Difference in the Incidence Trend of Nasopharyngeal and Oropharyngeal Carcinomas in Taiwan: Implication from Age-Period-Cohort Analysis

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Abstract

Lifestyle factors are considered important for the pathogenesis of both nasopharyngeal and oropharyngeal carcinomas. In Taiwan, the incidence of nasopharyngeal carcinoma gradually decreased over the past 20 years, whereas that of oropharyngeal carcinoma increased rapidly. To compare the incidence trends of nasopharyngeal and oropharyngeal carcinomas in Taiwan, the age-period-cohort model was used to analyze epidemiologic data from 1981 to 2000 obtained from the Taiwan Cancer Registry. The calendar time period of 1986 to 1990 and the 1931 to 1940 birth cohort were used as reference groups for estimates of relative risk. For nasopharyngeal carcinoma, the incidence seemed to decrease in most age groups and was more prominent in women (30%) than in men (23%). For oropharyngeal carcinoma, the incidence increased in all age groups and was more prominent in men (391.4%) than in women (59.2%). Cohort effect was found for both nasopharyngeal and oropharyngeal carcinomas. The relative risk of nasopharyngeal carcinoma for the 1971 to 1980 birth cohort was 0.38 for women and 0.68 for men. The relative risk of oropharyngeal carcinoma for the 1971 to 1980 cohort was 45.67 for men and 2.69 for women. Change in lifestyle seemed to be an important factor for the difference in the incidence trend between nasopharyngeal and oropharyngeal carcinomas and between men and women. (Cancer Epidemiol Biomarkers Prev 2006;15(5):856–61)

Introduction

Nasopharyngeal carcinoma (*International Classification of Diseases 9th version* code 147) is a special type of head and neck carcinoma that is endemic in ethnic Chinese populations, such as in southeast China, Hong Kong, Singapore, and Taiwan (1). Nasopharyngeal carcinoma arises from nasopharynx, and histologically, >90% are nonkeratinizing carcinoma (WHO type II) or undifferentiated carcinoma (type III) in these endemic areas (1). The incidence of nasopharyngeal carcinoma in Taiwan has decreased gradually in the past two decades. The age-adjusted incidence rate of nasopharyngeal carcinoma was 11.19 for men and 4.35 for women in the year 1981 and 8.60 for men and 3.02 for women in 2000 (2).

By contrast, the incidence of oropharyngeal carcinomas (*International Classification of Diseases 9th version* codes 140-149, excluding 142 and 147) in Taiwan has increased >5-fold in the same period of time (2). Oropharyngeal carcinoma includes carcinomas arising from lips (code 140), tongue (code 141), gingival (code 143), mouth floor (code 144), mouth (other sites)(code 145), oropharynx (code 146), hypopharynx (code 148), and other nonspecified sites in the oropharyngeal area (code 149). Histologically, >90% of oropharyngeal carcinoma are squamous cell carcinoma (3). This remarkable difference in incidence trend between nasopharyngeal and oropharyngeal carcinomas is not likely due to change in diagnostic style or practice because these two types of cancers arise in distinct anatomic sites and have different clinical and pathologic features. Therefore, different pathogenic mechanisms may be implicated in nasopharyngeal and oropharyngeal carcinomas.

Epidemiologic data suggested that environmental and lifestyle factors may play a significant role in the pathogenesis of nasopharyngeal and oropharyngeal carcinomas (4-10). Some of the most important lifestyle factors for nasopharyngeal carcinoma, such as consumption of salted fish and preserved food and occupational exposure to wood dust, are expected to decrease in prevalence as environmental hygiene improves, and as people adopt a more westernized diet habit. Therefore, the incidence of nasopharyngeal carcinoma may decline because of these lifestyle changes. Evidence supporting this hypothesis has been shown in a recent epidemiologic study in Hong Kong, the region with the highest incidence of nasopharyngeal carcinoma in the world. It showed a nearly 30% reduction of the incidence of nasopharyngeal carcinoma in the period of 1980 to 1999 (11). Lifestyle factors, particularly the increasing westernization of diet habit, were considered responsible for this reduction of incidence. For oropharyngeal carcinoma, lifestyle risk factors also play a central role in its pathogenesis. The most prominent factors include tobacco, alcohol, and betel quid use (3). Although these factors have been implicated in the pathogenesis of nasopharyngeal carcinoma, data from previous case-control studies are not very consistent, and the effects of these factors are mostly moderate (4, 6, 9, 10).

