

## RESEARCH ARTICLE

# Reproductive Risk Factors for Thyroid Cancer: A Prospective Cohort Study in Khon Kaen, Thailand

Wararat Sungwalee<sup>1</sup>, Patravoot Vatanasapt<sup>2,4\*</sup>, Siriporn Kamsa-ard<sup>3</sup>, Krittika Suwanrungruang<sup>4</sup>, Supanee Promthet<sup>1</sup>

### Abstract

**Background:** Because of the gender disparity in the incidence of thyroid cancer, this study aimed to determine the association between reproductive factors and thyroid cancer. **Methods:** A total of 10,767 eligible women from the Khon Kaen Cohort, recruited and interviewed between 1990 and 2001, were followed up until 2011. The data were linked to the Khon Kaen Population-Based Cancer Registry to detect thyroid cancer cases. **Results:** There was 17 thyroid cancer cases detected, an incidence of 11.2 per 100,000 person-years, of which 70.6 % were papillary tumors. The incidence was apparently greater among those with an early age of menarche, nulligravida women, and oral contraceptive users. **Conclusions:** There was a trend for thyroid cancer to develop in relation to longer estrogen exposure. This evidence is inconclusive but warrants further investigation.

**Keywords:** Risk factors - reproductive factors - thyroid cancer - cohort study - Thailand

*Asian Pac J Cancer Prev*, 14 (9), 5153-5155

### Introduction

Thyroid cancer is the most common cancer of the endocrine glands. The global age-standardized incidence rate (ASR) is 3.9 in males, and 12.3 in females per 100,000 person-years (Sassolas et al., 2009). In Thailand, it is among the top ten leading cancers in females, with an ASR of 1.0 in males and 3.7 in females (Khuhaprema et al., 2012). Moreover, its incidence has been growing during the last three-decade around the world (Pellegriti et al., 2013). The reason for this increasing incidence is unclear but it has been suggested that it may be due to more frequent use of sensitive diagnostic tools, such as doppler ultrasonography and PET scans; or a genuine increase. In fact, it can well be due to a combination of both factors (Pellegriti et al., 2013).

The thyroid is a radiosensitive organ in a position potentially exposed to the radioactive substances in the environment. Thus, it is known that exposure to ionizing radiation, especially in childhood, increases the risk of developing thyroid cancer (Silverman, 1984; IARC, 2001; Zielinski et al., 2009; Furukawa et al., 2013) However, it is still not clear why thyroid cancer is markedly predominant in females. Previous observational studies on the reproductive system have produced conflicting results (Akslen et al., 1992; Pham et al., 2009; Horn-Ross et al., 2011; Kabat et al., 2012). We, therefore, investigated potential risk factors for thyroid cancer using data from

the Khon Kaen Cohort Study, with the main objective of determining the effect of reproductive factors on the occurrence of thyroid cancer.

### Materials and Methods

A prospective cohort study was conducted based on the Khon Kaen Cohort Study (KKCS). A total of 24,528 subjects were recruited between 1990 and 2001. The details of the cohort have been described in a previous publication (Sriamporn et al., 2005). The inclusion criteria for this study were females in the age group 30-69. The resulting number of subjects in the analysis was 10,767 subjects.

The data on determinants, mainly reproductive factors; i.e. the age of onset of the menarche, gravidity, oral contraceptive use, and major risk factors for head and neck cancer, i.e. tobacco smoking and alcohol drinking, were obtained by questionnaire interview during the cohort recruitment phase.

The cohort was followed up until December 31st, 2011 to detect the occurrence of thyroid cancer (ICD-O: C73). The 13-digit ID number was used to link the cohort to the Khon Kaen population-based cancer registry and double-checked with the subject's name, birth date, and address in questionable cases. The medical records of all detected cases were reviewed to confirm the diagnosis.

The incidence of thyroid cancer was calculated in

<sup>1</sup>Department of Epidemiology, <sup>3</sup>Department of Biostatistics and Demography, Faculty of Public Health, <sup>2</sup>Department of Otorhinolaryngology, <sup>4</sup>Cancer Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand \*For correspondence: patvat@kku.ac.th

relation to the person-time of the population at risk. This was also stratified by potential risk factors related to thyroid cancer.

**Results**

A total of 10,767 female subjects were included in the analysis, with a mean age of 50.3 years old (SD=8.7). There were 17 cases of thyroid cancer diagnosed during 152,508.41 person-years, giving an incidence of 11.2 per 100,000 person-years. The most common histopathology

was papillary carcinoma (12 cases, 70.6%), followed by follicular carcinoma (3 cases, 17.6%) and undifferentiated carcinoma (2 cases, 11.8%).

