

Pregnancy Incidence in Female Nasopharyngeal Carcinoma Survivors of Reproductive Age

A Population-Based Study

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Abstract: This study evaluated the pregnancy incidence in female nasopharyngeal carcinoma (NPC) survivors of reproductive age.

In a nationwide cohort, 2816 female patients 15 to 50 years of age from 1998 to 2010 were identified from the Taiwan National Health Insurance Research database. Comorbidities, complications during pregnancy, and delivery status were recorded. All patients were followed up until a diagnosis of pregnancy, withdrawal from the National Health Insurance system, or December 31, 2011.

Overall, 155 patients (incidence rate [IR] = 9.50) were pregnant in the NPC group, whereas 251 patients (IR = 12.80) were pregnant in the non-NPC group. The cumulative incidence of pregnancy in the NPC group was lower than that in the non-NPC group (incidence rate

ratio = 0.74, 95% CI = 0.61–0.91). The adjusted hazard ratio of pregnancy in the NPC group was 0.79 with 95% CI = 0.61–0.96, compared with the non-NPC group.

The incidence of pregnancy is significantly lower among female NPC survivors of reproductive age than among those without NPC.

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Abbreviations: CCRT = concurrent chemoradiotherapy, CIs = confidence intervals, CT = chemotherapy, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IR = incidence rate, NHIRD = National Health Insurance Research database, NPC = nasopharyngeal carcinoma, ORs = odds ratios, RT = radiotherapy.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare head and neck cancer in most of the world, with an annual incidence rate of less than 1 per 100,000.¹ However, similar to Southern China, North Africa, and Alaska, NPC is endemic in Taiwan with an annual incidence rate of 5.7 per 100,000 in 2007.^{2–4} External beam radiotherapy (RT) remains the preferred treatment for early-stage NPC patients. For those who present with advanced locoregional disease, concurrent chemoradiotherapy (CCRT) has been proposed as the principal treatment because it results in improved treatment outcomes.^{5,6} Long-term survival can be expected in a significant proportion of patients.^{7–9}

Nevertheless, it has been shown that cancer treatment may cause gonadal toxicity,^{10–17} which is especially concerning since many affected female patients are of childbearing age. Additionally, Taiwan exhibits a trend of delaying childbirth, making fertility concerns more crucial to female NPC patients. To our knowledge, the literature on fertility concerns is scant regarding NPC patients after treatment. The aim of this study was to examine the reproductive outcome between NPC patients and the normal population by using population-based data.

METHODS

Data Source

The National Health Insurance program is a compulsory social health insurance system initiated in 1995 that covers over 99.9% of the population in Taiwan. The data used in this study were from the National Health Insurance Research database (NHIRD), which includes deidentified medical claims and registration files for all beneficiaries from 1998 to 2011. All diagnoses were identified based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board of China Medical

University (CMUH-104-REC2-115). The Institutional Review Board also specifically waived the consent requirement.

Study Patients

A total of 2816 female patients, aged 15 to 50, who were first diagnosed with NPC (ICD-9-CM code: 147) between 1998 and 2010, were identified from NHIRD in this study. The study index date was defined as the date of NPC diagnosis. We selected another 2816 females who have never been diagnosed with NPC as our controls and we randomly assigned them an index date with the same index year as that of an NPC patient. The study outcome was pregnancy. All patients were followed up from the index date to diagnosis of the mentioned outcomes or December 31, 2011, whichever came first. We also observed the following during pregnancy:¹ gestational hypertension (ICD-9-CM codes: 642.0–642.3, 642.7–642.9);² preeclampsia (ICD-9-CM codes: 642.4–642.7);³ gestational diabetes (ICD-9-CM codes: 648.0, 648.8);⁴ placenta abruption (ICD-9-CM code: 641.2);⁵ placenta previa (ICD-9-CM codes: 641.0, 641.1); and⁶ antepartum hemorrhage (ICD-9-CM codes: 641.1, 641.3, 641.8, 641.9). Additionally, the status at delivery was also recorded as follows:¹ successful delivery;² low birth weight (ICD-9-CM codes: 765, 765.01–765.08, 765.11–765.18); and³ preterm delivery (ICD-9-CM codes 644, 765). Comorbidities, which included abortion (ICD-9-CM codes 632, 634, 637), ectopic pregnancy (ICD-9-CM code 633), and infertility (ICD-9-CM 628), were identified before the index date. The number of patients who had RT and chemotherapy (CT) after an NPC diagnosis was also summarized.

