Risk of Cancer in Children, Adolescents, and Young Adults with Autistic Disorder

Huey-Ling Chiang, MD[1,2,3], Chia-Jen Liu, MD[4,5,6], Yu-Wen Hu, MD[5,6,7], San-Chi Chen, MD[4], Li-Yu Hu, MD[6,8], Cheng-Che Shen, MD[9], Chiu-Mei Yeh, MS[10], Tzeng-Ji Chen, MD[5,10], and Susan Shur-Fen Gau, MD, PhD[1,2]

Objectives To investigate whether individuals with autism have an increased risk for cancer relative to the general population.

Study design We enrolled patients with autistic disorder from the Taiwan National Health Insurance database in years 1997-2011. A total of 8438 patients diagnosed with autism were retrieved from the Registry for Catastrophic Illness Patients database. The diagnosis of cancers was also based on the certificate of catastrophic illness, which requires histological confirmation. The risk of cancer among the autism cohort was determined with a standardized incidence ratio (SIR).

Results During the observation period, cancer occurred in 20 individuals with autism, which was significantly higher than a total number of expected cancers with a SIR estimate of 1.94 (95% CI 1.18-2.99). The number of cancer in males was greater than the expected number with a SIR of 1.95 (1.11-3.16), but no excess risk was found for females with a SIR of 1.91 (0.52-4.88). Cancer developed more than expected in individuals age 15-19 years with the SIR of 3.58 (1.44-7.38), but did not differ in other age range groups. The number of cancers of genitourinary system was significantly in excess of the expected number (SIR 4.15; 95% CI 1.13-10.65), and increased risk was found in ovarian cancer with SIR of 9.21 (1.12-33.29).

Conclusions Our study demonstrated that patients with autistic disorder have an increased risk of cancer. *(J Pediatr 2014;■:■-■).*

Autism spectrum disorder (ASD) is a group of pervasive developmental disorders including autistic disorder (autism) with persistent deficits in social communication and interaction, and restricted, repetitive patterns of behaviors, interests, or activities from early childhood throughout lifespan.[1] Individuals with ASD are more likely to have physical problems, such as epilepsy,[2] gastrointestinal dysfunction,[3] and allergic manifestations.[4] Emerging data also suggest that individuals with ASD might have an increased risk for cancer for a number of reasons. First, Ingudomnukul et al reported that women with autistic symptoms were more likely to have a family history of ovarian, uterine, and prostate cancers, and that mothers of children with autistic symptoms reported more breast cancer and uterine cancer, and a family history of ovarian and uterine cancers, based on self-report questionnaires.[5] Second, among the potential common genetic variants in ASD, several of the susceptibility loci in autism correspond to candidate oncogenes and tumor-suppressor genes.[6] Similarly, copy number variants identified in children with autism are frequently associated with cancer predisposition genes.[7]

Until now, only 2 studies have attempted to investigate whether children with autism were overall more likely to have newly diagnosed cancers.[8,9] Lauritsen et al found a higher co-occurrence of malignant neoplasm of the brain in patients with autism but based upon only 1 case observed. Blatt et al did not suggest a significantly higher concordance between autism and overall or specific childhood cancer, but the method was limited by small sample size, and potential underestimation of the incidence of autism by reviewing medical records.[9] Hence, we conducted a national population-based cohort study using the database of Taiwan National Health Insurance Research Database (NHIRD) to investigate whether individuals with autism have an increased risk of cancer.

ASD	Autism spectrum disorder
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
NHIRD	National Health Insurance Research Database
RCIP	Registry for Catastrophic Illness Patients
SIR	Standardized incidence ratio

From the [1]Department of Psychiatry, National Taiwan University Hospital and College of Medicine; [2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [4]Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital; [5]School of Medicine and [6]Institute of Public Health, National Yang-Ming University; [7]Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan; [8]Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [9]Department of Psychiatry, Chiayi Branch, Taichung Veterans General Hospital, Chiayi, Taiwan; and [10]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Supported by the National Science Council Taiwan (101-2314-B-002-136-MY3), Taipei Veterans General Hospital (V103B-022 and V103E10-001), and Taiwan Clinical Oncology Research Foundation. This study is based in part on data from the National Health Insurance Research Database, provided by the Bureau of National Health Insurance, Ministry of Health and Welfare, managed by National Health Research Institutes, Taiwan. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Ministry of Health and Welfare or National Health Research Institutes, Taiwan. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.10.029