The purpose of this study was to explore the potential effects of patient age, calendar time period at diagnosis, and birth cohort on the incidence change of nasopharyngeal carcinoma in Taiwan. The incidence trend of oropharyngeal carcinoma was used as comparison. The age-period-cohort

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model was used in this study (12, 13). The age effect reflects physiologic differences among different age groups in susceptibility to a given disease. The calendar time period effect usually reflects factors that affect all age groups equally during a given period of time, such as introduction of new diagnostic or therapeutic techniques, improvement in the completeness of data registration, or an environmental carcinogen that may induce the same change in disease risk for everyone in the population. The birth cohort effect, on the other hand, indicates factors that may have different exposure levels in different birth cohorts. The effect of lifestyle factors, which may be fixed early in life, is most likely reflected by cohort effect. We hypothesized that cohort effect will be responsible for the opposing incidence trends of nasopharyngeal and oropharyngeal carcinomas. Because both nasopharyngeal and oropharyngeal carcinomas are more prevalent in men than in women, the incidence trends between men and women were compared.

Materials and Methods

Epidemiologic data (incidence rates, patient number, and population size) on nasopharyngeal and oropharyngeal carcinomas from 1981 to 2000 were obtained from the Taiwan Cancer Registry, which was founded in 1979 by the Department of Health of Taiwan (2). It is a population-based cancer registry, including data from hospitals with ≥50 beds throughout the country. This registry was estimated to encompass about 80% of all cancer cases in Taiwan (14). It has been used to show the decrease in incidence of childhood hepatocellular carcinoma after hepatitis B vaccination for children in Taiwan (15).

The diagnostic evaluation for nasopharyngeal and oropharyngeal carcinomas in routine practice includes a complete physical examination, indirect nasopharyngoscope, and computed tomography or magnetic resonance imaging of the head and neck area for staging. Fiber optic endoscopy was increasingly used after 1980. Staging was done according to the American Joint Committee on Cancer classification (16).

Incidence data were categorized by 5-year age intervals. Data from subjects with age younger than 20 years or older than 80 years were excluded because of the low case numbers. The trend of the incidence was first estimated using a linear model to calculate the average annual percentage change in incidence for different age groups (17). A second-order polynomial model with a quadratic trend term was used to detect possible nonlinear quadratic trends (18).

For the age-period-cohort analysis, the data were categorized into twelve 5-year age groups (20-24 to 75-79 years), four 5-year time period groups (1981-1985 to 1996-2000), and 15 overlapping 10-year birth cohort groups (1901-1910 to 1971-1980, represented by mid-year as 1905-1975). The calendar time period of 1986 to 1990 and the 1931 to 1940 birth cohort were used as reference groups for estimates of relative risk.

The age-period-cohort model was fitted based on two assumptions. First, the number of cases over the time period followed Poisson's distribution. Second, the incidence rate was a multiplicative function of age, time period, and birth cohort. In our model, patient sex was introduced as an independent factor because male preponderance has long been recognized for both nasopharyngeal and oropharyngeal carcinomas. Thus, the logarithm of the incidence rate was expressed as a combination of the effects of age, time period, birth cohort, and patient sex as follows:

$$ln(\lambda_{ijkl}) = ln(\frac{\mu_{ijkl}}{\eta_{ijkl}}) = \rho + \alpha_i + \beta_j + \gamma_k + \delta_l + (\text{interaction})$$

where λ_{ijkl}, μ_{ijkl}, and η_{ijkl} denote the incidence rate, the mean number of patients, and the number of individuals, respectively, in the ith age group(i = 1, 2, . . ., I), jth time period group (j = 1, 2, . . ., J), kth birth cohort group ($k = I - i + j$), and sex l (l = 0 or 1). The symbols α_i, β_j, γ_k, and δ_l represent the effects of the ith age group, jth time period, kth birth cohort group, and sex l, respectively. ρ is the intercept term. The interaction term represents sex-cohort and sex-period interactions plus a random error term.

