending upon the drug and the needs of the patient [9], although use drastically declined following the publication of the Women's Health Initiative trial results in 2002 [27; 28]. The composition of oral contraceptives are similarly variable [29]. Differences in study design are also present: out of 6 studies conducted on this topic, 2 are cohort and 4 are case-control studies, one includes larynx, one oral cavity, the other 4 head and neck tumors. thus making the comparison across studies very difficult.

While the mechanisms behind the potential protective effect of HRT are largely unknown, a role in alteration of HNSCC risk is biologically plausible, as the head and neck epithelium undergoes gender-specific changes during puberty [30; 31]. This is particularly evident in the larynx, although the present study is too small to properly evaluate the effect in a site-specific manner. Sex hormone receptors are present in both benign [12; 13; 14; 15] and malignant [16; 17; 18] head and neck tissue. ERβ functions as a tumor suppressor via inhibition of proliferation and induction of differentiation and apoptosis [32; 33], which could potentially eliminate precancerous defect cells prior to malignant conversion, and may

be the prevalent subtype of estrogen receptor expressed in the head and neck: a study of benign buccal and gingival epithelium [12] reported ERβ to be widely expressed, while ERα, which appears to act as a tumor promoter through stimulation of cellular proliferation [34; 35], was not detected.

The major strengths of this study include the collection of detailed exposure history for female reproductive factors for assessment, as well as detailed collection of other potentially confounding exposures, such as smoking dose, educational attainment and family history of cancer. However, there were also several limitations to this study. There may have been insufficient statistical power for detection of certain associations, due to our moderate sample size, and therefore larger scale studies are needed before ruling out small to moderate effects. Additionally, although the statistical models were adjusted for smoking dose, there is a potential for residual confounding due to the categorization of the covariate. It should be noted, however, that the ORs for postmenopausal hormone use among never-smokers, although imprecise, were consistent with the adjusted ORs for postmenopausal hormone use among the greater study population. Another issue is that we did not have specific data regarding type of HRT drug used or the dosage, even though there are many different kinds available with differing doses and forms of hormones. Likewise, our study does not include data on the type of oral contraception used.

The findings of this study do not support a link between HNSCC and reproductive factors, but the evidence is not sufficient to fully refute the hormonal theory. The borderline association of HRT with HNSCC may warrant further evaluation in future studies that should include larger study populations, with more in-depth examination of the effects of specific forms and doses of HRT and oral contraception. Future studies should also seek to evaluate the effects of estrogen and metabolite levels on HNSCC risk. Continued assessment of hormonal and non-hormonal gender differences may eventually provide insight as to why men have substantially higher incidence of this disease and advance our knowledge regarding the development of head and neck cancer.

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Table I

Sociodemographic and health behavior characteristics of the study population

	Cases n = 149	Controls n = 158	$P_{difference}$	Crude OR[a] (95% CI)
Age				
Years, median (range)	59.9 (21-80)	59.5 (20-80)	0.73[b]	---
Race, n (%)				
White	144 (96.6%)	148 (93.7%)	0.29[c]	*1.00 (reference)*
Black	5 (3.4%)	10 (6.3%)		0.50 (0.16-1.54)
Family history of cancer, n (%)				
No	52 (34.9%)	71 (44.9%)	0.08[c]	*1.00 (reference)*
Yes	97 (65.1%)	87 (55.1%)		1.56 (0.97-2.50)
Highest level of education, n (%)				
High school or less	100 (67.1%)	48 (30.4%)	< 0.001[c]	*1.00 (reference)*
Some college or tech school	14 (9.4%)	14 (8.9%)		0.45 (0.20-1.03)
College or more	35 (23.5%)	96 (60.8%)		0.17 (0.10-0.29)
Body mass index (BMI)				
kg/m^2, median (range)	26.6 (14.7-65.7)	27.4 (18.1-47.8)	0.37[b]	1.00 (0.97-1.03)[d]
Smoking, n (%)				
Never smoker	40 (26.9%)	92 (58.2%)	< 0.001[c]	*1.00 (reference)*
≤ 10 pack-years	17 (11.4%)	28 (17.7%)		1.40 (0.69-2.85)
> 10 pack-years	92 (61.7%)	38 (24.1%)		5.60 (3.29-9.52)
Alcohol consumption				
Never drinker	62 (41.6%)	80 (50.6%)	0.002[c]	*1.00 (reference)*
≤ 1 drink/day	53 (35.6%)	65 (41.1%)		1.06 (0.65-1.75)
> 1 drink/day	34 (22.8%)	13 (8.2%)		3.46 (1.67-7.16)
Tumor site, n (%)				
Oral cavity	62 (41.6%)	---		---
Pharynx	53 (35.6%)	---		---
Larynx	34 (22.8%)	---		---

Abbreviations: OR = odds ratio; CI = confidence interval

[a] Crude models include the frequency-matched factor (age)

[b] Rank-sum test

[c] Fisher's exact test

[d] Per BMI unit increase, centered at the median (27.1 kg/m2)

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Table II

Association of reproductive factors with head and neck squamous cell carcinoma (HNSCC) in women.