Methods

Since March 1, 1995, Taiwan implemented a single-payer mandatory national health insurance to provide comprehensive medical care coverage, which covers more than 99% of the Taiwanese population of 23 million.[10] This study included data from the Registry for Catastrophic Illness Patients (RCIP) and data from the NHIRD, which is a database of all registry and claims data including patients' demographic characteristics, diagnoses, and prescription claims data in ambulatory and inpatient care. All the diseases coded in the NHIRD are based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), 2001 edition. The RCIP is a separate National Health Insurance database that includes patients with severe diseases such as cancer and autism. The "catastrophic illnesses" are a set of diseases defined by the Taiwan government, and patients with catastrophic illness certificate get free health care for their illness or related conditions. The regulations about application for a catastrophic illness certificate of autism are strict including sufficient medical records of autism for 1 year and the process of independent peer reviews. Therefore, the diagnoses from the RCIP database are even more convincing, compared with the use of clinical diagnosis only. To protect patients' confidentiality, information that could be used to identify beneficiaries and medical care providers was scrambled in NHIRD. Our dataset only contained unidentifiable secondary data for research purposes, so this study is exempt from full review by the institutional review board of Taipei Veterans General Hospital (2013-10-002CE).

We conducted a retrospective cohort study by including all individuals who were enrolled from January 1, 1997 to December 31, 2011. A total of 10 249 patients diagnosed with ASD (ICD-9-CM code: 299.0, 299.00, and 299.01) were retrieved from the RCIP database. According to the regulations about application for a catastrophic illness certificate of autism, only participants with autistic disorder were included, but not Asperger disorder or pervasive developmental disorder not otherwise specified. Exclusion criteria included age of enrollment older than 20 years in the RCIP database (n = 1546); presence of antecedent cancer (n = 8); comorbidity with other major psychiatric disorders (n = 103), such as schizophrenia (295), episodic mood disorders (296), and organic problems (294); and those lost to follow-up within 1 year of enrollment (n = 154). Finally, a total of 8438 patients with autism were enrolled as the study cohort (**Figure**; available at www.jpeds.com).

The diagnosis of all the cancers was also based on the RCIP database. Application for a catastrophic illness certificate for cancer requires histologic confirmation, with or without associated laboratory and imaging studies provided for peer review. Any of the diagnoses of cancer is recognized according to ICD-9-CM codes 140-208. Eleven groups of cancer were evaluated: hematologic malignancies, cancer of central nervous system, eye cancer, head and neck cancer, bone and soft tissue cancer, genitourinary cancer, breast cancer, digestive cancer, lung and mediastinum cancer, skin cancer, and thyroid cancer (**Table I**).

Statistical Analyses

The main dependent variable was occurrence of incident cancer, the first diagnosis of 1 kind of cancer. The patients with autism were followed until the development of cancer (the first time of diagnosis of a particular cancer based on National Health Insurance record), death, dropout from the national health insurance program, or the end of the year 2011.

The risk of cancer among the autism cohort was determined based on the standardized incidence ratio (SIR), which is defined as the observed number of cancer occurrences divided by the expected number. The expected number of cancers was calculated by multiplying the national cancer incidence rate specific for sex, calendar year, and age in a 5-year interval by the corresponding stratum-specific person-time accrued in the cohort. The incidence rates of cancers among the general population were derived from the Taiwan National Cancer Registry.[10] The 95% CIs of SIRs were calculated on the assumption that the observed number of cancers followed a Poisson probability distribution. We computed the SIRs for 12 subgroups based on the stratification of sex and 6 age groups (ie, 0-4, 5-9, 10-14, 15-19, 20-24, >25 years old; **Table I**). A P value of less than .05 level, calculated based on the Poisson regression analysis, was used to indicate statistical significance. All statistical analyses were performed with the SPSS statistical software v 17.0 for Windows (SPSS, Inc, Chicago, Illinois).

