Original Article

# Risk of Cancer in Patients with Eating Disorders: A Population-based Study

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## Abstract

**Objectives:** Patients with eating disorder (ED) have been associated with some risk factors for cancer, including nutritional deficiency, chaotic life styles, alcohol or tobacco use, dysfunctional immune system, and impaired organ functions. In this study, we intended to study the risk of cancer in ED patients. **Methods:** During the period of January 1998 to December 2013, 13,755 ED patients were identified from Taiwan's National Health Insurance Research Database. We enrolled 13,276 patients as study cohort, and 53,104 patients that had never been diagnosed with ED as age- and sex-matched comparisons. Participants were monitored for diagnoses of cancer during the follow-up period. We used the Cox proportional hazards model to investigate the risk of cancer between patients with ED and those without ED. **Results:** Compared with the non-ED controls, the study cohort had significantly higher prevalence of comorbidities, alcohol abuse, tobacco use disorder, and chronic obstructive pulmonary disease. After adjusting demographic data and comorbidities, there was no significant risk for later occurrence of cancer in ED patients, irrespective of anorexia nervosa (AN) type (hazard ratio [HR] = 1.10, 95% confidence interval [CI], = 0.83 – 1.47, nonsignificant difference) or non-AN type (HR = 0.98, 95% CI = 0.79 – 1.23, nonsignificant difference). **Conclusion:** There is no established evidence to support the relationship between cancer incidence and ED.

**Key words: anorexia nervosa, bulimia nervosa, cancer, carcinogenicity**
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## Introduction

Eating disorders have great impact on health and psychosocial functioning [1-3]. According to the fifth edition of *the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, EDs include anorexia nervosa (AN), bulimia nervosa (BN), pica, rumination disorder, avoidant/restrictive food intake disorder, binge ED, and other specified feeding or ED. Lifetime prevalence of AN in female patients is ranged from 1.7% [4] to 3.6% [5], and in males is 0.1% [4]. The point prevalence in young female BN patients is about 0.6% [4, 5]. Binge ED, an appendix in the *DSM-IV*, is a full-fledged diagnosis in the *DSM-5*. Its lifetime prevalence is from 1.52% to 2.03% based on *DSM-IV-TR* and *DSM-5* criteria, respectively [6]. Lifetime prevalence of other specified ED is about 11% [7]. ED is common, and many severe medical complications can occur during extreme food restricting or recurrent purging behaviors [2, 3, 8]. As AN and BN become chronic and progressive, most of vital organs are influenced [3]. Therefore, EDs have been related with elevated mortality risk [1]. ED patients also have increased incidence of substance use, including cigarette and alcohol which are known risk factors of certain types of cancer [9, 10].

Karamanis et al. in 2014 reported that AN is not associated with cancer incidence [11]. Mellemkjaer et al. in 2015 have found an increased incidence of esophageal

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and lung cancer in female AN patients but has not found any overall cancer incidence in both female and male AN patients [12]. Michels and Ekbom and Papadopoulos et al. did some research to have explore the specific relationship between breast cancer as well as AN [13, 14]. Their results indicated that women with the diagnosis of AN, especially those with early onset and experienced parity in the later life, have the lower breast cancer risk compared to those in general population [13]. In reviewing the previous research, we found that most of the study patients are focused on more severe patients that have at least once admission with main or secondary diagnosis of AN [11-15]. Generalization of the results from studies of the severe AN to overall patients with AN might be difficult.

Different types of EDs have different clinical presentations and courses. For example, changing trends of body weight and existence of maladaptive compensatory behaviors like purging vary between AN and other types of EDs. Scarce data exist to investigate the relationship between different types of EDs and cancer.

To investigate the risk of cancer among patients diagnosed with different types of EDs comprehensively, we did a nationwide-based data linkage study in Taiwan. Our hypothesis was that the difference of incidence of cancer would exist between AN and non-AN ED patients.