Statistical Analysis

A χ^2 test was used to examine differences in demographic characteristics, and a *t* test was used to evaluate the difference in mean age between the NPC and non-NPC groups. Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Logistic regression models were used to compute odds ratios (ORs) and corresponding 95% CIs. All statistical analyses were computed using SAS 9.3 statistical software (SAS Institute Inc, Cary, NC).

RESULTS

A comparison of baseline characteristics between NPC and non-NPC groups is shown in Table 1. Patients with NPC were slightly older than those without NPC (mean ages were 40.2 and 39.7 years, respectively). Most patients in the 2 groups were white-collar workers. Females without NPC were more likely to have abortions (8.88% vs. 5.22%, $P < 0.001$) and infertility (4.65% vs. 3.16%) than females with NPC before the index date. The mean follow-up time was 5.80 years (SD = 3.87) for the NPC group and 6.96 years (SD = 3.98) for the non-NPC group.

Overall, 155 patients (incidence rate [IR] = 9.50) were pregnant in the NPC group, whereas 251 patients (IR = 12.80) were pregnant in the non-NPC group (Table 2). The cumulative incidence of pregnancy in the NPC group was lower than that in the non-NPC group (incidence rate ratio [IRR] = 0.74, 95% CI = 0.61–0.91). After adjustment for comorbidities and other confounding factors, the adjusted HR of pregnancy in the NPC group was 0.79 with 95% CI = 0.61 to 0.96, compared with the non-NPC group. We then conducted a stratified analysis by using baseline characteristics. The NPC group had a significantly lower pregnancy rate than that of the non-NPC group, within the following stratifications: patients aged 25 to 34 years (HR = 0.71, 95% CI = 0.55–0.93),

TABLE 1. Demographic Characteristics and Baseline Comorbidity Between 2 Cohorts

	With NPC N = 2816		Without NPC N = 2816		P Value
	n	%	n	%	
Age, y					0.003
15–24	97	3.44	151	5.36	
25–34	525	18.6	575	20.4	
35–44	1351	48.0	1286	45.7	
≥45	843	29.9	804	28.6	
Mean (SD)*	40.2	7.05	39.7	7.39	0.02
Occupation					<0.001
White collar	1529	54.3	1657	58.8	
Blue collar	987	35.1	830	29.5	
Others	300	10.7	329	11.7	
Comorbidity					
Abortion	147	5.22	250	8.88	<0.001
Ectopic pregnancy	44	1.56	48	1.70	0.67
Infertility	89	3.16	131	4.65	0.004
Treatment					
Radiotherapy	2498	88.7	—	—	
Chemotherapy	2062	73.2	—	—	

χ^2 test.
**t* test.

white-collar workers (HR = 0.74, 95% CI = 0.57–0.96), patients who did not have an abortion (HR = 0.77, 95% CI = 0.62–0.96), patients without ectopic pregnancy (HR = 0.78, 95% CI = 0.64–0.96), and patients with infertility (HR = 0.45, 95% CI = 0.21–0.96).

Notably, among pregnant patients aged 25 to 34 years, those with NPC had a higher proportion of successful deliveries compared with the non-NPC group (adjusted OR = 2.99, 95% CI = 1.71–5.22) (Table 3).

Table 4 lists the risks of the other 8 outcomes between the 2 groups. There were no significant results.

DISCUSSION

RT and CCRT are currently the primary treatments for NPC, because the tumor is susceptible to both RT and CT and is often located in difficult anatomical locations.⁶ Over a 90% 5-year-survival rate can be achieved in patients with early-stage NPC when treated with RT.⁹ For patients with nonmetastatic, locally advanced NPC at diagnosis, the 5-year-survival rate with CCRT treatment is approximately 68% to 75%.^{7,8} Many female NPC patients are expected to have long-term survival after treatment, making treatment-related gonadal toxicity concerning.

Previous studies have shown that the human oocyte is susceptible to radiation, and the median lethal dose is less than 2 gray (Gy).¹⁸ Sanders et al¹⁹ followed 708 postpubescent women who received total body irradiation for bone marrow transplant, and ovarian failure occurred in 598 (84.5%) of patients. Similar findings were reported in patients receiving abdominal irradiation, with 97% of females experiencing ovarian failure.²⁰ In addition, deficient gonadotropin secretion after high-dose brain irradiation may cause delayed gonadal development.¹¹

The ovary is also sensitive to CT-related damage, particularly with alkylating agents such as cyclophosphamide and

TABLE 2. Incidence and Hazard Ratio for Pregnancy Compared With Comparisons Stratified by Age, Occupation, and Comorbidity