Results

A total of 8438 patients with autism were identified according to the inclusion and exclusion criteria, and 82.1% of them were male (**Table II**). Overall, the cohort was observed for 76 332 person-years from 1997-2011. The median age of enrollment in the RCIP database was 5.3 years old. The median follow-up period was 9.13 years (**Table II**).

Characteristics of Patients with Autism and Cancer

During the observation period, 20 patients with autism developed cancers, whose information about the age of cancer diagnosis, cancer type, and psychiatric comorbidities of intellectual disabilities and epilepsy are presented in **Table III**.

Overall Cancer Risk

The number of patients with autism who developed cancer (n = 20) was significantly higher than a total number of expected cancers (n = 10.31) in the general population with a SIR estimate of 1.94 (95% CI 1.18-2.99; P = .01) (**Table I**). Stratification according to sex and age of cancer diagnosis showed that this excess risk was largely conferred by males and by the age group of 15-19 years old. The number of cancer in males was significantly greater than the expected number with a SIR of 1.95 (95% CI 1.11-3.16; P = .021),

Table I. SIRs according to sex and age at diagnosis of cancer, and specific cancer type

Characteristics	Total			M			F		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	20	10.31	1.94 (1.18-2.99)†	16	8.21	1.95 (1.11-3.16)*	4	2.10	1.91 (0.52-4.88)
Age (y)									
0-4	1	0.91	1.09 (0.03-6.10)	1	0.8	1.25 (0.03-6.97)	0	0.11	0 (0-32.49)
5-9	3	2.31	1.30 (0.27-3.80)	3	2.01	1.49 (0.31-4.36)	0	0.3	0 (0-12.34)
10-14	4	2.16	1.86 (0.51-4.75)	3	1.82	1.65 (0.34-4.82)	1	0.34	2.96 (0.07-16.48)
15-19	7	1.95	3.58 (1.44-7.38)†	5	1.59	3.15 (1.02-7.36)*	2	0.37	5.45 (0.66-19.69)
20-24	3	1.61	1.86 (0.38-5.43)	2	1.15	1.73 (0.21-6.26)	1	0.46	2.17 (0.06-12.10)
>25	2	1.37	1.46 (0.18-5.28)	2	0.85	2.36 (0.29-8.53)	0	0.52	0 (0-7.07)
Hematologic	6	3.87	1.55 (0.57-3.37)	5	3.32	1.51 (0.49-3.52)	1	0.55	1.81 (0.05-10.07)
Leukemia	5	2.44	2.05 (0.67-4.79)	4	2.09	1.91 (0.52-4.89)	1	0.34	2.90 (0.07-16.16)
Lymphoma	1	1.42	0.71 (0.02-3.93)	1	1.21	0.83 (0.02-4.61)	0	0.21	0 (0-17.71)
CNS	3	1.70	1.77 (0.36-5.17)	3	1.46	2.05 (0.42-6.00)	0	0.23	0 (0-15.80)
Eye	1	0.11	9.44 (0.24-52.59)	1	0.09	10.61 (0.27-59.13)	0	0.01	0 (0-315.08)
Head and neck	1	0.57	1.77 (0.04-9.85)	0	0.48	0 (0-7.75)	1	0.09	11.17 (0.28-62.26)
Bone and Soft tissue	2	0.96	2.09 (0.25-7.56)	2	0.79	2.52 (0.31-9.12)	0	0.16	0 (0-22.55)
Genitourinary	4	0.96	4.16 (1.13-10.65)*	0	0.19	0 (0-19.43)	2	0.31	6.38 (0.77-23.06)
Cervix	0	0.03	0 (0-120.93)	-	-	-	0	0.03	0 (0-120.93)
Uterus	0	0.03	0 (0-108.33)	-	-	-	0	0.03	0 (0-108.33)
Ovary	2	0.22	9.22 (1.12-33.29)*	-	-	-	2	0.22	9.22 (1.12-33.29)
Testis	2	0.46	4.33 (0.52-15.65)	2	0.46	4.33 (0.52-15.65)	-	-	-
Bladder	0	0.05	0 (0-75.33)	0	0.04	0 (0-82.13)	0	0.00	0 (0-909.88)
Kidney	0	0.17	0 (0-21.72)	0	0.14	0 (0-25.95)	0	0.03	0 (0-133.13)
Breast	0	0.15	0 (0-23.89)	0	0.00	0 (0-1027.53)	0	0.15	0 (0-24.46)
Digestive	2	0.67	2.99 (0.36-10.8)	2	0.55	3.67 (0.44-13.25)	0	0.12	0 (0-29.76)
Esophagus	0	0.01	0 (0-574.55)	0	0.01	0 (0-585.79)	0	0.00	0 (0-29941.96)
Stomach	0	0.05	0 (0-69.27)	0	0.04	0 (0-95.17)	0	0.01	0 (0-254.55)
Colon and rectum	0	0.24	0 (0-15.59)	0	0.18	0 (0-20.20)	0	0.05	0 (0-68.36)
Liver and biliary tract	2	0.34	5.89 (0.71-21.27)	2	0.30	6.67 (0.81-24.09)	0	0.04	0 (0-92.84)
Pancreas	0	0.03	0 (0-111.15)	0	0.02	0 (0-210.19)	0	0.02	0 (0-235.88)
Lung and mediastinum	1	0.22	4.53 (0.11-25.26)	1	0.19	5.15 (0.13-28.68)	0	0.03	0 (0-140.17)
Skin	0	0.13	0 (0-27.36)	0	0.10	0 (0-36.38)	0	0.03	0 (0-110.32)
Thyroid	0	0.56	0 (0-6.55)	0	0.23	0 (0-16.33)	0	0.34	0 (0-10.93)

