Reproductive factors and risk of esophageal squamous cell carcinoma in northern Iran: a case–control study in a high-risk area and literature review

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Several epidemiologic studies have suggested an inverse association between female reproductive factors and the risk of esophageal squamous cell carcinoma (ESCC), but the evidence is not conclusive. We examined the association of the number of pregnancies, live births, and miscarriages/stillbirths in women and the association of the number of children in both sexes with the risk of ESCC in Golestan Province, a high-risk area in Iran. Data from 297 histopathologically confirmed ESCC cases (149 women) and 568 controls (290 women) individually matched to cases for age, sex, and neighborhood of residence were included in this analysis. Conditional logistic regression was used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). The average numbers of live births and miscarriages/stillbirths among the controls were 8.2 and 0.8, respectively. Women with six or more live births were at ~1/3 the risk of ESCC as those with 0–3 live births; the OR (95% CI) for having 6–7 live births was 0.33 (0.12–0.92). In contrast, the number of miscarriages/stillbirths was associated with an increase in the risk of ESCC. The OR (95% CI) for at least three versus no miscarriages/stillbirths was 4.43 (2.11–9.33). The number of children in women was suggestive of an inverse association with ESCC, but this association was not statistically significant; in men, no association was observed. The findings of this study support a protective influence of female hormonal factors on the risk of ESCC. However, further epidemiological and mechanistic studies are required to prove a protective association. ***European Journal of Cancer Prevention*** **00:000–000 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Cancer Prevention 2012, **00**:000–000

Keywords: case–control study, esophageal cancer, miscarriage, parity, reproductive, squamous cell carcinoma

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Received 25 October 2012 **Accepted** 31 October 2012

Introduction

An inverse association between indicators of higher exposure to female hormonal factors and the risk of gastrointestinal cancers, primarily gastric (Camargo *et al.*, 2012) and colon (Grodstein *et al.*, 1999) cancers, has been shown in several studies. Experimental studies have also pointed to the plausibility of an inverse association between exposure to estrogen and the risk of the above cancers (Chandanos and Lagergren, 2008, 2009). For example, the incidence of gastric cancer following treatment with *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, a carcinogenic *N*-nitroso compound, is significantly higher in male than in female rats (Furukawa *et al.*, 1982). In male rats treated with the above *N*-nitroso compound, administration of estrogen has been shown to influence antral and duodenal gland differentiation (Campbell-Thompson *et al.*, 1999) and to reduce the incidence of gastric cancer (Furukawa *et al.*, 1982).

Several epidemiologic studies have also reported an inverse association between indicators of higher exposure to estrogen, derived endogenously (Miller *et al.*, 1980; Green *et al.*, 1988; Gallus *et al.*, 2001; Yu *et al.*, 2011; Green *et al.*, 2012b) or exogenously (Gallus *et al.*, 2001; Bodelon *et al.*, 2011; Green *et al.*, 2012b), and the risk of esophageal squamous cell carcinoma (ESCC). However, the evidence for the association is still inconclusive, because the number of these studies is limited, many of the studies had a small number of female ESCC cases, and there are a few studies that did not show such associations (La Vecchia *et al.*, 1993; Chen *et al.*, 2011). Therefore,

All supplementary digital content is available directly from the corresponding author.

0959-8278 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e32835c7f87

further investigations are warranted. Here, we report the association of the number of pregnancies, live births, and miscarriages/stillbirths in women and the association of the number of children in both sexes with a risk of ESCC in the Golestan Case–Control Study, a population-based case–control study carried out in the eastern parts of Golestan Province, a mainly rural area in northeast Iran with a high incidence of ESCC (Mahboubi *et al.*, 1973; Roshandel *et al.*, 2012).

Methods

The details of participant selection have been reported elsewhere (Nasrollahzadeh *et al.*, 2008). Briefly, all case participants were incident cases with histopathologically confirmed ESCC recruited at Atrak Clinic, the only specialized clinic for upper gastrointestinal tract cancers in eastern Golestan, from December 2003 to June 2007. For each case participant, we attempted to select two population-based control individuals, individually matched to the case for neighborhood of residence, age (± 2 years), and sex, using the family health census that is conducted annually by the Iranian Primary Health Care System. Of 300 cases of ESCC enrolled in this study, 29 had only one matched control; thus, the total number of controls was 571.