## Methods

### Data source

Taiwan National Health Insurance (NHI) established in 1995, is a compulsory single-payer NHI. The NHI has covered 99.6% of medical claims in Taiwan. The disbursement of insurance includes outpatient, inpatient, dental, and ambulatory services. The Bureau of NHI (BNHI) has demanded and managed registration of all medical claims. The National Health Research Institute in Taiwan established the NHI Research Database (NHIRD) encompassing medical claim files representative of the entire Taiwan population in 1996. Based on the registration claim data, NHIRD provide a Longitudinal Health Insurance Database (LHID). The LHID contains the claim data of 1,000,000 people randomly sampled from all beneficiaries of the NHI program. The patients in sampled group of the LHID do not differ in sex distribution, age, or average insured amount from those in the original NHI enrolled population.

In the present study, we used the Psychiatric Patient Medical Claims database, a subset of the NHIRD including a cohort of patients diagnosed for any mental disorder between 1998 and 2013 ($n$ = 2,409,919) to recruit the patients with EDs. The database encompasses patients with at least three ambulatory claims with diagnosis made by psychiatrists within one year or at least one discharge diagnosis of mental illness based on *the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 290-319. We used the LHID to select the comparing control group. Based on the study conducted at NHRI in Taiwan [16], we categorized urbanization levels as very high, high, moderate, and low. We integrated seven urbanization levels of the study [16] at NHRI into 4 levels as follows: highly urbanized city, medium urbanized city and boom town, general and aging township, as well as rural and remote township. The overall observation period is limited from 1998 to 2013. The present study protocol was approved by the institutional review board of Chang Gung Memorial Hospital, without the need of obtaining informed consents from participating patients.

### Study samples

According to *the ICD-9-CM* code, ED comprises AN (307.1), BN (307.51), other disorders of eating (307.59), and ED, unspecified (307.50). During the observation period, those who had at least three ambulatory claims with diagnosis of ED within one year or any inpatient diagnosis of ED were defined and included as cases with ED. As shown in Figure 1, we identified 13,755 cases with ED. We excluded those with the diagnosis of any type of cancer (*ICD-9-CM* 140-209, 230-239) before the diagnosis of EDs (158 cases) and enrollees younger than 10 years of age (133 cases). After removing those who had been diagnosed with EDs at any time, and those with cancer before enrollment, we randomly

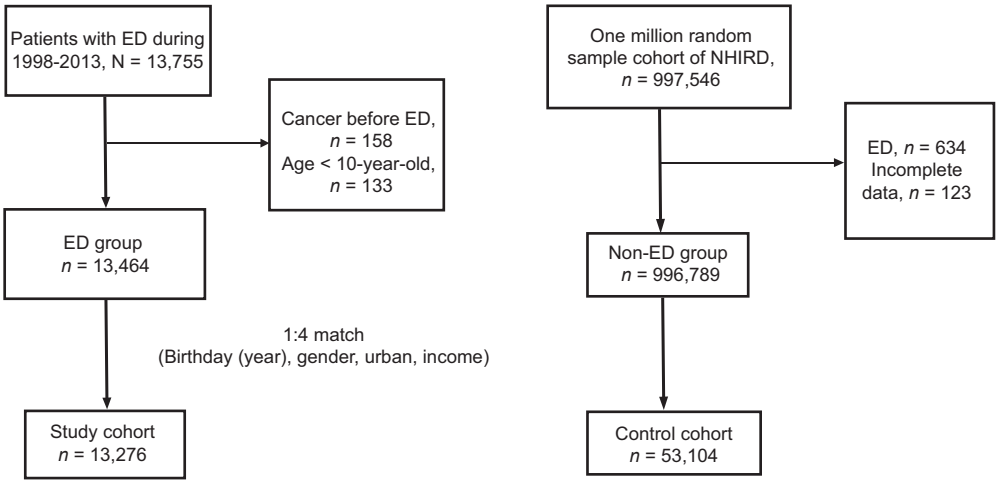


**Figure 1.** Flow chart of sample selection. ED, eating disorder.

identified and matched the control cohort by age, gender, income, and level of urbanization (1: 4). We defined the index date as the first date of recording the diagnosis of EDs. The follow-up period began from the index date and terminated while the first date of cancer diagnosis being made, death or the end of 2013. Comorbidities included alcohol abuse (305.0, 305.00, 305.01, 305.02, 305.03), tobacco use disorder (305.1), and chronic obstructive pulmonary disease (490,491,492, 4,996) (Figure 1).