CNS, central nervous system; *F*, female; *M*, male.
*$P < .05$.
†$P < .01$.

but no excess risk was found for females with a SIR of 1.91 (0.52-4.88). Cancer developed significantly more than expected in individuals aged 15-19 years with a SIR of 3.58 (95% CI 1.44-7.38; $P = .008$), but did not differ significantly in other age groups.

Cancer Risk According to Cancer Type

The number of cancers of genitourinary system in this study cohort was significantly in excess of the expected number (4 observed vs 0.96 expected; SIR 4.15; 95% CI 1.13-10.65; $P = .034$), with 2 cases of ovarian cancer and 2 cases of testis cancer (Table I). Significantly increased risk of specific cancer type was found only for ovarian cancer (2 observed vs 0.22 expected; SIR 9.21; 95% CI 1.12-33.29; $P = .041$). There were no statistically significant risk increase in leukemia, lymphoma, retinoblastoma, or cancers of breast, lung, mediastinum, skin, thyroid, central nervous system, and digestive system in patients with autism compared with the general population.

Discussion

This 15-year cohort study provided a population-based sample to investigate the risk of cancers in patients with well-characterized autism. Only patients who had been clinically diagnosed with autism for more than 1 year were eligible to apply for the catastrophic illness certificate of autism. We found that individuals with autism had significant increase in the overall risk of cancer, especially in males and at the age range of 15-19 years; and that the significantly increased risk was found specifically for ovarian cancer.

Our finding of an increased risk of overall cancers in patients with autism, relative to the general population of the same age range and sex is novel. Our results are consistent with the work of Lauritsen et al reporting higher co-occurrence of malignant neoplasm of the brain in patients with autism, in which overall cancer incidence was not reported.[8] However, our results are consistent with a lack of significant increase in the prevalence of autism (n = 7) among pediatric patients with cancer (n = 702) reported by Blatt et al.[9] That study investigating the cross-sectional association between autism and cancer risk based on medical record review did not support an association between autism and childhood cancer.[9] However, patients whose medical records did not allow determination of neurodevelopmental status were excluded, so the incidence of autism may be underestimated. In addition, the small number of patients with cancer to examine the rate of autism among these patients may

Table II. Characteristics of patients with autistic disorder

	Total	M	F
Number of patients	8438	6931	1507
Person-years at risk	76 331.7	62 350.3	13 981.4
Median follow-up, y (IQR)	9.13 (5.99-12.38)	9.04 (5.91-12.33)	9.50 (6.27-12.52)
Median age, y (IQR)	5.30 (3.81-9.27)	5.18 (3.77-8.63)	5.98 (4.03-12.47)

partially explain the lack of statistical significance in the association between ASD and overall childhood cancer. With a much larger natural sample size and a prospective study design over a 15-year span, our results provide evidence to support that patients with autism may have an increased overall risk of cancer. Studies investigating the causes of death in individuals with autism[11] and ASD[12] also provided collateral evidence for our results. Shavelle et al have reported an elevated standardized mortality rate of cancer in individuals with autism as 1.9 in those who had no or mild intellectual disabilities and up to 2.9 in those who had moderate to profound intellectual disabilities, compared with the general population of the same sex and age.[11]