Thyroid cancer tended to occur in non-farmers with the higher incidence in the younger age group (Table 1). Although the incidence was high in the young, there was only one case found in a single female. The body mass index (BMI) between 18.5-22.9 was found to have the lowest incidence of thyroid cancer. Tobacco smoking and alcohol drinking slightly increased the risk of thyroid cancer, especially after excluding undifferentiated carcinoma.

For reproductive factors, the incidence of thyroid cancer was found to be apparently higher among those with an early age at menarche and nulligravida women (Table 2). Moreover, the incidence of thyroid cancer was lower in those with higher parity. No difference was found among different ages of first pregnancy. The incidence of well-differentiated thyroid carcinoma was also higher among oral contraceptive users, especially for those who had used the pill for five years or more.

**Table 1. Incidence of Thyroid Cancer and Harzard Ratio (HR) Across Different Factors**

Factors	Number of cases			Person-years	Incidence rate (per 100,000 person-year)		
	Pappillary	Follicular	Undiff		*undiff. excluded		
Age	30-44	4	1	0	45356.5	11.0	11.0
	45-50	4	0	0	38383.9	10.4	10.4
	51-57	3	1	1	36961.7	13.5	10.8
	58-69	1	1	1	31806.3	9.4	6.3
Occupation	Non-farmer	4	0	0	26512.5	15.1	15.1
	Farmer	8	3	2	125995.9	10.3	8.7
Household income (Baht/month)	≤1000	4	1	0	60236.1	8.3	8.3
	1001-3000	7	1	1	63674.9	14.1	12.6
	>3000	1	1	1	28597.5	21.0	7.0
Marital status	Single	1	0	0	3659.1	27.3	27.3
	Married	10	3	2	124108.2	12.1	10.5
	Separated	1	0	0	24741.1	4.0	4.0
BMI	<18.5	1	0	0	6996.4	14.3	14.3
	18.5-22.9	3	1	0	55603.1	7.2	7.2
	>23.0	8	2	2	89909.0	13.4	11.1
Smoking	Never	11	3	2	151103.4	10.6	9.3
	Ever	1	0	0	1405.0	71.2	71.2
Alcohol	Never	8	2	2	112779.8	10.6	8.9
	Ever	4	1	0	39728.6	12.6	12.6

**Discussion**

The incidence of thyroid cancer in this cohort was 11.2 per 100,000 with papillary carcinoma being the most common type found. The pattern of disease occurrence in this cohort is comparable to that from the population-based cancer registry of the same province (Khuhaprema et al., 2012). Unlike cancer of the upper aerodigestive tract in the same cohort, thyroid cancer tended to occur in relatively high socioeconomic status individuals (Kampangsri et al., 2013). As the number of cases of tobacco smokers and alcohol drinkers were limited, we could not make any conclusions about the relevance of these factors. The previous pooled analysis, nevertheless, showed that smoking associated with reducing the risk of thyroid cancer (Mack et al., 2003), due to its anti-estrogenic effect, and its tendency to lower TSH (Wiersinga, 2013).

**Table 2. Incidence of Thyroid Cancer in Relation to Reproductive Factors**

Factors	Number of cases			Person-years	Incidence rate (per 100,000 person-year)		
	Pappillary	Follicular	Undiff		*undiff. excluded		
Age at menarche	<14	3	0	0	5877.3	51.0	51.0
	≥14	9	3	2	146631.1	9.6	8.2
Pregnancy	Never	2	0	0	6916.3	28.9	28.9
	Ever	10	3	2	145592.1	10.3	8.9
Number of parity	1-3	7	0	0	52386.6	13.4	13.4
	≥4	3	3	2	66205.5	12.1	9.1
Age at first parity	<20	1	2	0	40951.9	7.3	7.3
	20-21	4	1	0	44905.2	11.1	11.1
	22-23	2	0	2	26715.7	15.0	7.5
	≥24	3	0	0	33012.4	9.1	9.1
OC.	Never	1	1	1	29495.1	10.2	6.8
	Ever	11	2	1	123013.4	11.4	10.6
Duration of OC.	<5 years	4	1	1	54859.6	10.9	9.1
	≥5 years	7	1	0	68153.7	11.7	11.7

Our study showed an apparently high incidence of thyroid cancer in those with an early age at menarche. Likewise, the previous study found a long reproductive period increased risk of papillary thyroid cancer (Akslen, 1992). However, the California Teacher Study showed later age of menarche was associated with an increased risk of thyroid cancer in young women, but not in the elderly (Horn-Ross et al., 2011). Those with less reproductive life (ie: never been pregnant or limited gravidity) were more likely to have thyroid cancer in our study. This reflects a trend of thyroid cancer to be associated with longer exposure to estrogen, agreeing with a previous study that revealed that estrogen significantly increased proliferation, migration and invasive properties in thyroid cancer cell lines (Rajoria et al., 2010).