### *Statistical analysis*

We compared both of distribution of demographic factors and comorbidities between the ED group and non-ED group. We also further stratified the study cohort into the AN group and non-AN group. Each enrollee's new diagnosis of cancer during the entire follow-up time was applied in the calculation of incidence of cancer with 95% confidence interval (95% CI). The follow-up time began from the index dates of first diagnosis of ED to cancer, death, migration, or the end of December 31, 2013. The results of Kaplan–Meier analysis revealed the cumulative incidence of cancer in both groups, and the differences between two groups were tested using the log-rank test. After adjusting the demographic data (age, gender, urbanization, and income) and three comorbidities mentioned above, we used Cox proportional hazards models to compute the hazard ratios (HRs) with 95% CIs.

All study data were computed with the Statistical Analytic System software version 9.4 (SAS Institute, Cary, North Carolina, USA). Differences between the groups were considered significant if $p$ values were smaller than 0.05.

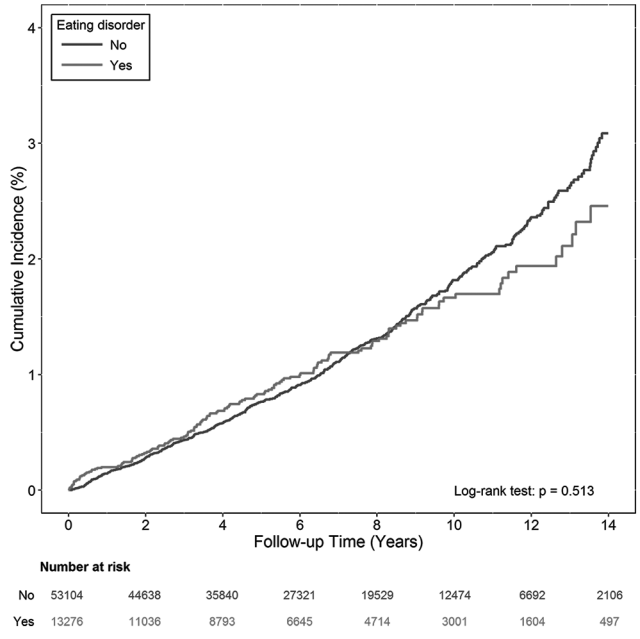


**Figure 2.** Cumulative incidences of cancer between ED group and the matched non-ED group. The differences between two groups were not significant using modified long-rank test. ED, eating disorders; CI, confidence interval.

## Results

A total of 13,276 persons with ED and 53,104 age- and sex-matched non-ED controls were enrolled. Of the ED group, there was 143 cases with diagnoses of cancer. There were total 85403.2 person-years. The mean follow-up time was 6.4 years. The incidence (95% CI) was 167.4 (142.1 – 197.3). Of the non-ED group, there were 662 cases with diagnoses of cancer. There were total 348769.7 person-years. The mean follow-up time was 6.6 years. The incidence (95% CI) was 178.3 (164.9 – 192.9). Among the case cohort (Figure 1), we found 2,368 (17.8%) cases of AN and 10,908 (82.2%) cases of non-AN covering BN, other disorder of eating, and ED, unspecified.

