Objective: This study aims to estimate the population-based incidence of gestational trophoblastic diseases (GTDs) and to identify the characteristics of gestational trophoblastic neoplasia (GTN) in Japan.

Methods: The annual number of GTD and live births from 1974 to 2018 were used to estimate the incidence of GTD. The data of 1,574 GTN cases from 1999 to 2018 were analyzed to identify the characteristics of low-risk GTN, high-risk GTN, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

Results: The incidence of hydatidiform mole was 2.02 per 1,000 live births on average which decreased from 1974 to 2008 and increased from 2009 to 2018. The incidence of low-risk GTN, high-risk GTN, PSTT, and ETT was 15.3, 3.5, 0.3, and 0.07 per 100,000 live births, respectively. The estimated incidence of post-molar GTN was 9.8% of molar patients. High-risk GTN was diagnosed more pathologically, had more various kinds of antecedent pregnancies, and had longer intervals after the antecedent pregnancy compared to low-risk GTN. Furthermore, 8.2% of high-risk GTN occurred after the subsequent non-molar pregnancy of hydatidiform mole. The cumulative percentage of developing high-risk GTN after hydatidiform mole reached 89.3% at the 60th month.

Conclusion: The incidence of hydatidiform mole, low-risk GTN, high-risk GTN was 2.02 per 1,000 live births, 15.3 per 100,000 live births, and 3.5 per 100,000 live births, respectively. High-risk GTN was diagnosed more pathologically, had more various kinds of antecedent pregnancies, and had longer intervals after the antecedent pregnancy compared to low-risk GTN. Following molar patients for 5 years is needed to improve the mortality of malignant GTN.

Keywords: Epidemiology; Gestational Trophoblastic Disease; Gestational Trophoblastic Neoplasia; Hydatidiform Mole; Japan
INTRODUCTION

Gestational trophoblastic diseases (GTDs) consist of hydatidiform mole and gestational trophoblastic neoplasia (GTN). Hydatidiform mole is an abnormal pregnancy and categorized into complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) based on pathological examination and genetic origins. GTNs include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). GTN needs operation and/or chemotherapy due to the potential of metastasis. The mortality of GTNs was improved greatly by follow-up after hydatidiform mole and the development of anticancer drugs, human chorionic gonadotrophin (hCG) measurement, and drugs for adverse effects by chemotherapy [1]. The cure rate of invasive mole is almost 100% [2,3], but that of choriocarcinoma remains approximately 85% [4-6].

A regional registration system of hydatidiform mole started in the UK, the Netherlands, and Japan in the 1970s and contributed to a decrease in the incidence and mortality of choriocarcinoma [7-10]. In Japan, the first regional registration of hydatidiform mole started in Aichi prefecture in 1962. The outcomes of 7,723 molar pregnancies in Aichi prefecture from 1962 to 1991 showed that the incidence and mortality of choriocarcinoma after hydatidiform mole decreased from 2.7% to 0.34% and from 54.1% to 0%, respectively [11]. The Japanese GTD registration system started in 14 prefectures in 1974 and expanded to 22 prefectures in 1992. However, most previous studies on GTDs in Japan were hospital-based studies and there has been only one study on the population-based incidence of GTDs but using the data from only one prefecture [12]. The Japanese GTD guidelines were established in 1988 and revised in 1996 and 2011 in terms of the disease classification and the diagnostic criteria [13,14]. To improve the outcome of GTN, appropriate guidelines for diagnosis and treatment should be developed and the incidence and characteristics of diseases should be understood. This study aims to identify the trend of the population-based incidence of GTDs and the characteristics of GTNs in Japan.

MATERIALS AND METHODS

1. The Japanese GTD registration system

The registration areas included 14 out of 47 prefectures in 1974 and gradually increased to 22 prefectures in 1992. Each year the prefectoral registration center in each prefecture asks all hospitals and clinics that have obstetrics departments and/or gynecology departments to report new GTD cases. The data of a new GTD case at diagnosis is reported from a hospital or clinic where the initial treatment was provided. The prefectoral registration center gathers the data of all new GTD cases in the prefecture and reports to the Japan Society of Obstetrics and Gynecology (JSOG) every year. The collected data was only for diagnoses before 1999. The following data has been collected since 1999; age, history of pregnancies, antecedent pregnancy and the date of termination, diagnosis of GTN, the date of diagnosis, pathological examination, the hCG level when GTN was diagnosed, sites of GTN, the Japanese GTN score, and International Federation of Gynecology and Obstetrics (FIGO) stage and score.