After obtaining written informed consent, participants were interviewed by trained interviewers who collected detailed information on sociodemographic characteristics, dietary data, potential confounders of interest, such as life-long history of tobacco, opium, or alcohol use, and, in women, reproductive history, including the number of pregnancies and live births, using a structured questionnaire. The difference between the number of pregnancies and live births is the number of miscarriages, stillbirths, and induced abortions. We did not collect data on these different subcategories of pregnancies that did not result in a live birth. However, as has been documented previously in Iranians with age cohorts similar to those of our study participants (Kavoussi, 1977) and as is accepted practice in this population because of religious beliefs, induced abortions among women participating in our study are likely to have been rare. Therefore, we assumed that the difference between the number of pregnancies and live births represents the number of miscarriages and stillbirths. This study was reviewed and approved by the Institutional Review Boards of the Digestive Disease Research Center of Tehran University of Medical Sciences and the US National Cancer Institute.

Statistical analysis

Numbers and percentages by case status were calculated and presented for categorical variables. Similar to our earlier analyses, we used a composite wealth score (including information on ownership of personal car, motorbike, B/W TV, color TV, refrigerator, freezer, vacuum and washing machine, as well as house ownership, house structure, house size, having a bath in the residence and occupation), calculated using multiple correspondence analysis, to estimate socioeconomic status (Islami *et al.*, 2009a). The scores were calculated and categorized as quintiles according to the observed coordinates among control participants.

In accord with the matched design of the study, conditional logistic regression was used to calculate unadjusted and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). By design, case and control participants were matched for age, sex, and place of residence. Conditional logistic regression models were adjusted for potential confounders, including duration of residence in rural areas, ethnicity, education level, marital status, consumption of opium and/or tobacco (including cigarette, pipe and hookah smoking, and nass chewing), the wealth score, and daily vegetable intake (in logarithmic scale). None of the women were ever alcohol drinkers and there was no difference in the frequency of alcohol drinking in case and control men (4.7 and 5.0%, respectively, $P = 0.89$); therefore, alcohol drinking was not included in the models. P values for trend were obtained from the same conditional logistic regression models by assigning consecutive numbers to categories within each categorical variable. All statistical analyses were carried out using STATA software, version 11 (StataCorp., College Station, Texas, USA).

Results

After the exclusion of those with missing values in variables of interest, 297 ESCC cases (149 women) and 568 controls (290 women) remained for further analyses. Sociodemographic characteristics and the mean daily vegetable intake of study participants are shown in Supplementary Table 1.

Although the risk estimates for the association between the number of pregnancies and the risk of ESCC were lower than unity (Table 1), this association was not statistically significant. Also, the OR for the highest category (≥ 11 pregnancies) was higher than that of the preceding categories. The risk of ESCC was reduced by 14% with each live birth (OR = 0.86, 95% CI: 0.79–0.95). Using categorical variables, women with six or more live births were at $\sim 1/3$ the risk of ESCC as those with 0–3 live births. In contrast, the number of miscarriages/stillbirths was associated with an increase in the risk of ESCC. The OR (95% CI) for each miscarriage/stillbirth was 1.49 (1.24–1.78) when the number of miscarriages/stillbirths was included as a continuous variable.