**Table 1.** Demographic data, comorbidities, and incidence of cancer among patients with eating disorder and controls

| Variables | ED ($n$=13,276), $n$ (%) | Non-ED ($n$=53,104), $n$ (%) |
|---|---|---|
| Type of eating disorder | | |
| AN | 2368 (17.8) | |
| All eating disorders except AN | 10,908 (82.2) | |
| Gender | | |
| Male | 1417 (10.7) | 5668 (10.7) |
| Female | 11,859 (89.3) | 47,436 (89.3) |
| Age (years) | | |
| 10-19 | 1980 (14.9) | 7920 (14.9) |
| 20-29 | 5441 (41.0) | 21,764 (41.0) |
| 30-39 | 3173 (23.9) | 12,692 (23.9) |
| 40-49 | 1547 (11.7) | 6188 (11.7) |
| 50-59 | 487 (3.7) | 1948 (3.7) |
| ≥ 60 | 648 (4.9) | 2592 (4.9) |
| Urbanization | | |
| 1 (city) | 3838 (28.9) | 15,352 (28.9) |
| 2 | 4751 (35.8) | 19,004 (35.8) |
| 3 | 1243 (9.4) | 4972 (9.4) |
| 4 (villages) | 3444 (25.9) | 13,776 (25.9) |
| Income | | |
| 0 | 8682 (65.4) | 34,728 (65.4) |
| 1-15,840 | 1853 (14.0) | 7412 (14.0) |
| 15,841-25,000 | 2154 (16.2) | 8616 (16.2) |
| > 25,000 | 587 (4.4) | 2348 (4.4) |
| Comorbidities | | |
| Alcohol abuse*** | 258 (1.9) | 61 (0.1) |
| Tobacco use disorder*** | 397 (3.0) | 298 (0.6) |
| COPD*** | 1346 (10.1) | 3312 (6.2) |
| Cancer | | |
| Yes | 143 (1.1) | 622 (1.2) |
| No | 13,133 (98.9) | 52,482 (98.8) |
| Death*** | | |
| Yes | 407 (3.1) | 416 (0.8) |
| No | 12,869 (96.9) | 52,688 (99.2) |

*$p$ < 0.05, **$p$ < 0.01, ***$p$ < 0.001 significantly different.
ED, eating disorders; AN, anorexia nervosa; COPD, constrictive obstructive pulmonary diseases

**Table 2.** Cox regression analyses of the risk of cancer among patients with eating disorders and controls†

| Variables | Crude | | Adjusted† | | Adjusted† | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Eating disorder | | | | | | |
| Yes | 0.94 | 0.79 - 1.13 | 1.02 | 0.85 - 1.2 | | |
| No | 1.00 | Reference | 1.00 | Reference | | |
| Subtype of eating disorder | | | | | | |
| AN | 1.51 | 1.14 - 2.01** | | | 1.10 | 0.83 - 1.47 |
| All ED except AN | 0.77 | 0.62 - 0.96* | | | 0.98 | 0.79 - 1.23 |
| Non-ED | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
| Gender | | | | | | |
| Male | 2.83 | 2.41 - 3.32*** | 1.34 | 1.12 - 1.61** | 1.34 | 1.12 - 1.60* |
| Female | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
| Age (year) | | | | | | |
| 10-19 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
| 20-29 | 1.79 | 1.14 - 2.81* | 1.79 | 1.14 - 2.82* | 1.80 | 1.15 - 2.83* |
| 30-39 | 5.10 | 3.28 - 7.91*** | 4.94 | 3.11 - 7.83*** | 4.96 | 3.13 - 7.87*** |
| 40-49 | 11.25 | 7.25 - 17.5*** | 10.67 | 6.67 - 17.05*** | 10.72 | 6.70 - 17.14*** |
| 50-59 | 17.33 | 10.9 - 27.7*** | 16.24 | 9.87 - 26.72*** | 16.27 | 9.88 - 26.76*** |
| ≥60 | 30.97 | 20.2 - 47.4*** | 27.49 | 17.48 - 43.23*** | 27.42 | 17.43 - 43.11*** |
| Urbanization level | | | | | | |
| 1 (city) | 1.19 | 0.99 - 1.43 | 1.24 | 1.03 - 1.49* | 1.24 | 1.03 - 1.49* |
| 2 | 0.99 | 0.82 - 1.2 | 1.15 | 0.95 - 1.39 | 1.15 | 0.95 - 1.39 |
| 3 | 1.15 | 0.88 - 1.5 | 1.09 | 0.83 - 1.42 | 1.09 | 0.83 - 1.42 |
| 4 (villages) | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
| Income | | | | | | |
| 0 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
| 1-15,840 | 3.08 | 2.54 - 3.73*** | 1.07 | 0.86 - 1.33 | 1.07 | 0.86 - 1.33 |
| 15,841-25,000 | 3.78 | 3.19 - 4.5*** | 1.14 | 0.93 - 1.39 | 1.14 | 0.93 - 1.39 |
| > 25,000 | 3.31 | 2.53 - 4.34*** | 0.93 | 0.69 - 1.26 | 0.93 | 0.69 - 1.25 |
| Comorbidity (yes/no) | | | | | | |
| Alcohol abuse | 0.29 | 0.04 - 2.04 | 0.34 | 0.05 - 2.45 | 0.35 | 0.05 - 2.48 |
| Tobacco use disorder | 0.51 | 0.19 - 1.37 | 0.55 | 0.21 - 1.48 | 0.56 | 0.21 - 1.49 |
| COPD | 2.76 | 2.30 - 3.31*** | 0.90 | 0.74 - 1.10 | 0.90 | 0.74 - 1.10 |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ significantly different using cox proportional hazards models,
†Adjusting for all covariates (gender, age, urbanization, income, and comorbidities).
AN, anorexia nervosa; CI, confidence interval; COPD, constrictive obstructive pulmonary diseases; ED, eating disorder; HR, hazard ratio