2. The number of GTD cases

The annual number of GTDs from 1974 to 2018 was extracted from the JSOG GTD database. Hydatidiform moles were diagnosed macroscopically and/or pathologically and choriocarcinoma, invasive mole, PSTT, and ETT were diagnosed pathologically.
When a tumor was detected with an increase of hCG but pathological examination was not performed, the tumor was clinically diagnosed with clinical GTN. Clinical GTN was categorized into clinical invasive mole or clinical choriocarcinoma according to the Japanese GTN scoring system [13,14].

The annual number of GTD was included in this study, such as hydatidiform moles from 1974 to 2018; CHM and PHM from 1992 to 2018; choriocarcinoma, invasive mole, and clinical GTN from 1974 to 2018; clinical invasive mole and clinical choriocarcinoma from 1992 to 2018; PSTT from 1994 to 2018; and ETT from 2010 to 2018. In this study, pathological invasive mole and clinical invasive mole were categorized into “low-risk GTN” and pathological choriocarcinoma and clinical choriocarcinoma were categorized into “high-risk GTN.” Of the GTN cases included in this study, 991 cases were clinical GTN cases (899 clinical invasive mole and 92 clinical choriocarcinoma) that could be categorized into FIGO score ≤6 (n=931) or FIGO score ≥7 (n=60). Of the 931 cases of FIGO score ≤6, 887 cases (95.3%) were clinical invasive mole. Of the 60 cases of FIGO score ≥7, 48 cases (80.0%) were clinical choriocarcinoma.

3. The number of live births in the registration areas
The annual number of live births in each prefecture from 1974 to 2018 was collected from the dynamic of population statistics of the Ministry of Health, Labour, and Welfare, which were extracted from the Portal Site of Official Statistics of Japan website (https://www.e-stat.go.jp/) [15,16].

4. GTN cases
A total of 1,687 GTN cases were registered from 1999 to 2018, but 1,574 GTN cases were analyzed after excluding 113 cases because of double registration (n=6), uncertain diagnosis (n=49), hydatidiform mole (n=37), spontaneous remission (n=5), recurrent choriocarcinoma (n=5), non-gestational choriocarcinoma (n=7), and missing data (n=4). The data of GTN cases in this study included age, gravida, parity, antecedent pregnancy, the date of termination of the antecedent pregnancy, history of hydatidiform mole other than the antecedent pregnancy and the date, diagnosis of GTN, the date of diagnosis, pathological examination, the hCG level when GTN was diagnosed, sites of GTN, and FIGO stage [17]. Antecedent pregnancies were categorized into hydatidiform mole (CHM, PHM, unclassified, and CHM with coexistent fetus), miscarriage-abortion, ectopic pregnancy, delivery (term and preterm delivery), and unknown. The hCG level in both serum and urine that were measured with the unit of IU/L was included but not the unit of ng/ml. When the diagnosis was not consistent with the answer to the pathological examination, the case was excluded from the analysis. The interval from the antecedent pregnancy to GTN was calculated using the date of termination of antecedent pregnancy and the date of treatment for GTN.

5. Statistical analysis
The incidence of hydatidiform mole and GTN was calculated as the number of cases per 1,000 live births and per 100,000 live births. In terms of the follow-up after hydatidiform mole, CHM is more important than PHM because it is reported that post-molar GTN mostly occurs after CHM. Therefore, the percentage of CHM to hydatidiform mole was calculated. To understand the incidence of invasive mole after hydatidiform mole, the percentage of low-risk GTN to a total number of hydatidiform mole cases in each year was calculated. The ratio of clinical diagnosis in GTN cases was estimated to understand the trend of diagnosis methods using the number of clinical GTN (clinical invasive mole and clinical choriocarcinoma) and pathological GTN (invasive mole and choriocarcinoma). Descriptive
analysis was performed using the data of 4 groups of GTN (low-risk GTN, high-risk GTN, PSTT, and ETT). The t-test, Mann-Whitney’s U test, and χ² test was performed to examine the difference of the mean, the median, and distribution, respectively. The p-value <0.05 was considered as significantly different.