A meta-analysis and systematic review of cancer incidence showed that the presence of central nervous system disorders was associated with a reduced risk of cancer.[13] Although a lower risk of cancer was detected in patients with neurodegenerative disorders (effect size = 0.8), patients with Down syndrome had a higher risk of cancer (effect size = 1.46). Our finding of increasing cancer risk in autism is in line with that found in Down syndrome.[13] The pathogenesis involving neurodevelopmental process of autism and Down syndrome may relate to increased cancer risk. Therefore, future studies investigating the cancer risk in other neurodevelopmental disorders, such as developmental and intellectual delays and attention-deficit hyperactivity disorder, are warranted.

In the year 2007, the prevalence of autism in Taiwan has been reported to be 1.23% in general population, and 3.2 times more males than females are affected,[14] which are similar with other large-scale surveys in other countries.[15,16] The current study recruited predominantly male patients with autism with male to female ratio of 4.6. Although the SIR of overall cancer was similar in males and females (1.95 vs 1.91), the statistical significances of excess cancer risk presented only in the male patients. The results in female patients need to be tested by studies with a greater number of person-year observations. Similarly, the SIRs across all age groups were greater than 1, and an increasing trend of SIRs from 0-4 to 10-14 years old groups, peaked at the 15-19 years old group, followed by a decreasing trend. Although an excess cancer risk by age was shown only at the range of 15-19 years, this trend suggests that the increased SIRs in the age groups of 10-14-year-olds and 20-24-year-olds may not simply be due to a random chance. Cancer occurring in such a young age range is apparently a rare event. In spite of using Taiwan's national sample, cancer as a rare event in patients with autism may have limited power to reach statistical significance. It warrants a validation study in other countries with larger population.

Elevated fetal testosterone[17] and other steroidogenic activity[18] have been proposed to contribute to the development of ASD. More symptoms of hormone abnormalities (eg, irregular menstrual cycle, polycystic ovary syndrome, and severe acne) and family history of ovarian, uterine, and prostate cancers have been reported in women with ASD.[5] Until now, some cancers have been known to be potentiated or mediated by sex hormones, such as cancers of the breast,

Table III. Characteristics of patients with autistic disorder and cancer

Patient	Sex	Age of enrollment (y)	Cancer site	Age at cancer diagnosis	Age of death	Age of last follow-up	Comorbidities
1	M	8.09	AML	19.62	-	20.17	-
2	M	7.56	AML	16.64	-	24.31	Intellectual disability, epilepsy
3	F	17.09	AML	20.24	-	30.56	Epilepsy
4	M	2.61	ALL	10.22	-	16.80	Intellectual disability
5	M	2.95	ALL	6.09	-	18.94	Epilepsy
6	M	4.84	Lymphoma	19.49	-	21.07	-
7	M	2.66	CNS	7.63	11.19	-	Intellectual disability
8	M	2.82	CNS	7.69	-	10.93	Epilepsy
9	M	2.57	CNS	13.51	-	15.26	-
10	M	2.60	Eye	4.44	-	6.24	-
11	F	14.84	Salivary gland	18.66	-	21.12	Intellectual disability
12	M	15.47	Connective tissue	22.38	-	32.18	-
13	M	5.11	Bone	15.09	16.10	-	-
14	M	13.25	Testis	22.60	-	28.25	-
15	M	7.45	Testis	19.93	-	21.98	-
16	F	13.83	Ovary	15.67	18.60	-	Intellectual disability, epilepsy
17	F	3.34	Ovary	14.30	-	15.52	Intellectual disability
18	M	4.02	Liver	11.39	-	14.86	-
19	M	20.00	Liver	27.93	27.97	-	Intellectual disability
20	M	17.02	Mediastinum	31.28	-	31.62	-

ALL, acute lymphoblastic leukemia; *AML*, acute myelogenous leukemia.