It is well recognized that age is an important predictor of disease incidence. Adjusted R^2 was used to determine the amount of variation that can be explained by factors other than age (19). The adjusted R^2 also allows difference in the numbers of variables for cohorts and periods. For example, the following expression represents the reduction of variation after introduction of patient sex (S) into a model containing age (A) alone:

$$1 - (G^2_{A+S}/df_{A+S})/(G^2_A/df_A)$$

The G^2 and df denote the deviance and the degree of freedom of each model, respectively.

Model fitting, using the maximum likelihood method, was done sequentially: First, the age model; second, the age-sex model; third, the age-sex-drift, the age-sex-period, and the age-sex-cohort models; and finally, the full age-sex-period-cohort model (12, 13). The age-sex-drift model was a log-linear model that described the temporal variation of incidence without differentiation between the period and the cohort effects. The deviance with its df was used to measure the goodness-of-fit of each model. A smaller deviance implies a better fit of a given model.

The statistical significance was tested based on the assumption of Poisson distribution, in which the variance equals to the mean. Because the variation of population based incidence data can be much greater than that assumed by the Poisson distribution, an alternative assumption is that the variance is proportional to the mean using a quasi-likelihood approach (19). Based on this assumption, the significance of differences in deviance between the full age-sex-period-cohort model and the three-factor (age-sex-period and age-sex-cohort) models was determined by the F test:

$$F = (\Delta G^2/\Delta df)/(X^2/df)$$

The X^2 and the df are the Pearson χ^2 and the degree of freedom of the full age-sex-period-cohort model, respectively. The $\Delta G^2/\Delta df$ is the corresponding differences in the likelihood ratio between the full model and the three-factor models.

Owing to the linear dependence among age, time period, and birth cohort (age = time period − birth cohort), the individual estimate of the effect of the three main factors cannot be uniquely identified. Therefore, the regression coefficients of the first and last periods were constrained as zero to provide first-order relative risk estimates of cohort effect. Similarly, the regression coefficients of the first and the last cohorts were constrained as zero to provide estimates of period effect. The estimates of relative risk, reflecting the individual effect of time period and birth cohort, were generated by the maximum likelihood method. The analyses were conducted with SAS software (version 8.1).

Results

From 1981 to 2000, a total of 23,389 cases (16,859 men and 6,530 women) of nasopharyngeal carcinoma and 29,689 cases (26,174 men and 3515 women) of oropharyngeal carcinoma were diagnosed. Histologic/cytologic diagnosis was confirmed for >90% cases of both nasopharyngeal and oropharyngeal

carcinomas. Table 1 summarizes the age-specific incidence rates of nasopharyngeal and oropharyngeal carcinomas. For nasopharyngeal carcinoma, the incidence seemed to decrease in most age groups, except for the 70 to 74 and 75 to 79 groups. For oropharyngeal carcinoma, the incidence increased in all age groups. Overall, the age-adjusted incidence rate of nasopharyngeal carcinoma decreased by 23% for men (11.19-8.60 per 100,000 men) and by 30% for women (4.35-3.02 per 100,000 women) from 1981 to 2000. By contrast, the age-adjusted incidence rates of oropharyngeal carcinoma increased by 391.4% for men (5.37-26.39 per 100,000 men) and by 59.2% for women (1.69-2.69 per 100,000 women) in the same period.

Table 1 also summarizes the average annual percentage change of incidence (AAPC) in different age groups. The second-order quadratic terms of AAPC were listed in the Supplementary Data. For nasopharyngeal carcinoma, the AAPC was negative, indicating that incidence was decreasing in the majority of age groups and was most significant in age groups 45 to 49 and 50 to 54. The AAPC was positive in age groups 70 to 74 and 75 to 79. However, the number of cases in these groups was relatively small (20 men and 8 women in 1981 and 83 men and 34 women in 2000, respectively). The quadratic term was positive in all groups with negative AAPC and was also most significant statistically in these groups. It implied that the trend of decreasing incidence will enlarge in the future. For oropharyngeal carcinoma, the AAPC was positive and is highly significant in all age groups. However, the quadratic trend term did not show a consistent pattern.

Figure 1 compares the difference in AAPC between men and women. For nasopharyngeal carcinoma, women seemed to have a more prominent change in incidence than men. The reverse is true for oropharyngeal carcinoma, in which men had more prominent change than women in most age groups.

Figure 2 shows the age-specific incidence of representative birth cohorts for nasopharyngeal and oropharyngeal carcinomas. No apparent difference among different birth cohorts can be found for nasopharyngeal carcinoma in the figure. For oropharyngeal carcinoma, by contrast, the incidence is higher for later birth cohort in every age group.