6. Ethical approval statement
This study was approved by the Ethics Committee of Nagoya University Hospital (approval number 2017-0168) and JSOG (approval number 2017-79).

RESULTS

1. The incidence of hydatidiform mole and GTN from 1974 to 2018
The incidence of hydatidiform mole (per 1,000 live births) from 1974 to 2018 was 2.02. The incidence was 2.70 in 1974, decreased to 1.02 in 2008, and then increased to 1.69 in 2018 (Fig. 1A, black line). The incidence of GTN (per 100,000 live births) was 38.9 in 1974, decreased to 12.6 in 2007, and increased to 18.1 in 2018 (Fig. 1A, yellow line). The trend of the incidence of hydatidiform mole from 1974 to 2018 was almost the same as that of GTN. The annual numbers of low-risk GTN and high-risk GTN were available from 1992 to 2018. Low-risk GTNs accounted for 70.0%–88.1% (average, 81.6%) of all GTNs. The mean incidence (per 100,000 live births) of low-risk GTN and high-risk GTN from 1992 to 2018 was 15.3 (range, 10.2–21.3) and 3.5 (range, 1.9–5.5), respectively (Fig. 1A, red and green dotted lines). To understand the trend of diagnosis methods of GTNs, the rate of clinical diagnosis in low- and high-risk GTN was estimated. It was 43.7% in 1974 and increased from 53.4% in 1990 to 77.3% in 2018 (Fig. 1B).

The registration of PSTT and ETT started in 1994 and 2010, respectively. The incidence of PSTT between 1994 and 2018 was estimated to be 0.3 per 100,000 live births and 1.81% of GTN. The incidence of ETT between 2010 and 2018 was estimated as 0.07 per 100,000 live births and 0.3% of GTN.

![Graph A](https://example.com/graph_a.png)

**Graph A**. The trend of the incidence from 1974 to 2018. (A) The population-based incidence of hydatidiform mole and GTN. The incidence was estimated using the number of live births in the same prefectures. (B) The percentage of clinical diagnosis in GTN. The percentage increased from 44.1% in 1974 to 77.3% in 2018. GTN, gestational trophoblastic neoplasia.

![Graph B](https://example.com/graph_b.png)

**Graph B**. The trend of the percentage of clinical diagnosis in GTN from 1974 to 2018.
2. Estimation of the percentage of CHM of hydatidiform mole

Hydatidiform mole consists of CHM and PHM and CHM is one of the risk factors for post-molar GTN. The percentage of CHM in hydatidiform mole was 53.3% in 1992, gradually decreased to 37.3% in 2010, and increased to 58.8% in 2018 (Fig. 2, solid line). Between 1992 and 2018, the average percentage of CHM was 46.5% and the incidence of CHM and PHM was 0.73 and 0.84 per 1,000 live births, respectively.

3. Estimation of the rate of low-risk GTN to hydatidiform mole

To understand the incidence of developing post-molar GTN (low-risk GTN after hydatidiform mole), we calculated the percentage of the number of low-risk GTN cases divided by the number of hydatidiform mole cases in each year. The percentage ranged from 7.6% in 2010 to 12.4% in 2005 and the average was 9.8% between 1992 and 2018 and it remained stable at approximately 10% during the 26 years (Fig. 2, dotted line).

4. Characteristics of low-risk GTN and high-risk GTN

From 1999 to 2018, 1,687 GTN cases were registered but 113 cases were excluded from the analysis in this study (Fig. 3). The clinical data of 1,574 GTN cases included 1,277 cases (81.1%) of low-risk GTN, 261 cases (16.6%) of high-risk GTN, 33 cases (2.1%) of PSTT, and 3 cases (0.2%) of ETT.