Figure 2 depicts cumulative incidences of cancer between ED group and the matched non-ED group. Table 1 describes demographic data, comorbidities, and incidence of cancer among patients with ED and controls. Table 2 shows Cox regression analyses of the risk of cancer among patients with ED and controls. Table 3 lists the types of cancer for the 143 ED patients (Figure 2 and Tables 1 and 2).

## Discussion

As far as we know, this is the first nationwide population-based study to investigate the risk of all type of cancer in ED patients after controlling for age, sex, urbanization, and other comorbid illnesses. In our study (Figure 2), ED patients did not have greater incidence of cancer than those without the disease.

Our results were in line with previous studies [17]. Mellemkjaer et al. [17] used the Danish Psychiatric Case Register and the Danish Cancer Registry database between 1970 and 1997, included all admissions to psychiatric department information and comprehensive national coverage of all cancer, to do a retrospective cohort. They found that predominated female patients (92%) have been reported in their study cases and most of them were under 50 years old, that the mean follow-up period difference in gender is between 11 and 13 years, and that no significant relationship exists between the incidence of overall cancer and AN [17]. Karamanis et al. [11] did a similar retrospective register-based cohort from Swedish data during 1973–2003 and included only female patients with discharge diagnosis with AN at age 10–40 years. The investigators found that the overall cancer occurrence among cases with AN resembled that of population in comparisons (SIR = 1.1, CI = 0.8–1.3) [11].

Mellemkjaer, Fotios, Papadopoulos, et al. did a more recent and large-scale study based on National Hospital Registries and Cancer Registries of Sweden, Denmark, and Finland during 1968–2010 [12]. The investigators identified 24,332 patients with AN and 241,249 controls and found that no difference of cancer incidence exists between AN patients and the general