We also found a higher incidence of thyroid cancer in oral contraceptive users with a dose-response relationship. However, the association between oral contraceptives and thyroid cancer requires further clarification, as the lower risk of thyroid cancer is related to a higher progesterone-to-estrogen ratio (Zivaljevic et al., 2003). In addition, the progesterone-to-estrogen ratio was different among

various populations, i.e. that in African Americans is higher than that in White Americans (Potischman et al., 2005). Exposure to high levels of estrogen, not progesterone, is likely to increase the risk of thyroid cancer. However, there was no conclusive evidence in relationship to the risk of any reproductive factor (Pham et al., 2009; Kabat et al., 2012).

This study is the first cohort study in Thailand to determine the incidence of thyroid cancer according to its risk factors with long term follow up. It was conducted in a province where a population-based cancer registry is well established. A few limitations, however, have to be addressed including: 1) the case number in the cohort is insufficient to use Cox's regression for analysis of the association, 2) thyroid cancer occurrence is likely to be under estimated, because of asymptomatic undiagnosed cases, due to the dormant nature of this cancer, 3) some data were collected at the initial assessment during the recruitment of the subjects in the cohort without follow-up information, resulting in potential misclassification.

In conclusion, this study showed a tendency for early menarche and low gravidity to be associated with an increased risk of thyroid cancer. It is still unclear how reproductive factors relate to thyroid cancer. Further research is needed to explain the greater incidence of thyroid cancer among females

## Acknowledgements

The authors would like to acknowledge the instructors for epidemiology program at the Faculty of Public Health, Khon Kaen University, for assistance on the research proposal development' the staff at Khon Kaen Cancer Registry for data management' and Prof. Robert Mills for English language editing of the manuscript. Finally, we would like to acknowledge Prof. Vanchai Vatanasapt for initiating the Khon Kaen Cohort Study.

## References

- Akslen L A, Nilssen S, Kvåle G. (1992). Reproductive factors and risk of thyroid cancer. A prospective study of 63,090 women from Norway. *Brit J Cancer*, **65**, 772-4.
- Furukawa K, Preston D, Funamoto S, et al (2013). Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. *Int J Cancer Journal international du cancer*, **132**, 1222-6.
- Horn-Ross PL, Canchola AJ, Ma H, Reynolds P, Bernstein L (2011). Hormonal factors and the risk of papillary thyroid cancer in the California Teachers Study cohort. *Cancer epidemiology, biomarkers and prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, **20**, 1751-9
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2001. Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides. Lyon: IARC Press. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 78.
- Kabat GC, Kim MY, Wactawski-Wende J, et al (2012). Smoking and alcohol consumption in relation to risk of thyroid cancer in postmenopausal women. *Cancer epidemiol*, **36**, 335-40.
- Kampangri W, Vatanasapt P, Kamsa-ard S, et al (2013). Betel Quid Chewing and Upeer Aerodigestive Tract Cancers: A

- Prospective Cohort Study in Khon Kaen, Thailand. *Asian Pac J Cancer Prevention*, **14**, 4335-8.
- Khuhaprema T, Attasara P, Sriplung H, et al (2012). Cancer in Thailand, *Bangkok: Ministry of Public Health*, **6**, 2004-6.
- Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R (2013). Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol*, 965212.
- Pham T-M, Fujino Y, Mikami H, et al (2009). Japan Collaborative Cohort Study Group. Reproductive and menstrual factors and thyroid cancer among Japanese women: the Japan Collaborative Cohort Study. *J Women's Health*, **18**, 331-5.
- Potischman N, Troisi R, Thadhani R, Hoover RN, Dodd K, Davis WW, Ballard-Barbash, R. (2005). Pregnancy hormone concentrations across ethnic groups: implications for later cancer risk. *Cancer Epidemiol Biomarkers Prev*, **14**, 1514-20.
- Sassolas G, Hafdi-Nejjari Z, Remontet L, et al (2009). Thyroid cancer: is the incidence rise abating? *Eur J Endocrinol*, **160**, 71-9.
- Silverman C (1984). Thyroid tumors associated with radiation exposure. *Public Health Rep*, **99**, 369-73.
- Sriamporn S, Parkin DM, Pisani P, et al (2005). A prospective study of diet, lifestyle, and genetic factors and the risk of cancer in Khon Kaen Province, northeast Thailand: description of the cohort. *Asian Pac J Cancer Prev: APJCP*, **6**, 295-303.
- Zielinski JM, Garner M J, Band PR, et al (2009). Health outcomes of low-dose ionizing radiation exposure among medical workers: a cohort study of the Canadian national dose registry of radiation workers. *Int J Occup Med Environ Health*, **22**, 149-56.
- Zivaljevic V, Vlajinac H, Jankovic R, et al (2003). Case-control study of female thyroid cancer--menstrual, reproductive and hormonal factors. *Eur J Cancer Prev (ECP)*, **12**, 63-6.