The characteristics of low-risk GTN and high-risk GTN were compared (Table 1). The mean age of low-risk GTN cases was 34.2 years, which was significantly younger than that of high-risk GTN cases (35.8 years, p=0.014). Low-risk GTN had a higher percentage of clinical diagnosis (81.5%) compared to high-risk GTN (41.4%, p<0.001). Most antecedent pregnancy of low-risk GTN was hydatidiform mole (n=1,096, 85.8%), especially CHM (n=798, 62.5%). Of the 261 high-risk GTN cases, 124 cases (47.5%) had deliveries, 66 cases (25.3%) had miscarriages or abortions, and 63 cases (24.1%) had hydatidiform moles. The percentage of having a history of hydatidiform mole was 86.4% in the low-risk GTN group and 32.3% in the high-risk GTN group. In terms of the FIGO stage, most patients of low-risk GTN were diagnosed with stage I (n=811, 63.5%) followed by stage III (n=445, 34.8%). Of the high-risk GTN cases, stage I accounted for one-third (n=98, 37.5%) as well as stage III (n=95, 36.4%) and 18.8% cases (n=49) were diagnosed with stage IV. Metastatic sites of high-risk GTN were mostly the lung (n=136, 52.1%) followed by the liver (n=22, 8.4%) and the brain (n=21, 8.0%).
There were 11 cases (4.2%) of choriocarcinoma that were pathologically diagnosed and had lesions in the placenta. The mean of hCG level before treatment was significantly higher in high-risk GTN (18,773.2 IU/L) than low-risk GTN (3,757.7 IU/L, p<0.001). The median interval from antecedent pregnancy to diagnosis of low-risk GTN was 1.6 months, while that of high-risk GTN was 8.8 months and significantly longer than low-risk GTN (p<0.001).

5. Development of GTN after hydatidiform mole
There were 1,096 low-risk GTN cases and 63 high-risk GTN cases whose antecedent pregnancies were hydatidiform mole. The accumulated percentage of diagnosis with low-risk GTN and high-risk GTN were calculated according to the months after hydatidiform mole. The cumulative percentage of developing low-risk GTN after hydatidiform mole reached 96.9% at the 6th month (Fig. 4). On the other hand, the cumulative percentage of developing high-risk GTN after hydatidiform mole was 32.1% at the 6th month, 39.3% at the 12th month, 53.6% at the 24th month, 76.8% at 36th month, 85.7% at the 48th month, and 89.3% at the 60th month.

6. Characteristics of PSTT and ETT
The average age of 33 PSTT cases was 32.9 years old (range, 20–49) and the major antecedent pregnancy was delivery (n=18, 54.5%) followed by miscarriage-abortion (n=8, 24.2%) and hydatidiform mole (n=4, 12.1%) (Table 2). Five patients (15.2%) had a history of hydatidiform mole. Most PSTT cases were stage I (n=25, 75.8%) followed by stage III (n=4, 12.1%). Two cases (6.1%) were stage IV and had metastases to the hipbone and subcutaneous tissue. The mean hCG level at diagnosis was 378.9 IU/L, which was much lower than those of low- and high-risk GTN.

The average age of ETT cases was 49.3 years, which was much older compared to other GTNs (Table 2). Antecedent pregnancy was CHM in one case and delivery in two cases. Two cases were stage I and 1 case was stage III with metastases to the lung and pelvic organs. The mean of pre-treatment serum hCG was 2,065.2 IU/L (range, 154.6–322,800 IU/L), which was higher than that of PSTT.
DISCUSSION

This is the first report of the trend of population-based incidence and characteristics of GTD patients using the data of the Japanese GTD registration system. The incidence of hydatidiform mole was 2.02 per 1,000 live births on average. The reason for the decrease from 1974 to 2008 may be an increase of hydatidiform mole cases that were diagnosed as miscarriage. The diagnosis of hydatidiform mole had been made macroscopically based on the first edition (established in 1988) and the second edition (revised in 1996) of the Japanese guidelines of GTD [13]. The diagnosis criteria of hydatidiform mole was that a short diameter of hydropic villi was 2 mm or more. Two studies validated the macroscopic diagnosis by DNA polymorphisms and found that 27.8%–76% of hydropic abortion (hydropic villi <2 mm in a short diameter) was