	With NPC		Without NPC		IRR (95% CI)	Adjusted HR (95% CI)
	Case No.	IR	Case No.	IR		
Overall	155	9.50	251	12.8	0.74 (0.61, 0.91)**	0.79 (0.64, 0.96)*
Age, y						
15–24	21	38.4	45	48.3	0.79 (0.47, 1.33)	0.74 (0.43, 1.27)
25–34	95	35.3	149	44.4	0.80 (0.61, 1.03)	0.71 (0.55, 0.93)*
35–44	37	4.50	53	5.65	0.80 (0.52, 1.21)	0.66 (0.43, 1.01)
≥45	2	0.41	4	0.68	0.61 (0.11, 3.33)	0.54 (0.10, 2.94)
Occupation						
White collar	88	9.82	166	15.1	0.65 (0.50, 0.84)**	0.74 (0.57, 0.96)*
Blue collar	45	7.69	55	8.64	0.89 (0.60, 1.32)	0.87 (0.58, 1.30)
Others	22	14.7	30	13.7	1.07 (0.62, 1.86)	0.89 (0.51, 1.55)
Comorbidity						
Abortion						
No	135	8.60	209	11.3	0.76 (0.61, 0.94)*	0.77 (0.62, 0.96)*
Yes	20	31.9	42	37.1	0.86 (0.50, 1.46)	0.85 (0.50, 1.46)
Ectopic pregnancy						
No	151	9.38	247	12.7	0.74 (0.60, 0.90)**	0.78 (0.64, 0.96)*
Yes	4	18.7	4	19.6	0.95 (0.24, 3.81)	0.40 (0.07, 2.28)
Infertility						
No	146	9.17	222	11.7	0.79 (0.64, 0.97)*	0.82 (0.66, 1.01)
Yes	9	22.4	29	50.0	0.45 (0.21, 0.95)*	0.45 (0.21, 0.96)*

IR = per 1000 person-yr, IRR = incidence rate ratio.
 Mutually adjusted for age, occupation, comorbidities of abortion, ectopic pregnancy, and infertility.
 **P* < 0.05.
 ***P* < 0.01.

procarbazine.¹⁰ A large cohort study involving >14,000 participants with childhood or adolescent cancer has shown that increased doses of alkylating agents result in elevated risk of premature menopause and ovarian failure.¹² However, despite the well-known association between CT and premature ovarian failure, the gonadal toxicity of individual chemotherapeutic agents has not been established thoroughly.

Because of the distance between the pelvic cavity and nasopharynx, locoregional RT may play a limited role in gonadal damage. Modern external-beam RT enables focusing

a radiation beam accurately on a defined target region, thereby minimizing out-of-field radiation doses, although gonadotropin deficiency may still be a concern.^{11,21,22} In patients with distant metastasis of NPC, of whom the incidence is approximately 4.4% to 6% at initial diagnosis,^{23–25} RT delivered to affected organs such as the liver, lung, or para-aortic lymph nodes²⁶ could have caused irradiation of the ovaries and uterus. However, we also postulate that the decreased pregnancy rate in female NPC survivors was attributable to the effect of CT or CCRT. Cisplatin, bleomycin, doxorubicin, 5-fluorouracil,

TABLE 3. Risk for Succeed Delivery Compared With Comparison in Pregnancy Women Among Age Group

Outcome	With NPC N = 155		Without NPC N = 251		OR (95% CI)	
	n	%	n	%	Crude	Adjusted [†]
Succeed delivery						
15–24 y	12	57.1	16	35.6	2.42 (0.84, 6.96)	2.77 (0.85, 9.00)
25–34 y	57	60.0	48	32.2	3.16 (1.85, 5.39)*	2.99 (1.71, 5.22)*
35+ y	9	23.1	7	12.3	2.14 (0.72, 6.35)	2.53 (0.78, 8.17)
Overall [†]	78	50.3	71	28.3	2.57 (1.69, 3.90)*	2.85 (1.83, 4.43)*

[†]Adjusted for age, occupation, comorbidities of abortion, ectopic pregnancy, infertility.
 **P* < 0.001.