ovary, uterus,[19] and testis.[20] Because increased sex steroid has been thought to be a shared etiology between ASD and sex steroid-related conditions,[21] sex hormones might also be the possible shared etiology between ASD and steroid-sensitive cancer. In line with previous reports, 2 of our findings provide evidence to support that testosterone and other sex hormones play a role in the development of ASD.[17,18,21] First, we found an excess cancer risk in age range of 15-19 years old. Second, our data also revealed a higher risk of ovarian cancer and an elevated SIR in testis cancer (though not reaching statistically significant). Puberty starts between ages 9-14 years with pulsatile release of luteinizing hormone and the follicle-stimulating hormone, which stimulate gonadal maturation and production of sex steroids, most notably testosterone in boys and estradiol in girls.[22] Most malignant tumors of the ovary and testis in pediatric patients are of germ cell origin, and sex steroids are assumed to be important for the rise and progression of germ cell cancer.[23] Even intrauterine hormonal exposure (ie, synthetic estrogen diethylstilbestrol) has been linked to risk of testicular cancer.[24] Therefore, our finding implies that patients with autism might have exposure to an abnormal level of sex hormones,[25] which may contribute to the pathogenesis of ASD and cancers in the gonadal system. However, such an assumption needs to be validated in future investigation.

Although the etiology of autism is still unclear, it is believed to be underpinned by genetic factors and gene-environment interactions which contribute to atypical neural development, a pattern of overgrowth in head circumference,[26] and increased cortical thickness, and reduced surface area of brain.[27] Among the potential common genetic variants in autism, several of the susceptibility loci in autism correspond to candidate oncogenes and tumor-suppressor genes.[6] In 2 studies of patients with ASD, the tumor suppressor gene, *PTEN*, had mutation in those with macrocephaly,[28] and individuals with germline mutations of *PTEN* have been reported to have increased age-adjusted SIR of cancer, namely breast cancer, endometrial cancer, thyroid cancer, colorectal cancer, kidney cancer, and melanoma.[29] Among the copy number variants identified in children with ASD by Gannon et al, 63% of the microdeletions or duplications at these candidate loci have been reported to be associated with cancer.[7] These findings also suggested that individuals with autism may be at an increased risk of cancer, relative to the general population.

In addition to common genetic variants with small effect as the etiology of autism,[7] around 10% of patients with autism have associated genetic syndromes such as tuberous sclerosis, which belongs to rare mutations with large effects.[30] The genetic deficits of tuberous sclerosis have been found to be associated with signal transduction to regulate cell growth and survival.[31] The etiology of tuberous sclerosis is mutations in either TSC1 or TSC2 genes. These are tumor-suppressor genes, and their gene products form a heterodimer, the TSC1-TSC2 complex, to regulate as the sensor and integrator of cell growth, and lead to the formation of hamartomas in multiple organs, including brain, kidney, skin, and lung.[32] Taken together, our results suggest that autism and cancer might have shared genetic variants related to the etiologies of autism and cancer as well.

Several limitations of this study need to be considered when interpreting the results. First, personal information such as body mass index, dietary habits, parental and maternal age, family history of autism and cancers, information of syndromic autism linked to identifiable genetic deficits, and the use of anti-epileptic medications were not available in our dataset. Therefore, we were not able to take these potential confounding and interacting factors into our statistical analyses. Second, the age of enrollment in patients with autism was below 20 years old with an average follow-up of 9.13 years, so our results cannot provide sufficient evidence in those cancers that are generally more prevalent in adults and elderly. Nevertheless, this study provides more reliable evidence in the risk of cancer from childhood to young adulthood. Research with a longer follow-up period is needed to demonstrate whether there is an increased cancer risk in adults with ASD. Third, the overall sample size of this study is relatively large, but there is still limited power to conduct subgroup analysis of SIR in most of the cancer types, age groups, and in females because cancer is a rare event in children, adolescents, and young adults with autism. The findings for female patients with autism are tentative given the small number of patients. Despite above-mentioned methodological limitations of this study, a novel topic, a national large-scale sample, a careful, strict, and comprehensive diagnostic procedure of ASD and cancer, and a prospective follow-up study design constitute the strengths of this study.