| Characteristics                             | Low-risk GTN (n=1,277) | High-risk GTN (n=261) | p-value |
|---------------------------------------------|------------------------|-----------------------|---------|
| Mean age (yr)                               | 34.2 (15–59)           | 35.8 (27–78)          | 0.014   |
| Diagnosis                                   |                        |                       | < 0.001 |
| Pathological diagnosis                      | 236 (18.5)             | 153 (58.6)            |         |
| Clinical diagnosis                          | 1,041 (81.5)           | 108 (41.4)            |         |
| Antecedent pregnancy                        |                        |                       |         |
| Hydatidiform mole                           | 1,096 (85.8)           | 63 (24.1)             |         |
| CHM                                         | 798 (62.5)             | 43 (16.5)             |         |
| PHM                                         | 255 (20.0)             | 12 (4.6)              |         |
| Unclassified                                 | 34 (2.7)               | 5 (1.9)               |         |
| CHMCF                                       | 9 (0.7)                | 3 (1.1)               |         |
| Miscarriage/abortion                         | 134 (10.5)             | 66 (25.3)             |         |
| Ectopic pregnancy                           | 5 (0.4)                | 3 (1.1)               |         |
| Delivery                                    | 0 (0)                  | 124 (47.5)            |         |
| Unknown                                     | 42 (3.3)               | 5 (1.9)               |         |
| History of hydatidiform mole                |                        |                       |         |
| Yes                                         | 1,103 (86.4)           | 84 (32.3)             |         |
| No                                          | 174 (13.6)             | 177 (67.7)            |         |
| Sites of metastases when diagnosed          |                        |                       |         |
| Vagina                                      | 23 (1.8)               | 11 (4.2)              |         |
| Ovary                                       | 6 (0.5)                | 12 (4.6)              |         |
| Tube                                        | 1 (0.1)                | 9 (2.4)               |         |
| Pelvic other than vagina and adnexae*       | 4 (0.3)                | 6 (2.3)               |         |
| Lung                                        | 445 (34.8)             | 136 (52.1)            |         |
| Liver                                       | 0 (0)                  | 22 (8.4)              |         |
| Kidney                                      | 0 (0)                  | 8 (3.1)               |         |
| Spleen                                      | 0 (0)                  | 3 (1.1)               |         |
| Intestine                                   | 0 (0)                  | 3 (1.1)               |         |
| Brain                                       | 0 (0)                  | 21 (8.0)              |         |
| Placenta                                    | 0 (0)                  | 11 (4.2)              |         |
| Others†                                     | 0 (0)                  | 7 (2.7)               |         |
| Mean pre-treatment serum hCG (IU/L)‡        | 3,757.7 (1.5–14,882,000)| 18,773.2 (3–5,000,000)| <0.001 |
| FIGO stage                                  |                        |                       |         |
| I                                           | 811 (63.5)             | 98 (37.5)             |         |
| II                                          | 21 (1.6)               | 19 (7.3)              |         |
| III                                         | 445 (34.8)             | 95 (36.4)             |         |
| IV                                          | 0 (0)                  | 49 (18.8)             |         |
| Median of interval from the termination of the antecedent pregnancy to treatment of GTN (mo) | 1.6 (0–27.6)           | 8.8 (0–439)           | <0.001 |

Values are presented as mean/median (range) or number of patients (%).
CHM, complete hydatidiform mole; CHMCF, complete hydatidiform mole with coexistent fetus; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotrophin; PHM, partial hydatidiform mole.
*Broad ligament of the uterus (n=1) and unknown lesions (n=3) among low-risk GTN cases; peritoneum (n=4), parametrium (n=1), uterine cervix (n=1), and bladder (n=1) among high-risk GTN cases.
†Others include eye, skin, breast, para-aortic lymph node, inferior vena cava, glutinous minimus, and vertebral canal.
‡Geometric mean computed on the log-transformed variable and converted to the original scale of measurement.
genetically hydatidiform mole [18,19]. From 1970 to 2000, ultrasonography was developing, and a pregnancy test was becoming common in Japan especially after 1990. As pregnancies and miscarriages were diagnosed in earlier gestational weeks, more hydatidiform moles in early gestational weeks might have been diagnosed as miscarriages. It is consistent with the data in