As some of the children died after birth or later in life, the number of children was smaller than the number of live births for women (Table 2). In women, the number of children as a continuous or a categorical variable was

Table 1 Association between reproductive factors and the risk of esophageal squamous cell carcinoma among women participating in the Golestan Case–Control Study

Reproductive factors	ESCC cases (%) ($N=149$)	Controls (%) ($N=290$)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Number of pregnancies				
Continuous	8.4 (3.5)[a]	9.0 (3.4)[a]	0.95 (0.89–1.01)	0.98 (0.91–1.06)
Arbitrary categories				
0–3	11 (7.4)	15 (5.2)	Referent	Referent
4–6	33 (22.1)	45 (15.5)	1.06 (0.43–2.66)	0.83 (0.25–2.77)
7–8	31 (20.8)	69 (23.8)	0.63 (0.26–1.50)	0.50 (0.16–1.57)
9–10	32 (21.5)	77 (26.5)	0.56 (0.23–1.34)	0.47 (0.15–1.50)
≥ 11	42 (28.2)	84 (29.0)	0.67 (0.28–1.61)	0.73 (0.24–2.26)
P trend			0.12	0.59
Quartiles				
Quartile 1 (0–6)	44 (29.5)	60 (20.7)	Referent	Referent
Quartile 2 (7–8)	31 (20.8)	69 (23.8)	0.60 (0.34–1.07)	0.57 (0.29–1.14)
Quartile 3 (9–10)	32 (21.5)	77 (26.5)	0.53 (0.30–0.96)	0.55 (0.28–1.09)
Quartile 4 (≥ 11)	42 (28.2)	84 (29.0)	0.64 (0.36–1.15)	0.84 (0.43–1.64)
P trend			0.14	0.69
Number of live births				
Continuous	6.8 (3.0)[a]	8.2 (3.2)[a]	0.85 (0.79–0.92)	0.86 (0.79–0.95)
Arbitrary categories				
0–3	18 (12.1)	19 (6.6)	Referent	Referent
4–5	32 (21.5)	30 (10.3)	1.23 (0.51–2.96)	0.90 (0.29–2.80)
6–7	34 (22.8)	66 (22.8)	0.58 (0.26–1.28)	0.33 (0.12–0.92)
8–9	33 (22.1)	87 (30.0)	0.39 (0.18–0.85)	0.31 (0.11–0.85)
≥ 10	32 (21.5)	88 (30.3)	0.35 (0.16–0.77)	0.34 (0.12–0.93)
P trend			<0.001	0.003
Quartiles				
Quartile 1 (0–5)	50 (33.6)	49 (16.9)	Referent	Referent
Quartile 2 (6–7)	34 (22.8)	66 (22.8)	0.51 (0.28–0.91)	0.36 (0.17–0.73)
Quartile 3 (8–9)	33 (22.1)	87 (30.0)	0.34 (0.19–0.61)	0.33 (0.16–0.67)
Quartile 4 (≥ 10)	32 (21.5)	88 (30.3)	0.31 (0.17–0.57)	0.36 (0.17–0.76)
P trend			<0.001	0.005
Number of miscarriages/stillbirths				
Continuous	1.5 (2.1)[a]	0.8 (1.2)[a]	1.37 (1.19–1.57)	1.49 (1.24–1.78)
Arbitrary categories				
0	69 (46.3)	175 (60.3)	Referent	Referent
1	25 (16.8)	56 (19.3)	1.15 (0.67–1.97)	1.38 (0.71–2.69)
2	19 (12.7)	24 (8.3)	2.10 (1.07–4.11)	2.54 (1.10–5.86)
≥ 3	36 (24.2)	35 (12.1)	3.04 (1.68–5.51)	4.43 (2.11–9.33)
P trend			<0.001	<0.001

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; OR, odds ratio.
[a]Mean (SD).
[b]Multivariate models were adjusted for duration of residence in rural areas, ethnicity, education level, marital status, tobacco and opium use, quintiles of wealth score, and daily vegetable intake (variables as shown in Supplementary Table 1). Results for the number of live births were additionally adjusted for quartiles of miscarriages/stillbirths and results for miscarriage/stillbirth were additionally adjusted for the quartiles of live births.

suggestive of an inverse association with ESCC, although this association was not statistically significant. There was no apparent association between the number of children and the risk of ESCC in men.

Discussion

We found an inverse association between the number of live births and the risk of ESCC in women, whereas the number of miscarriages/stillbirths showed a positive association with this risk.