This nationwide population-based study provided the first direct evidence to support a temporal relationship of increased risks of cancer in patients with autism prospectively. Because of relatively short follow-up period (15 years) in comparison with long lifespan (60-80 years), our novel findings were limited only to the cancer occurring at childhood to young adulthood. Further investigations with a longer follow-up period, larger sample-sized study, different ethnic groups, and inclusion of potential risk factors, such as body mass index, dietary habits, infection, and lifestyle, are needed to clarify the association between autism and cancer. ■

We would like to thank Chung-Jen Teng, MD, for his assistance in statistical analysis.

Submitted for publication Jul 2, 2014; last revision received Sep 2, 2014; accepted Oct 13, 2014.

Reprint requests: Susan Shur-Fen Gau, MD, PhD, Department of Psychiatry, National Taiwan University Hospital and College of Medicine, No. 7, Chung-Shan South Rd, Taipei 10002, Taiwan. E-mail: gaushufe@ntu.edu.tw

References

1. Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet 2014;383:896-910.
2. Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, et al. Epilepsy in autism is associated with intellectual disability

and gender: evidence from a meta-analysis. Biol Psychiatry 2008;64:577-82.
3. Gorrindo P, Williams KC, Lee EB, Walker LS, McGrew SG, Levitt P. Gastrointestinal dysfunction in autism: parental report, clinical evaluation, and associated factors. Autism Res 2012;5:101-8.
4. Mostafa GA, Al-Ayadhi LY. The possible relationship between allergic manifestations and elevated serum levels of brain specific autoantibodies in autistic children. J Neuroimmunol 2013;261:77-81.
5. Ingudomnukul E, Baron-Cohen S, Wheelwright S, Knickmeyer R. Elevated rates of testosterone-related disorders in women with autism spectrum conditions. Horm Behav 2007;51:597-604.
6. Tabares-Seisdedos R, Rubenstein JL. Chromosome 8p as a potential hub for developmental neuropsychiatric disorders: implications for schizophrenia, autism and cancer. Mol Psychiatry 2009;14:563-89.
7. Gannon WT, Martinez JE, Anderson SJ, Swingle HM. Cancer and copy number variants in an autism diagnostic clinic. J Dev Behav Pediatr 2013;34:379-81.
8. Lauritsen MB, Mors O, Mortensen PB, Ewald H. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord 2002;32:115-9.
9. Blatt J, Deal AM, Mesibov G. Autism in children and adolescents with cancer. Pediatr Blood Cancer 2010;54:144-7.
10. Bureau of National Health Insurance Department of Health Executive Yuan Taiwan. Universal Health Coverage in Taiwan. National Health Insurance Administration, Ministry of Health and Welfare About NHI: NHI profile. http://www.nhi.gov.tw/Resource/webdata/21717_1_20120808UniversalHealthCoverage.pdf. Published 2012. Accessed April 13, 2014.
11. Shavelle RM, Strauss DJ, Pickett J. Causes of death in autism. J Autism Dev Disord 2001;31:569-76.
12. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder—epilepsy and mortality. Dev Med Child Neurol 2012;54:306-12.
13. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, Valderas JM, Gómez-Beneyto M, Martinez S, et al. Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 577 013 participants of 50 observational studies. Psychother Psychosom 2014;83:89-105.
14. Hsu SW, Chiang PH, Lin LP, Lin JD. Disparity in autism spectrum disorder prevalence among Taiwan National Health Insurance enrollees: age, gender and urbanization effects. Res Autism Spectr Disord 2012;6:836-41.
15. Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry 2011;168:904-12.
16. Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism-spectrum conditions: UK school-based population study. Br J Psychiatry 2009;194:500-9.
17. Baron-Cohen S, Lombardo MV, Auyeung B, Ashwin E, Chakrabarti B, Knickmeyer R. Why are autism spectrum conditions more prevalent in males? PLoS Biol 2011;9:e1001081.
18. Baron-Cohen S, Auyeung B, Norgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, et al. Elevated fetal steroidogenic activity in autism. Mol Psychiatry 2014; http://dx.doi.org/10.1038/mp.2014.48.
19. Henderson BE, Bernstein L, Ross RK. Hormones and the etiology of cancer. Chapter 13. Holland-Frei cancer medicine. 5th ed. Hamilton (ON): BC Decker; 2000.
20. Giannandrea F, Paoli D, Figa-Talamanca I, Lombardo F, Lenzi A, Gandini L. Effect of endogenous and exogenous hormones on testicular cancer: the epidemiological evidence. Int J Dev Biol 2013;57:255-63.
21. Pohl A, Cassidy S, Auyeung B, Baron-Cohen S. Uncovering steroidopathy in women with autism: a latent class analysis. Mol Autism 2014;5:27.
22. Veldhuis JD. Neuroendocrine mechanisms mediating awakening of the human gonadotropic axis in puberty. Pediatr Nephrol 1996;10:304-17.
23. Vastermark A, Giwercman YL, Hagstromer O, Rajpert De-Meyts E, Eberhard J, Ståhl O, et al. Polymorphic variation in the androgen receptor gene: association with risk of testicular germ cell cancer and metastatic disease. Eur J Cancer 2011;47:413-9.
24. Strohsnitter WC, Noller KL, Hoover RN, Robboy SJ, Palmer JR, Titus-Ernstoff L, et al. Cancer risk in men exposed in utero to diethylstilbestrol. J Natl Cancer Inst 2001;93:545-51.
25. Ruta L, Ingudomnukul E, Taylor K, Chakrabarti B, Baron-Cohen S. Increased serum androstenedione in adults with autism spectrum conditions. Psychoneuroendocrinology 2011;36:1154-63.
26. Mraz KD, Dixon J, Dumont-Mathieu T, Fein D. Accelerated head and body growth in infants later diagnosed with autism spectrum disorders: a comparative study of optimal outcome children. J Child Neurol 2009;24:833-45.
27. Ecker C, Ginestet C, Feng Y, Johnston P, Lombardo MV, Lai MC, et al. Brain surface anatomy in adults with autism: the relationship between surface area, cortical thickness, and autistic symptoms. JAMA Psychiatry 2013;70:59-70.
28. Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet 2005;42:318-21.
29. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18:400-7.
30. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. J Clin Psychiatry 2005;66(Suppl 10):3-8.
31. Crespi B. Autism and cancer risk. Autism Res 2011;4:302-10.
32. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355:1345-56.