Table 2. The clinical features of PSTT and ETT

| Characteristics                        | PSTT (n=33) | ETT (n=3) |
|----------------------------------------|-------------|-----------|
| Mean age (yr)                          | 32.9 [20–49] | 49.3 [45–53] |
| Antecedent pregnancy                   |             |           |
| Hydatidiform mole                      | 4 (12.1)    | 1 (33.3)  |
| CHM                                    | 2 (6.1)     | 1 (33.3)  |
| PHM                                    | 1 (3.0)     | 0 (0)     |
| Unclassified                           | 1 (3.0)     | 0 (0)     |
| Miscarriage abortion                   | 8 (24.2)    | 0 (0)     |
| Delivery                               | 18 (54.5)   | 2 (66.7)  |
| Unknown                                | 3 (9.1)     | 0 (0)     |
| History of hydatidiform mole           |             |           |
| Yes                                    | 5 (15.2)    | 1 (33.3)  |
| No                                     | 18 (84.8)   | 2 (66.7)  |
| Sites of metastases when diagnosed     |             |           |
| Pelvic organs                          | 3 (1.8)     | 1 (33.3)  |
| Lung                                   | 5 (34.8)    | 1 (33.3)  |
| Hipbone                                | 1 (0)       | 0 (0)     |
| Subcutaneous tissue                    | 1 (0)       | 0 (0)     |
| Mean pre-treatment serum hCG (IU/L)*   | 378.9 (0.1–251,800) | 2,065.2 (154.6–322,800) |
| FIGO stage                             |             |           |
| I                                      | 25 (75.8)   | 2 (66.7)  |
| II                                     | 2 (6.1)     | 0 (0)     |
| III                                    | 4 (12.1)    | 1 (33.3)  |
| IV                                     | 2 (6.1)     | 0 (0)     |
| Median of interval from the termination of the antecedent pregnancy to treatment of GTN (mo) | 7.8 (0–119.4) | 114.2 (39.4–189.0) |

Values are presented as mean/median (range) or number of patients (%).
CHM, complete hydatidiform mole; ETT, epithelioid trophoblastic tumor; FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotrophin; PHM, partial hydatidiform mole; PSTT, placental site trophoblastic tumor.
*Geometric mean computed on the log-transformed variable and converted to the original scale of measurement.

Fig. 4. The cumulative percentage of developing low-risk GTN and high-risk GTN after hydatidiform mole. After hydatidiform mole, 96.9% of low-risk GTN were diagnosed at the 6th month but 89.3% of high-risk GTN were diagnosed at the 60th month.

GTN, gestational trophoblastic neoplasia.
this study that 10.5% of antecedent pregnancies of low-risk GTN were miscarriage or abortion although they must have been hydatidiform mole.

The incidence of hydatidiform mole started increasing around 2010. The main reason may be that the diagnosis criteria was changed from macroscopic findings to pathological examination according to the third edition of the guidelines (revised in 2011) [20]. The guidelines also recommend immunostaining using an antibody P57kip2 to identify CHM from PHM and biparental diploid pregnancy [21,22]. Recently P57kip2 immunohistochemistry is commonly used for diagnosis of hydatidiform mole, especially at general hospitals [3]. This may also contribute to an increase in the proportion of CHM from 2010 to 2018. Another reason for the increase of incidence of hydatidiform mole may be the aging of mothers because maternal age of 40 years old or older is the biggest risk factor of hydatidiform mole [23,24]. In Japan, the proportion of mothers who were 40 years old or older in all live births was 0.6% in 1985, gradually increased to 1.9% in 2005, and then rapidly increased from 3.3% in 2010 to 5.9% in 2020 [25]. The average incidence of hydatidiform mole should be considered as representative data of Japan because the incidence is influenced by many factors, especially diagnostic methods.

This study suggested that the incidence of post-molar GTN (low-risk GTN after hydatidiform mole) was stable at 9.8% from 1992 to 2018. The hospital-based incidence was reported to be 14%-20.6% [2,3,18], which was higher because molar cases with risks for post-molar GTN might have treatment at hospitals rather than clinics. Matsui et al reported that the population-based incidence in Chiba Prefecture was 9.4% from 1974 to 2000 [12]. These results suggest that the population-based incidence of post-molar GTN in Japan may have been approximately 10% in the past 50 years. The trend of the incidence of post-molar GTN after CHM and PHM from 1947 to 2018 could not be identified but the clinical GTN data between 1999 and 2018 suggested that the incidence was 12.4% after CHM, which was lower than that after PHM (3.3%). However, these incidences must be underestimated because the missing data were excluded from the analysis.