The results of previous studies on the association between reproductive factors and the risk of ESCC are summarized in Table 3. Similar to our study, the majority of the studies have shown an inverse association between female reproductive factors and the risk of ESCC. However, some studies did not find significant associations, including an earlier study in Golestan, which showed a nonsignificant inverse association between higher parity and ESCC (Cook-Mozaffari *et al.*, 1979). Some of the previous studies may have lacked sufficient statistical power to identify such associations. Also, variation in the number of pregnancies and duration of breastfeeding in different populations and age cohorts may be another important factor: small numbers of pregnancies and a short duration of breastfeeding can reduce the ability to identify any associations with respect to these factors, particularly in small studies. We did not collect data on breastfeeding, but Iranian women, particularly in rural areas, usually breastfeed their infants (Malekafzali and Beigi, 1989). Therefore, women with high numbers of live births in our study are likely to have had long durations of breastfeeding. It should be noted that the inverse association between live births and the risk of ESCC in Golestan may be stronger than what we observed, as the reference group in our analyses was women with 0 to 3 live births rather than only nulliparous women; this was because of the very small number of women in the latter group. Both the presence of estrogen receptors in esophageal tissue and ESCC and

Table 2 Association between the number of children and esophageal squamous cell carcinoma in men and women participating in the Golestan Case–Control Study

Number of children	ESCC cases (%)	Controls (%)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Women	149 (100)	290 (100)		
Continuous	6.2 (2.8)[a]	6.9 (2.6)[a]	0.90 (0.84–0.98)	0.93 (0.85–1.02)
Categories				
0–3	22 (14.8)	30 (10.3)	Referent	Referent
4–5	37 (24.8)	51 (17.6)	1.05 (0.53–2.07)	1.05 (0.46–2.39)
6–7	35 (23.5)	89 (30.7)	0.54 (0.28–1.06)	0.51 (0.23–1.11)
8–9	41 (27.5)	74 (25.5)	0.77 (0.39–1.51)	0.88 (0.39–2.00)
≥ 10	14 (9.4)	46 (15.9)	0.37 (0.16–0.86)	0.47 (0.18–1.22)
P trend			0.02	0.13
Men	148 (100)	278 (100)		
Continuous	7.0 (3.5)[a]	7.1 (3.1)[a]	1.00 (0.73–1.06)	1.01 (0.94–1.10)
Categories				
0–3	20 (13.5)	27 (9.7)	Referent	Referent
4–5	29 (19.6)	55 (19.8)	0.76 (0.36–1.62)	0.80 (0.31–2.05)
6–7	32 (21.6)	74 (26.6)	0.62 (0.29–1.31)	0.65 (0.26–1.62)
8–9	34 (23.0)	70 (25.2)	0.71 (0.34–1.50)	0.77 (0.31–1.94)
≥ 10	33 (22.3)	52 (18.7)	0.90 (0.41–1.97)	1.03 (0.39–2.70)
P trend			0.97	0.74

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; OR, odds ratio.
[a]Mean (SD).
[b]Multivariate models were adjusted for duration of residence in rural areas, ethnicity, education level, marital status, tobacco and opium use, quintiles of wealth score, and daily vegetable intake (variables as shown in Supplementary Table 1).

the tumor growth-inhibitory effect of estrogenic compounds reported in in-vitro and in-vivo studies support the protective effect of female reproductive hormones against ESCC (Chandanos and Lagergren, 2009; Rashid *et al.*, 2010; Zuguchi *et al.*, 2012).

However, the association between parity and ESCC may be confounded by other factors, including low socioeconomic status, which have been shown to be associated with a higher risk of ESCC (Islami *et al.*, 2009a). Lu and Lagergren (2012) reported similar inverse associations between parity status in women and having children in men with a risk of ESCC (Table 3), suggesting that hormones may not play an important role in observed associations between reproductive factors and ESCC. However, when the number of children was considered, the risk estimates showed a much stronger inverse association in women than in men (Lu and Lagergren, 2012). The results of our study also suggest an inverse association between the number of children and the risk of ESCC in women but not in men. The association between miscarriages/stillbirths and ESCC may also be, at least partly, related to hormonal factors, as one cause of recurrent miscarriages may be hormonal dysfunction (Arck *et al.*, 2008). However, the confounding effect of other factors, such as socioeconomic status at younger ages, cannot be ruled out.