The statistics comparing the adjusted R^2 and the goodness-of-fit for different models are listed in Supplementary Table S2. The full age-sex-period-cohort model had the best goodness of fit for both nasopharyngeal and oropharyngeal carcinomas. For nasopharyngeal carcinoma, the difference of the adjusted R^2 was statistically significant between the three-factor (age-sex-period and age-sex-cohort) models and the full model, suggesting both cohort effect and period effect are present in the incidence trend of nasopharyngeal carcinoma. For oropharyngeal carcinoma, the difference of the adjusted R^2 was statistically significant only between the age-sex-period model and the full model, suggesting a stronger cohort effect than period effect.

Figure 3 compares the relative risk of nasopharyngeal and oropharyngeal carcinomas between men and women in terms of cohort effect and period effect. Cohort effect was prominent for both men and women, but the trend was different between nasopharyngeal and oropharyngeal carcinomas. For nasopharyngeal carcinoma, women seemed to have a more prominent decrease in relative risk than men from the cohort 1936 to 1945 onwards, and the difference, compared with that of the reference cohort (1931-1940), was significant in all subsequent cohorts. The relative risk of nasopharyngeal carcinoma for the 1971 to 1980 cohort was 0.38 (95% confidence interval, 0.25-0.58) for women and 0.68 (95% confidence interval, 0.50-0.93) for men compared with the reference cohort. The relative risk of nasopharyngeal carcinoma before the reference cohort did not show a consistent pattern of change. For oropharyngeal carcinoma, by contrast, men had a more prominent increase in relative risk than women, and the trend persisted throughout the birth cohorts studied. The relative risk of oropharyngeal carcinoma for the 1971 to 1980 cohort was 45.67 (95% confidence interval, 28.68-72.74) for men and 2.69 (95% confidence interval, 1.25-5.80) for women.

Although data from model fitting suggest a period effect on the incidence trend of nasopharyngeal carcinoma, difference in relative risk among different time periods was not obvious. The curves of the period effect on nasopharyngeal carcinoma incidence were virtually flat for both men and women. By contrast, period effect was seen on the incidence trend of oropharyngeal carcinoma and was more prominent in men. The relative risk of oropharyngeal carcinoma in the 1996 to 2000 time period was 2.37 (95% confidence interval, 2.19-2.57) for men and 1.64 (95% confidence interval, 1.41-1.90) for women.

Discussion

This study showed a significant difference in the incidence trends of nasopharyngeal and oropharyngeal carcinomas in Taiwan. The incidence of nasopharyngeal carcinoma continues to decrease in younger birth cohorts, and this trend seems

Table 1. Age-specific incidence rates (per 100,000 persons) and age-specific AAPC of nasopharyngeal carcinoma and oropharyngeal carcinoma in Taiwan, 1981-2000

Age at diagnosis (y)	Time period (calendar year)									
	Nasopharyngeal carcinoma					Oropharyngeal carcinoma				
	1981-1985	1986-1990	1991-1995	1996-2000	AAPC	1981-1985	1986-1990	1991-1995	1996-2000	AAPC
20-24	1.31	1.06	0.97	1.04	−1.66*	0.22	0.28	0.42	0.48	4.84†
25-29	2.54	2.25	2.09	2.02	−1.56*	0.59	0.79	0.99	1.84	8.71‡
30-34	5.68	4.61	4.39	4.71	−0.82	1.24	1.84	3.34	5.64	11.37‡
35-39	9.09	8.64	8.74	8.21	−0.41	2.82	4.13	7.30	12.60	11.02‡
40-44	13.73	12.59	12.84	11.93	−1.50‡	5.70	8.45	14.04	22.10	9.70‡
45-49	18.69	15.06	14.23	13.97	−2.00‡	7.95	12.11	21.26	32.37	9.40‡
50-54	22.20	17.21	16.89	16.54	−1.98‡	10.95	15.76	24.52	41.15	9.17‡
55-59	19.08	16.99	18.84	16.97	−0.60	12.04	17.40	27.43	42.06	9.01‡
60-64	19.02	15.43	17.63	16.09	−0.62	14.41	17.13	27.16	40.00	7.86‡
65-69	16.04	11.74	14.20	14.44	0.01	19.63	18.86	24.85	35.03	4.99‡
70-74	10.59	12.02	10.68	13.18	1.30*	16.08	22.20	26.43	33.22	4.69‡
75-79	5.84	6.26	8.84	10.00	3.93‡	12.83	18.90	26.69	30.86	5.18‡