**Table 3.** The types of cancer for the 143 eating disorder patients

| ICD-9CM | Diagnosis | *n* (%) |
|---|---|---|
| 141.9 | Malignant neoplasm of tongue, unspecified | 2 (1.4) |
| 142.9 | Malignant neoplasm of salivary gland, unspecified | 2 (1.4) |
| 145 | Malignant neoplasm of other and unspecified parts of mouth | 2 (1.4) |
| 145.0 | Malignant neoplasm of cheek mucosa | 1 (0.7) |
| 147 | Malignant neoplasm of nasopharynx | 3 (2.1) |
| 150.9 | Malignant neoplasm of esophagus, unspecified | 1 (0.7) |
| 151 | Malignant neoplasm of stomach | 2 (1.4) |
| 151.2 | Malignant neoplasm of pyloric antrum of stomach | 1 (0.7) |
| 151.9 | Malignant neoplasm of stomach, unspecified | 1 (0.7) |
| 153 | Malignant neoplasm of colon | 4 (2.8) |
| 153.1 | Malignant neoplasm of transverse colon | 2 (1.4) |
| 153.2 | Malignant neoplasm of descending colon | 1 (0.7) |
| 153.3 | Malignant neoplasm of sigmoid colon | 3 (2.1) |
| 153.7 | Malignant neoplasm of splenic flexure | 1 (0.7) |
| 153.9 | Malignant neoplasm of colon, unspecified | 5 (3.5) |
| 154 | Malignant neoplasm of rectum, rectosigmoid junction, and anus | 2 (1.4) |
| 154.1 | Malignant neoplasm of rectum | 1 (0.7) |
| 155 | Malignant neoplasm of liver and intrahepatic bile ducts | 2 (1.4) |
| 155.0 | Malignant neoplasm of liver, primary | 7 (4.9) |
| 157 | Malignant neoplasm of pancreas | 1 (0.7) |
| 162 | Malignant neoplasm of trachea, bronchus, and lung | 5 (3.5) |
| 162.3 | Malignant neoplasm of upper lobe, bronchus, or lung | 1 (0.7) |
| 162.9 | Malignant neoplasm of bronchus and lung, unspecified | 6 (4.2) |
| 170.2 | Malignant neoplasm of vertebral column, excluding sacrum and coccyx | 2 (1.4) |
| 172.9 | Malignant melanoma of skin, site unspecified | 1 (0.7) |
| 173.9 | Malignant neoplasm of skin, site unspecified | 1 (0.7) |
| 174 | Malignant neoplasm of female breast | 16 (11.19) |
| 174.0 | Malignant neoplasm of female breast, nipple, and areola | 1 (0.7) |
| 174.1 | Malignant neoplasm of female breast, central portion | 1 (0.7) |
| 174.2 | Malignant neoplasm of female breast, upper-inner quadrant | 1 (0.7) |
| 174.3 | Malignant neoplasm of female breast, lower-inner quadrant | 1 (0.7) |
| 174.4 | Malignant neoplasm of female breast, upper-outer quadrant | 2 (1.4) |
| 174.8 | Malignant neoplasm of other specified sites of female breast | 1 (0.7) |
| 174.9 | Malignant neoplasm of female breast, unspecified | 9 (6.29) |
| 180 | Malignant neoplasm of cervix uteri | 1 (0.7) |
| 180.1 | Malignant neoplasm of exocervix | 1 (0.7) |
| 180.8 | Malignant neoplasm of other specified sites of cervix | 1 (0.7) |
| 180.9 | Malignant neoplasm of cervix uteri, unspecified | 4 (2.8) |
| 181 | Malignant neoplasm of placenta | 1 (0.7) |
| 182.0 | Malignant neoplasm of corpus uteri, except isthmus | 1 (0.7) |
| 183 | Malignant neoplasm of ovary and other uterine adnexa | 1 (0.7) |
| 183.0 | Malignant neoplasm of ovary | 2 (1.4) |
| 184.0 | Malignant neoplasm of vagina | 1 (0.7) |
| 185 | Malignant neoplasm of prostate | 3 (2.1) |
| 188.9 | Malignant neoplasm of bladder, part unspecified | 1 (0.7) |
| 189 | Malignant neoplasm of kidney and other and unspecified urinary organs | 1 (0.7) |
| 189.0 | Malignant neoplasm of kidney, except pelvis | 1 (0.7) |
| 191 | Malignant neoplasm of brain | 3 (2.1) |
| 191.1 | Malignant neoplasm of frontal lobe | 1 (0.7) |
| 191.9 | Malignant neoplasm of brain, unspecified | 3 (2.1) |
| 193 | Malignant neoplasm of thyroid gland | 12 (8.39) |
| 197.0 | Secondary malignant neoplasm of lung | 1 (0.7) |
| 198.3 | Secondary malignant neoplasm of brain and spinal cord | 1 (0.7) |
| 201 | Hodgkin's disease | 1 (0.7) |
| 202 | Other malignant neoplasms of lymphoid and histiocytic tissue | 3 (2.1) |
| 203.00 | Multiple myeloma, without mention of remission | 1 (0.7) |
| 204 | Lymphoid leukemia | 1 (0.7) |
| 204.10 | Chronic lymphoid leukemia, without mention of remission | 1 (0.7) |
| 205 | Myeloid leukemia | 2 (1.4) |
| 205.20 | Subacute myeloid leukemia, without mention of remission | 1 (0.7) |
| 208.90 | Unspecified leukemia, without mention of remission | 1 (0.7) |

ICD, International Classification of Diseases

population. The finding is consistent with that in our study. However, Mellemkjaer et al. have found lower risk of breast cancer and excessive risk of lung, liver, and esophageal cancer among female AN patients [12]. Overall, studies mentioned above have an important limitation that they only enrolled hospitalized patients as study cohort. We suggest that large amount of AN population who have never been hospitalized are excluded.