Although a higher prevalence and intensity of tobacco and alcohol use, known risk factors of ESCC, among men may explain most of the 3–4 : 1 male predominance in the incidence of ESCC in western countries (Kamangar *et al.*, 2009), a part of this pattern may also be related to a possible protective role of female reproductive hormones against ESCC. In high-risk areas for ESCC, where tobacco use and heavy alcohol drinking are not major risk factors (Kamangar *et al.*, 2009), the incidence of ESCC is usually more similar in men and women, with a male : female ratio typically around 1.5 : 1 (He *et al.*, 2008; Roshandel *et al.*, 2012). The primary etiologic factors of ESCC in these high-incidence areas, including Golestan, are mainly unknown (Kamangar *et al.*, 2009). There is little sex difference in the prevalence of some suggested risk factors for ESCC in Golestan, including hot tea drinking (Islami *et al.*, 2009c), but we have shown that vitamin intake, a potential protective factor, is considerably lower among women than men in Golestan, particularly in rural areas (Islami *et al.*, 2009b). Thus, female hormonal factors and sex differences in other known and unknown risk factors may be responsible for the slight male predominance in the incidence of ESCC in Golestan and other high-risk populations, but additional studies are required to further evaluate these hypotheses.

If there is an inverse association between estrogen and the risk of gastrointestinal cancers, then the use of antiestrogenic medicines, including tamoxifen, which is used in the treatment of breast cancer, might be associated with an increased risk of those cancers. A recent meta-analysis has reported an increased risk of gastric cancer associated with intake of tamoxifen, on the basis of nine clinical trials and five cohort studies, although the majority of studies had only a small number of gastric cancer cases (Camargo *et al.*, 2012). The evidence for the association between tamoxifen use and the risk of colorectal and esophageal cancer is less consistent; however, the statistical power in many of those studies has also been poor (Chandanos and Lagergren, 2009).

In the current study, women had a high mean number of pregnancies. As the mean age of the study participants at enrollment was 63 years and the study finished enrolling

Table 3 Summary of previous studies on reproductive factors and esophageal cancer (all histological types combined) or the risk of esophageal squamous cell carcinoma [a]

References; country; cancer case number	Study design; outcome; associations with the outcome
Cook-Mozaffari *et al.* (1979); Iran; 121	Case–control; EC incidence; nonsignificant ↓ with higher parity
Miller *et al.* (1980); Canada; 36	Parity data from women in cancer registries were compared with data from census; EC incidence; ↓ with three or more parities
Green *et al.* (1988); UK; 27	Parity data from women in mortality registries were compared with data from census; EC mortality; ↓ with the number of parity
La Vecchia *et al.* (1993); Italy; 58	Case–control; EC incidence; nonsignificant ↑ with parity
Gallus *et al.* (2001); Italy and Switzerland; 112	Case–control; ESCC incidence; nonsignificant ↑ with parity. ↓with OCP use and HRT
Freedman *et al.* (2010); USA; 56	Cohort; ESCC incidence; nonsignificant ↓ with higher parity, later menopause, and HRT
Yu *et al.* (2011); China; 88	Case–control; ESCC incidence; nonsignificant ↓ with the number of children, breastfeeding, and HRT
Chen *et al.* (2011); China; 68	Case–control; ESCC incidence; ↔ with the number of live births or factors related to menstruation
Bodelon *et al.* (2011); USA; 34	Follow-up after a clinical trial of HRT; ESCC incidence; ↓ with HRT. ↑ with the number of term pregnancies. ↔ with breastfeeding or menstrual history
Green *et al.* (2012b); UK; 578	Cohort; ESCC incidence; ↓ with parity status (being parous versus nonparous) but ↔ with the number of full-term pregnancies. ↓ with later menopause. ↔ with age at menarche and breastfeeding
Lu and Lagergren (2012); Sweden; 363 women and 917 men	Case–control study nested within the Swedish Multi-Generation Register; ESCC incidence; similar ↓ with parity status (being parous versus nonparous) in women and having children (any number of children versus no child) in men. The OR (95% CI) for having three or more children versus one child was 0.72 (0.51–1.00) for women and 0.90 (0.71–1.13) for men. When only cases ≥ 50 years of age were considered, the OR (95% CI) was 0.63 (0.48–0.98) for women and 0.91 (0.71–1.17) for men
Green *et al.* (2012a); UK; 1054	Case–control study nested within the General Practice Research Database; EC incidence; ↓ with HRT