*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

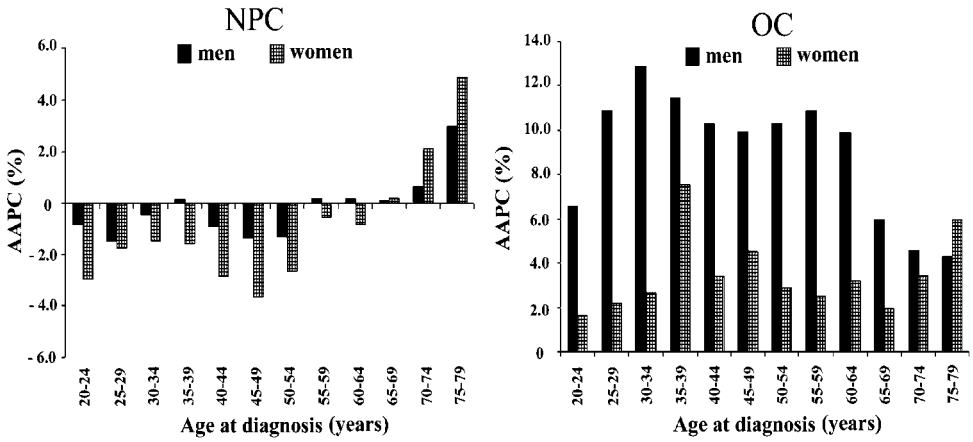

Figure 1. Comparison between men and women of the AAPC of incidence of nasopharyngeal carcinoma (*NPC*) and oropharyngeal carcinoma (*OC*) in Taiwan (1981-2000).

more prominent in women than in men. By contrast, the incidence of oropharyngeal carcinoma increases much more rapidly in men than in women. Our data from the age-period-cohort analysis suggest that lifestyle factors play an important role in these trends.

Modulation of lifestyle has been considered a key way to prevent cancers (20, 21). Change in cancer incidence due to modulation of lifestyle is most likely reflected in cohort effect. A notable example is gastric cancer, in which cohort effect was found accountable for its decreasing incidence (22, 23). The decreasing incidence of gastric cancer was found to be related to the increased use of refrigerators, improved sanitation, and decreased consumption of preserved food (24-26). Preserved food and the potential carcinogens, such as nitrosamine, in it have also been regarded as an important risk factor for nasopharyngeal carcinoma. The westernization of lifestyle in Taiwan took place after World War II, which was coincident with the continuing decrease in nasopharyngeal carcinoma risk for birth cohorts 1936 to 1945 and onwards in our study. Our data further illustrate the importance of environmental and lifestyle factors on the pathogenesis of nasopharyngeal carcinoma found in previous migrant studies (27, 28). Westernization of lifestyle may influence the incidence trend of other cancers in Taiwan. For example, a shift in the incidence and age distribution pattern of female breast cancer in Taiwanese toward that of Caucasian Americans have been noted, and a strong cohort effect on this trend has been shown (29).

Both environmental and host factors may play a role in the difference of nasopharyngeal carcinoma incidence trend between men and women found in this study. However, such as difference was not found in Hong Kong (30). Because the population of Taiwan and Hong Kong had the same ethnic background, and because the composition of both populations remains relatively stationary in the past decades, environmental and lifestyle factors may be more important in accounting for the difference. Men in Taiwan may have greater exposure to other risk factors of nasopharyngeal carcinoma, thus negated the effect of westernization of lifestyle. For example, the prevalence rates of tobacco smoking and betel quid chewing were at least 10-fold higher in men than in women (31-33). Besides, men may be more susceptible than women to environmental insults. Evidence suggested that men had a higher level of the cytochrome *P*450 2E1 (CYP2E1) activity than women (34, 35). Genetic polymorphism of CYP2E1 enzyme has been found to be a determinant of nasopharyngeal carcinoma risk, and the CYP2E1 variant with a higher metabolic activity and thus a higher ability to activate carcinogens was associated with higher risk of nasopharyngeal carcinoma (36). It is also possible that the beneficial effects of lifestyle change on nasopharyngeal carcinoma risk involve factors that have differential effects between men and women.