	Cases/ Controls	Crude OR[a] (95% CI)	P_{trend}	Adjusted OR (95% CI)	P_{trend}
Age at menarche[b], n (%)					
≤ 11 years	33/31	*1.00 (reference)*		*1.00 (reference)*	
12-13 years	82/89	0.87 (0.49-1.54)		1.25 (0.63-2.49)	
≥ 14 years	34/38	0.84 (0.43-1.65)	0.62	0.91 (0.41-2.01)	0.76
Hysterectomy/oophorectomy status[b]					
Neither	93/105	*1.00 (reference)*		*1.00 (reference)*	
Hysterectomy[c]	47/47	1.16 (0.70-1.91)		1.00 (0.56-1.79)	
Bilateral oophorectomy[c]	19/22	0.98 (0.50-1.94)		1.03 (0.48-2.23)	
Exogenous female hormone (HRT) use[d,e]					
Never	81/58	*1.00 (reference)*		*1.00 (reference)*	
Ever	38/67	0.41 (0.24-0.70)		0.60 (0.31-1.06)	
≤ 5 years of use	23/31	0.53 (0.28-1.00)		0.69 (0.33-1.45)	
> 5 years of use	15/34	0.33 (0.16-0.66)	0.001[i]	0.47 (0.20-1.08)	0.06[i]
Oral contraceptive use[f]					
Never	51/55	*1.00 (reference)*		*1.00 (reference)*	
Ever	98/103	1.04 (0.63-1.71)		1.09 (0.60-1.98)	
Started taking at > 22 years old	32/52	0.69 (0.38-1.24)		0.75 (0.38-1.51)	
Started taking at ≤ 22 years old	66/51	1.66 (0.90-3.05)	0.13[j]	1.67 (0.81-3.44)	0.21[j]
Fertility medication[c], n (%)					
No	138/145	*1.00 (reference)*		*1.00 (reference)*	
Yes	8/12	0.70 (0.28-1.77)		0.51 (0.17-1.53)	
History of pregnancy					
Number of pregnancies[c]					
0	19/32	*1.00 (reference)*		*1.00 (reference)*	
1-2	52/57	1.55 (0.78-3.06)		0.85 (0.38-1.87)	
≥ 3	78/69	1.94 (1.00-3.76)	0.05	1.17 (0.55-2.51)	0.47

	Cases/ Controls	Crude OR[a] (95% CI)	P_{trend}	Adjusted OR (95% CI)	P_{trend}
Age at first pregnancy[c,g]					
≤ 18 years	33/17	*1.00 (reference)*		*1.00 (reference)*	
19-29 years	84/95	0.45 (0.24-0.88)		0.74 (0.35-1.56)	
≥ 30 years	13/14	0.48 (0.18-1.24)	0.06	1.21 (0.39-3.72)	0.96
History of live birth					
Parity[c]					
0	28/37	*1.00 (reference)*		*1.00 (reference)*	
1-2	54/74	0.98 (0.53-1.79)		0.67 (0.33-1.36)	
≥ 3	67/47	1.96 (1.04-3.68)	0.02	1.28 (0.61-2.66)	0.33
Age at first live birth[c,h]					
≤ 18 years	22/12	*1.00 (reference)*		*1.00 (reference)*	
19-29 years	86/92	0.51 (0.24-1.10)		0.84 (0.35-2.00)	
≥ 30 years	13/17	0.42 (0.15-1.14)	0.08	1.27 (0.38-4.18)	0.73

Abbreviations: OR = odds ratio; CI = confidence interval

[a] All crude models are adjusted for the frequency-matched factor (age)

[b] Adjusted for age, smoking, highest level of education and family history of cancer

[c] Hysterectomy and bilateral oophorectomy are not mutually exclusive

[d] Adjusted for age, smoking and highest level of education

[e] Restricted to postmenopausal women only

[f] Adjusted for age, smoking, highest level of education, family history of cancer and number of pregnancies

[g] Excludes women who have never been pregnant

[h] Excludes women who have never had a live birth

[i] Test of trend is across duration categories for female hormone use (never, ≤ 5 years, > 5 years)

[j] Test of trend is across categories of oral contraception start age (never, > 22 years old, ≤ 22 years old)

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Table III

Association of exogenous female hormone (HRT) use among postmenopausal women, stratified by smoking status and tumor site.

	Exogenous Female Hormone Use						
	Never (*reference*)	≤ 5 years			> 5 years		
Strata	**Cases/ Controls**	**Cases/ Controls**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**Cases/ Controls**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Smoking status[a]							
Never smoker	17/34	5/20	0.50 (0.16-1.58)	0.49 (0.14-1.70)	3/16	0.37 (0.10-1.46)	0.65 (0.15-2.86)
< 10 pack-years	8/10	3/2	2.00 (0.26-15.48)	3.37 (0.35-32.55)	3/10	0.56 (0.05-3.39)	1.84 (0.21-16.12)
≥ 10 pack-years	56/14	15/9	0.42 (0.15-1.15)	0.59 (0.20-1.74)	9/8	0.27 (0.09-0.84)	0.31 (0.09-1.01)
Tumor site[b]							
Oral cavity	36/58	10/31	0.52 (0.23-1.19)	0.67 (0.27-1.66)	8/34	0.38 (0.16-0.91)	0.54 (0.21-1.43)
Pharynx	22/58	8/31	0.69 (0.27-1.77)	1.29 (0.43-3.86)	3/34	0.31 (0.08-1.14)	0.31 (0.07-1.34)
Larynx	23/58	5/31	0.40 (0.14-1.15)	0.60 (0.13-2.73)	4/34	0.32 (0.10-1.00)	0.27 (0.06-1.24)

Abbreviations: OR = odds ratio; CI = confidence interval

[a] Crude and adjusted models include the frequency-matched factor (age); adjusted model additionally includes highest level of education

[b] Crude and adjusted models include the frequency-matched factor (age); adjusted model additionally includes