

7-1-2019

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Recommended Citation

S, Aseela Ms; R, Athirarani M. Ms; and Sasikala (2019) "Reproductive risk factors of thyroid cancer among females: A hospital based case control study," *Manipal Journal of Nursing and Health Sciences*: Vol. 5: Iss. 2, .

Available at: <https://impressions.manipal.edu/mjnhs/vol5/iss2/6>

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Reproductive risk factors of thyroid cancer among females: A hospital based case control study

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Abstract

Introduction: The most frequent endocrine malignancy seen in adults is thyroid cancer. The incidence of thyroid cancers are increasing all over the world. It is one of the cancers in women diagnosed at a younger age. The objective of the study was to identify reproductive risk factors of thyroid cancer among females. **Material and methods:** The research design used was a hospital-based-case-control study. The samples were 86 cases and 172 controls recruited from the surgical outpatient department of Medical college hospital, Thiruvananthapuram. Cases were patients who had undergone thyroidectomy and histopathological examination confirmed of thyroid cancer and controls were patients who had undergone thyroidectomy and histopathological examination confirmed of no thyroid cancer. An interview technique was used to assess socio-demographic factors and reproductive risk factors related to thyroid cancer. Socio-demographic variables were analyzed using frequency and percentage. The Pearson Chi-square test was used to find out the association between thyroid cancer and selected risk factors. The effect of different exposure variables on the outcome was assessed by logistic regression analysis. **Results:** Among the total of 258 females, 86 were cases and 172 were controls based on 1:2 for cases and controls. Regarding age, 51% of the samples were less than 40 years. The history of abortion and the achievement of menopause were identified as the risk factors for thyroid cancer. **Conclusion:** Reproductive risk factors like the history of abortion and the achievement of menopause were identified as significant risk factors of thyroid cancer. Age at menarche, menstrual irregularities, and duration of breastfeeding, number of deliveries, age at first pregnancy, age at last pregnancy and age at menopause were not related to the risk factors of thyroid cancer.

Key words: Case-control, reproductive risk factors, thyroid cancer, female, India

Introduction

According to Surveillance, Epidemiology, and End Results (SEER) stat fact sheets, in 2014, thyroid cancer incidences were 62,980 and it accounted for 3.8% of all the new cancer cases with the estimated deaths amounting to 1,890 (Lim, Devesa, Sosa, Check, & Kitahara, 2017). In India, the National Cancer Registry Program has reported thyroid as a leading site of cancer

accounting for 1.5% and 3.3% among men and women respectively (Xhaard et al., 2014). In the UK, in each year around 350 deaths occur annually among 3000 new diagnoses (Horn-Ross, Canchola, Ma, Reynolds, & Bernstein, 2011a).

There were approximately 3.2 times higher incidences of thyroid cancer in women than in men as per the International Agency of Research on Cancer (Sakoda & Horn-Ross, 2002) suggesting that the etiology of thyroid cancer may be related to female sex hormones and reproductive function. However, the results from epidemiological studies have been mixed. To assess this hypothesis, data on menstrual history, pregnancy history, and exogenous hormone use were analyzed from a population-based, case-control study conducted in the San Francisco Bay Area. Of 817 incident thyroid cancer patients (cases. A case-control study among

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Manuscript received: 10 March 2018

Revision accepted: 17 June 2019

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How to cite this article: Aseela. S., Athirarani. M.R., Sasikala (2019). Reproductive risk factors of thyroid cancer among females-A hospital based case control study. *Manipal Journal of Nursing and Health Sciences*, 5(2). 27-34.

Koreans found that females were associated with an increased risk of thyroid cancer with an odds ratio (OR) of 2.97. The incidence is approximately 4.5 times higher in women than in men. The explanation for this dissimilarity in incidences between men and women is unclear. Many studies showed that estrogen might be the cause of this difference in the incidence of thyroid cancer (A., M., & K., 2002a) we conducted a population-based case-control interview study among 238 women diagnosed with thyroid cancer and a similar number of individually matched controls in Kuwait. Among the demographic variables, women with 12+ years of education had a significantly reduced risk of thyroid cancer (OR = 0.4; 95% CI: 0.2-0.8; p-trend <0.05).

In India, among the endocrine disorders, thyroid disorders are reported among women as an important one. National Cancer Registry Program on thyroid cancer found 1.87% thyroid cancer and the male-female ratio of 1:2. Among all centres, the highest relative frequency of cases of thyroid cancer was found in Thiruvananthapuram (Zhou, Zhou, Qian, Gong, & Wang, 2015).