Decrease in incidence of nasopharyngeal carcinoma has been found only in populations with high endemic incidence. Lee et al. compared the incidence trend of nasopharyngeal carcinoma in Hong Kong, Singapore, United States, England, and Australia. Nasopharyngeal carcinoma incidence decreased only in Hong Kong, whereas the incidence in other countries remained stationary (11). However, analysis of the Chinese population in Singapore suggested that a decrease of nasopharyngeal carcinoma incidence may occur since mid-1990s (1). Cox et al. studied the incidence trend of oral cancers in New Zealand, a country with a low incidence of nasopharyngeal carcinoma (about 0.8%), from 1957 to 1991 and showed a cohort effect for the increase in incidence of both nasopharyngeal carcinoma and other head and neck carcinomas (37). In addition to differences in genetic background, diet and other environmental factors may account for the different incidence trends.

The incidence of oropharyngeal carcinoma in Taiwan rose rapidly in the last two decades, and betel quid use, which is popular as a stimulant and as a social etiquette, seemed to be

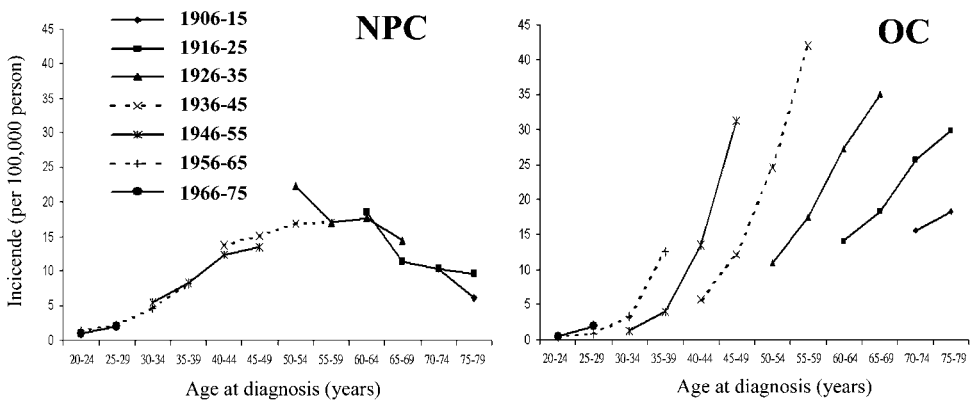

Figure 2. Age-specific incidence of representative birth cohorts for nasopharyngeal carcinoma (*NPC*) and oropharyngeal carcinoma (*OC*) in Taiwan (1981-2000).