In our study, we also enrolled patients with other types of ED than AN. For patients with ED, especially BN, are more prevalent to have maladaptive compensatory behaviors like self-induced vomiting. It may further lead to acidic damage to esophageal epithelium similar with the mechanism in gastroesophageal reflux disease, which is a known risk factor for esophageal cancer [18, 19]. Sporadic case reports and a retrospective study by Brewster et al. have revealed the possibly increased incidence of esophageal or gastric cardiac cancer in patients with the past history of BN [15]. Brewster et al. linked database of discharge records and cancer registrations in Scotland during 1981–2012 to survey the risk of esophageal cancer among patients with previous

history of hospitalization with ED [15]. The investigators found that the median duration of follow-up is nearly 14 years, and that seven patients of esophageal cancer have been identified with squamous cell carcinoma [15]. The results have revealed elevated risk of esophageal cancer among these patients (SIR = 6.1, CI = 2.5 – 12.6) [15]. But, the results are better explained by possibly higher carcinogen exposure such as tobacco and alcohol consumption in ED patients rather than gastric acid reflux [15]. Compared with the studies mentioned above, our study covered more patients with ED, including those who had never been hospitalized for ED, and expanded the target to nearly all origins of cancer (Table 1). The medium follow-up time in our study was 6.4 years, which are shorter than the study of Brewster et al. [15]. We also found that all types of cancer for all 143 ED patients were small in numbers (Table 3). Taken together, we suggest that the relatively low prevalence of substance use and short duration of observation in our study has no significant relationship between ED and cancer incidence.

The possible pathophysiological mechanism between ED and cancer was not known. Chaotic lifestyle, increased substance use, imbalanced diet, and malnutrition can all predispose people to poor health condition and even cancer in EDs patients. Patients with different type of EDs have varied manifestation. AN patients tend to have more emaciated physique than other type of ED. Maladaptive compensatory behaviors such as self-induced vomiting are more prevalent in BN patients than those with AN. In our study (Table 1), we stratified the ED into AN type and non-AN type. The results revealed that neither of them was related with increasing incidence of cancer overall. There are several other speculations about the mechanism. Booij et al. have demonstrated altered DNA methylation in AN patients based on a genome-wide study [20]. The longer the illness, the more marked alteration of methylation in genes, and gene pathways are involved in immunity and the peripheral organs [20]. Vaz-Leal et al. mentioned that different symptoms in BN have potential influence on lymphocyte subset counts [21]. The change in lymphocyte subset counts can disrupt the antitumor effects of the immune system [22-24].

### *Study limitations*

- NHIRD, as a medical claim database, failed to contain information of family history, lifestyle, smoking, alcohol use, body weight, or severity of ED
- Diagnoses of ED is mainly according to *ICD-9CM* by board certified psychiatrists in Taiwan. Whereas, inter- or intra-rater validation studies had not been carried out in EDs of NHIRD
- The prevalence of ED could be underestimated because only those who have sought medical service were registered in the database. But, to get a more entire approach to ED population, we need to include hospitalized patients as previous studies did and outpatient patients
- Our observation period was not long enough. It takes several years from normal tissues, dysplasia tissues, precancerous lesions, to finally cancer [25]. The longer follow-up may reveal the more exact relationship between them.

### *Summary*

This nationwide representative study in Taiwan did not provide evidence to support the relationship between cancer incidence and ED. More comprehensive studies with longer follow-up and individualized information on possible confounding factors are necessary in the future.

## Acknowledgment

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## Conflicts of Interest

There are no conflicts of interest.

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