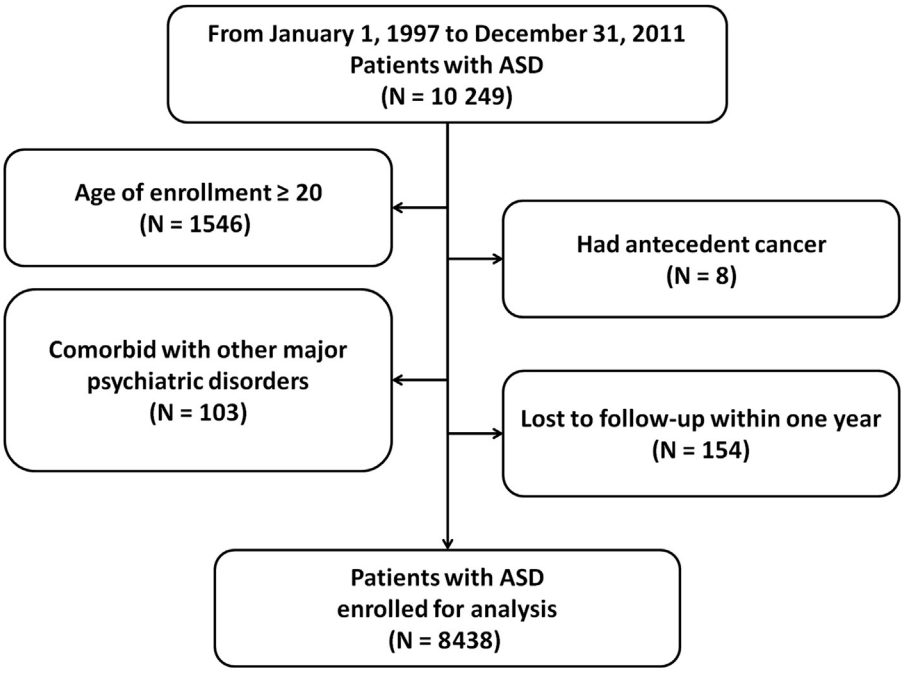

Figure. Flow chart for patient selection.