TABLE 4. Risk for Outcome Compared With Comparison in Pregnancy Women Among Age Group

Outcome	With NPC N = 155		Without NPC N = 251		OR (95% CI)	
	n	%	n	%	Crude	Adjusted [†]
Preterm delivery	15	9.68	13	5.18	1.96 (0.91, 4.24)	2.03 (0.92, 4.45)
Low-birth weight	3	1.94	3	1.20	1.63 (0.33, 8.19)	1.71 (0.33, 8.89)
Gestational hypertension	6	3.87	3	1.20	3.33 (0.82, 13.5)	3.30 (0.79, 13.8)
Preeclampsia	2	1.29	1	0.40	3.27 (0.29, 36.3)	3.48 (0.31, 39.1)
Gestational diabetes	5	3.23	10	3.98	0.80 (0.27, 2.40)	0.79 (0.26, 2.40)
Placenta abruption	0	0.00	1	0.40	—	—
Placenta praevia	3	1.94	4	1.59	1.22 (0.27, 5.52)	1.55 (0.33, 7.25)
Antepartum hemorrhage	3	1.94	6	2.39	0.81 (0.20, 3.27)	1.07 (0.25, 4.55)

[†]Adjusted for age, occupation, comorbidities of abortion, ectopic pregnancy, infertility.

methotrexate, and mitoxantrone are the most active chemotherapeutic agents in use for NPC;^{27–29} however, these agents may also damage the gonadal organ, mainly from the effects of the alkylating agents.^{12,16,17}

Most studies concerning the reproductive outcome after cancer treatments have focused on Hodgkin lymphoma, thyroid cancer, and neuroblastoma, and most of them have used premature infertility as their end-point.^{10,11,13–15,30,31} There are few literatures discussing the risks of infertility in female NPC survivors. Based on our research, this is the first study to investigate the pregnancy rate in NPC survivors by using a nationwide cohort of women with NPC. The results revealed that the cumulative incidence of pregnancy and adjusted HR in the NPC group was lower than that in the non-NPC group, suggesting a decrease in pregnant rate in female NPC survivors. Despite the fact that most patients from the NPC group received radiotherapy (88.7%) and chemotherapy (73.2%), the causal relationship between cancer treatment and pregnant rate in NPC patients has yet to be determined due to the retrospective nature of this study.

Administrative information from the NHIRD is available for research in Taiwan, and has been utilized extensively in epidemiological studies.^{32–34} The nationwide data, covering over 99.9% of the population in Taiwan, provide a favorable statistical resource for examining the relationship between female NPC patients of reproductive age and future pregnancy incidence and complications. The accuracy of the disease diagnosis and medication prescriptions in the NHIRD has been validated thoroughly.³⁵ The diagnoses of pregnancy and other comorbidities were made by physicians and recorded according to ICD-9-CM codes, not by self-reporting, thereby minimizing misclassification errors. In addition, the National Health Insurance Bureau strictly regulates the diagnosis of NPC, because it is related to reimbursement from the catastrophic illness registration, and each diagnosis of NPC must be proven through biopsy and tissue pathology. In analyzing population-based data from the NHIRD, methods for risk-adjustment greatly affect the quality of the study. We used a Cox proportional hazard model to compare the effects of NPC versus non-NPC patients on pregnancy incidence in order to adjust for comorbidities and other confounding factors.

Some limitations of our study must be mentioned. First, this is a retrospective cohort study and is subject to many biases due to lack of the necessary adjustments for possible

confounding factors. For example, we could not obtain the histological subtyping and TNM staging for each case of NPC because of the limitations of the NHIRD. However, the exclusion of the histological subtyping and TNM staging were unlikely to have introduced significant bias, because cancer treatment, rather than cancer itself, is suspected to be the cause of decreased pregnancy incidence, and was separated as RT or CT in the analysis. Another limitation was that the frequency of ectopic pregnancy or abortion might have been underestimated because a small proportion of the patients received treatment in self-paid private clinics, whose data are not collected by the NHIRD. Moreover, pregnancy incidence is influenced by each patient's desire to get pregnant, which this retrospective study was unable to estimate. In this study, the successful delivery rate is higher in patients with NPC (HR = 2.85, 95% CI = 1.83–4.43), especially in females between 25 to 34 years old (HR = 2.99, 95% CI = 1.71–5.22), which implied that the NPC population might be more interested in becoming pregnant and giving birth. Additionally, NPC group had lower rates of abortions ($P < 0.001$) and infertility ($P = 0.004$) than normal population before the index date. Taken together, these findings might even strengthen our conclusion rather than refute it, since the negative effect of NPC treatment had to be strong to lower the pregnant rate of the NPCs.

In summary, the incidence of pregnancy is 0.79 times lower among female NPC survivors of reproductive age than among those who do not have a diagnosis of NPC. Whether early fertility preservation strategies could help in improving the prognosis must be confirmed in future studies.

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