The incidence of hydatidiform mole and choriocarcinoma in this study was higher than that in Europe and North America, where the incidence of hydatidiform mole and choriocarcinoma is 0.57-4.1 per 1,000 pregnancies and 2-2.5 per 100,000 pregnancies, respectively [23,26]. The population-based incidence of PSTT and ETT is very low because PSTT and ETT are rarer GTN and relatively new diagnostic categories. The incidence of PSTT was reported as 1 in 100,000 deliveries using data from the Netherlands from 1995 and 2008 [27] and that of PSTT and/or ETT was 0.23% of GTN using the UK database from 1973 to 2014 [28]. This study showed that the incidence of PSTT was almost the same as that in the UK and that ETT is rarer than PSTT by approximately 5 times.

Clinical diagnosis of GTN was increasing in the study period and it was significantly more common in invasive mole compared to choriocarcinoma. Choriocarcinoma needs more surgery for diagnosis and treatment, because choriocarcinoma has more various symptoms due to metastases to various organs, occurs later from the antecedent pregnancy, and has more various kinds of antecedent pregnancies compared to invasive mole. This study showed that 32.3% of choriocarcinoma patients had a history of hydatidiform mole, which is one of the risk factors of choriocarcinoma [4,26], and that 8.2% developed choriocarcinoma after subsequent non-molar pregnancies of hydatidiform mole. Previous studies using DNA polymorphism revealed that molar villi can develop to choriocarcinoma after the subsequent non-molar pregnancy [29,30]. This study showed that 96.9% of low-risk GTN after hydatidiform mole was diagnosed
by the 6th month but that it took 5 years for 89.3% of high-risk GTN after hydatidiform mole was diagnosed. Ishizuka and Tomoda [31] reported that the cumulative percentage of choriocarcinoma developed after hydatidiform mole reached 42.0% at 12 months, 72.3% at 24 months, and 94.3% at 48 months. FIGO recommends monitoring hCG levels for 6 months and 1 year after PHM and CHM, respectively [32]. However, monitoring all molar patients for 5 years is necessary for early diagnosis and appropriate treatment of not only invasive mole but also choriocarcinoma and it would improve the mortality and morbidity of choriocarcinoma.

There were 11 cases of choriocarcinoma with lesions in the placenta. Choriocarcinoma in the placenta was registered as a metastatic lesion, but it can be a primary lesion as well as a metastatic lesion [33]. Seven cases were diagnosed when the pregnancy was terminated and the other four cases were diagnosed 10 days, 15 days, 1.5 months, and 7 months after the termination. The interval of intra-placental choriocarcinoma is short because it causes complications for mothers and babies, such as bleeding from the placenta, fetomaternal hemorrhage, and anemia of infants [34].

There are some limitations to this study. First, the Japanese registration system does not include all prefectures. However, it covers approximately half of the total population. The results in this study are useful to revise the guidelines to improve diagnosis accuracy, treatment strategy, and the outcome of GTDs. Second, this study did not show the outcome of GTDs because the registration data does not include the information of treatment and outcomes. In 2016, JSOG started another registration system to collect the data of GTN cases in all prefectures including treatment and outcome. Therefore, the outcome of GTN in Japan will be revealed soon. Third, missing data and incorrect data were found in the database and these data were excluded from the study. It may be because not all obstetrics and gynecological doctors can correctly diagnose GTD because the mortality of choriocarcinoma has been improved so much in Japan and GTN is rare disease. The registration system needs to be revised to collect correct data of GTD.

In conclusion, this is the first epidemiological study using the population-based database of GTD in Japan. The incidence of hydatidiform mole was 2.02 per 1,000 live births. The incidence of low-risk GTN, high-risk GTN, PSTT, and ETT was 15.3, 3.5, 0.3, and 0.07 per 100,000 live births, respectively. The incidence of hydatidiform mole and CHM might be changed by revision of the diagnosis criteria and the guidelines of GTD. However, the incidence of developing post-molar GTN was assumed to be stable at approximately 10%. High-risk GTN was diagnosed more pathologically, had more various kinds of antecedent pregnancies, and had a longer interval after the antecedent pregnancy compared to low-risk GTN. Furthermore, 8.2% of high-risk GTN occurred after the subsequent non-molar pregnancy of hydatidiform mole and it took 5 years until the cumulative percentage of developing high-risk GTN after hydatidiform mole reached 89.3%. Therefore, following molar patients for 5 years is necessary to reduce mortality and morbidity of choriocarcinoma.

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