↑, positive association; ↓, inverse association; ↔, no association; CI, confidence interval; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; HRT, hormone replacement therapy; OCP, oral contraceptive; OR, odds ratio.
[a]When results were presented by histological type, only ESCC results were chosen. The number of cancer cases shown is the number of women only, unless stated otherwise.

new patients in 2007, many of the women must have been in their most reproductive years before the mid-1980s. The average number of births for Iranian women decreased from over six births per woman in the 1980s to 1.9 in 2006 (Abbasi-Shavazi and McDonald, 2006; Abbasi-Shavazi *et al.*, 2009). The majority of this change occurred in the late 1980s and the early 1990s: from 7.1 children per woman in 1986 to 2.9 in 1996 (Simbar, 2012). One of the major reasons for this change was probably the wider implementation of family planning programs in Iran during this period. In 2000, the prevalence of contraceptive use in urban and rural areas of Iran was 77 and 67%, respectively; the respective rates were 74 and 52% in 1992 and 54 and 20% in 1977 (Aghajanian, 1995; Simbar, 2012). Transitions in socioeconomic factors, particularly among women, may have also played a role in this decrease. As an example of these changes, women's literacy in Iran increased from 36% in 1976 to 80% in 2006 (Abbasi-Shavazi *et al.*, 2009), and in 2005, 62% of students entering university in Iran were women (Moinifar, 2011).

Very low prevalence of tobacco and alcohol use, major risk factors for ESCC in western countries, among the study participants and extensive adjustments for many other potential confounding factors are among the strengths of this study. Although this study was carried out in a case–control setting, any major bias in recall of the number of pregnancies, live births, and children is unlikely. Lack of information on other reproductive factors, such as intake of exogenous hormones and age at menarche, first live birth, and menopause, is a limitation of this study. However, the high number of pregnancies, and consequently the probably long cumulative duration of breastfeeding, may offset the effects of many of these factors. Also, considering the high number of pregnancies and the age cohort of participating women, it is unlikely that many of the women received hormonal contraception. Hormonal replacement therapy is not a common practice in Golestan (Motie *et al.*, 2011).

Conclusion

The results of this study support the hypothesis that female hormones may exert protective effects against ESCC carcinogenesis. However, further epidemiological and mechanistic studies are required before there is conclusive evidence of a protective association.

Acknowledgements

The authors thank the Atrak Clinic staff, including Dr Noushin Taghavi, Dr Rabaeh Rajabzadeh, Monireh Badakhshan, Bita Mohammadi, Halimeh Eskandarnejhad, Safora Kor, Soleiman Kasalkheh, and Ashor Yolmeh. They are also grateful to Drs. Karim Aghcheli, Behnoush Abedi-Ardekani, Shahin Merat, Siavosh Nasseri-Moghaddam, Noorli Radgohar, Abdolazim Khozeini, Rahmat Ghaziani, Mohammad Hasan Brazandeh, Abdolhakim Ebadati, Naser Keramat, and Ahmad Nosrati for their valuable help. They thank and appreciate the local health networks and health workers (Behvarzes) in the study area for their assistance in the recruitment of controls and the Iranian Social Security Organization for their strong local support.

The Golestan Case–Control Study was supported by the Digestive Disease Research Center of Tehran University of Medical Sciences (grant number 82-603) and intramural funds of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. The funding sources had no role in the design,

conduct, statistical analysis and interpretation of results, or writing of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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