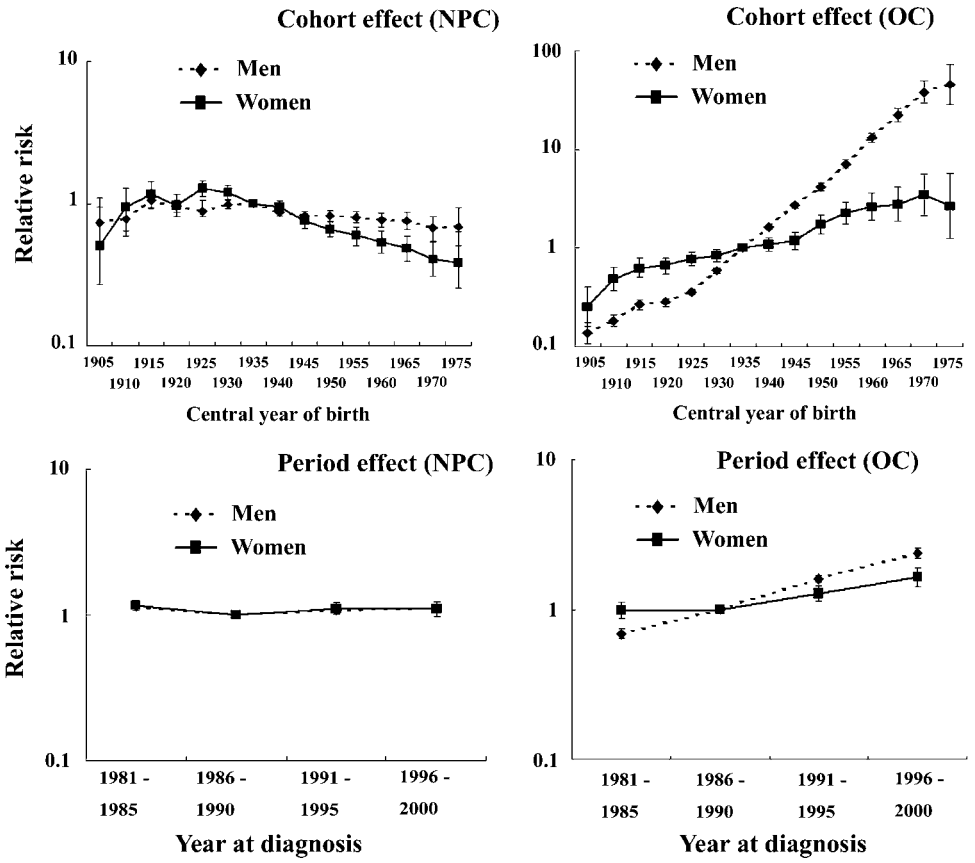

Figure 3. Comparison between men and women of the cohort effect (*top*) and period effect (*bottom*) on the relative risk of nasopharyngeal carcinoma (*NPC*) and oropharyngeal carcinoma (*OC*) in Taiwan (1981-2000). *Points,* RR; *bars,* 95% confidence interval.

the most prominent risk factor (38). Betel quid consumption has been shown to be an important risk factor for various cancers in the upper aerodigestive tract, and the risk for oropharyngeal carcinoma and precancerous lesions, including oral leukoplakia and submucosal fibrosis, increased with increasing amount and duration of betel quid use (39-44). The increase in oropharyngeal carcinoma incidence in Taiwan closely paralleled the increase in the estimated per capita consumption of betel quid (45, 46). Besides, the incidence increased more significantly for intraoral (including lip and mouth) sites, areas with more direct exposure to carcinogens in betel quid than for pharyngeal (including oropharynx and hypopharynx) sites (45). These evidences support the notion that betel quid consumption is the most prominent risk factor for the rise of oropharyngeal carcinoma incidence. The much stronger cohort effect for men on the relative risk of oropharyngeal carcinoma may also reflect the male predominance of betel quid use.

Multiple factors may result in a period effect on the incidence trends of diseases. In our study, improvement in diagnostic techniques or data registration is not likely the main cause of the period effect found in oropharyngeal carcinoma because the diagnostic techniques and data registration are essentially the same for nasopharyngeal and oropharyngeal carcinomas, but no such period effects were found in nasopharyngeal carcinoma. Although we cannot exclude the possibility that part of the period effect we found in oropharyngeal carcinoma may result from increased ascertainment of diagnosis over time, it cannot explain the stronger period effect in men. This may result from betel quid use because this habit is prevalent in a wide range of age groups and is much more prevalent in men in Taiwan (32, 33).

There are several limitations of this study. First, our hypothesis that lifestyle and other environmental factors are the main reasons for the incidence trend of nasopharyngeal and oropharyngeal carcinomas was based mainly on previous case-control studies using questionnaire interview. These studies are subject to recall bias, and it is difficult to confirm a dose-response relationship or to do longitudinal follow-up. Second, the age-period-cohort model may not fully capture the factors involved in the incidence trend of nasopharyngeal carcinoma because of the complex interaction of genetic and environmental factors in the pathogenesis of nasopharyngeal carcinoma. For example, our model cannot explain the increase in nasopharyngeal carcinoma incidence in age groups 70 to 74 and 75 to 79 years. Although this finding may be specious because of the low number of cases in these groups, especially in early years, we cannot exclude the possibility that some factors that act preferentially on the elderly became more prevalent in recent years. The effect of other important risk factors for nasopharyngeal carcinoma, such as EBV infection, was not addressed in this study.

In conclusion, our data indicate that the incidence trends for nasopharyngeal and oropharyngeal carcinomas in Taiwan are different in the past two decades. The difference may be due to change of different lifestyle risk factors for these two disease entities. Decrease in nasopharyngeal carcinoma incidence in Taiwan is expected to continue because of westernization of lifestyle. Increase in oropharyngeal carcinoma incidence, on the other hand, is most likely due to the increasing use of betel quid. Reduction of exposure to pivotal risk factors is essential for disease prevention.

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