It is evident from many studies that estrogen and its receptors have a significant part in the development of thyroid cancer (Iribarren, Haselkorn, Tekawa, & Friedman, 2001; Navarro Silvera, Miller, & Rohan, 2005; Wong et al., 2006). A meta-analysis was carried for identifying the reproductive risk factors of thyroid cancer. Late age at menopause was found as an increased risk of thyroid cancer with RR of 1.39. Other factors like the use of oral contraceptives, HRT, age at menarche, parity, age at first birth, menopausal status and breastfeeding did not find a significant association (Horn-Ross, Canchola, Ma, Reynolds, & Bernstein, 2011b). A case-control study on menstrual and reproductive factors in thyroid cancer conducted in New Caledonia found that hysterectomy was related to thyroid cancer. Many case-control studies and cohort studies found that hysterectomies were associated with approximately twofold excess risk of thyroid cancer (Truong et al., 2005)(Luoto, Grenman, Salonen, & Pukkala, 2003) (Rossing, Voigt, Wicklund, & Daling, 2000; Negri et al., 1999) and hence menstrual

and reproductive factors, play a role in thyroid cancer etiology. Epidemiological data, however, are limited and inconsistent, partly because of the small number of cases included in each study. To clarify the etiology of thyroid cancer, we conducted a pooled analysis of original data from 14 case-control studies, 4 from the United States, 2 from Asia, and 8 from Europe. This analysis included a total of 2,247 female cases of thyroid cancer (80% papillary. Women who had a history of irregular menstruation and age less than 45 years had an odds ratio (OR) of 3.6 and those with age less than 35 years had an OR of 2.2 (Ravichandran, 2007) sex, ethnicity and geographic region was observed. In general, it occurs more frequently in women than men and a substantially higher rate was observed particularly during fertile period of women compared with men of the same age. Papillary carcinoma is the most prevalent histological type, irrespective of gender and conditions like iodine level. Over the years the incidence of thyroid cancer, especially papillary type, increases around the world. Ionizing radiation, in particular radiotherapy to head and neck region was the most established risk factor for thyroid cancer. Goiter, miscarriage or abortion (particularly in the first pregnancy. The number of pregnancies, age at menarche and menopause and attainment of menopausal status were not found associated with thyroid cancer in a case-control study from Kuwait (Memon, Darif, Al-Saleh, & Suresh, 2002) we conducted a population-based case-control interview study among 238 women diagnosed with thyroid cancer and a similar number of individually matched controls in Kuwait. Among the demographic variables, women with 12+ years of education had a significantly reduced risk of thyroid cancer (OR = 0.4; 95% CI: 0.2-0.8; p-trend <0.05. Pooled analysis of case-control studies found feeble associations between TC and menstrual factors (Horn-Ross et al., 2011a).

Systematic review and meta-analysis were carried out to identify the relationship between parity and thyroid cancer. The study showed that there was a significant association between pregnancy and the risk of thyroid cancer with an RR of 1.09 for multiple pregnancies. As the number of parity increases, risk also increases

showing a dose-response relationship (Zhu et al., 2016).

A cohort study among Norwegian women evaluated the association between pregnancy and thyroid cancer. As the number of pregnancies increases, the incidence of thyroid cancer also increases (Kravdal, Glattre, & Haldorsen, 1991; Takezaki et al., 1996) using individual data on all (1.1 million). The increase was greater in 4 or more pregnancies with RR of 6.3 (Preston-Martin, Bernstein, Pike, Maldonado, & Henderson, 1987). The objective of this study was to assess the reproductive risk factors of thyroid cancer among women who were diagnosed by histopathological reports among female patients who had undergone total thyroidectomy.

Methodology

This study used a quantitative approach with a case-control design. Since the latent period between exposure and appearance of the disease is long for a prospective cohort study, a very large number of samples have to be recruited and have to be followed up for a longer period which would take an unusually long time and also involve a lot of expense. For an outcome like thyroid cancer with multiple causes, case-control design can be considered as a better choice than cohort design. Moreover, these studies offer the opportunity to investigate multiple etiologic factors simultaneously. Thyroid cancer was the outcome variable. This was confirmed by histopathological examination report of participants obtained from the pathological lab of Medical college hospital, Thiruvananthapuram after total thyroidectomy. Exposure variables were assessed by a structured interview schedule. The exposure variables included: Reproductive factors-history of pregnancy, delivery, breastfeeding, abortion, age at the first and last pregnancies, age at menarche and menopause, menstrual irregularity and achievement of menopause were associated with risk of thyroid cancer. The setting of the study was the surgical outpatient department of Medical college hospital, Thiruvananthapuram. This is a tertiary care centre in the Government sector catering to patients predominantly from the Thiruvananthapuram district. It also caters to parts of Kollam and Pathanamthitta district as well as adjoining

districts of Tamil Nadu.

The populations of the study were all adult patients of ≥ 18 years who had undergone total thyroidectomy in Medical college hospital, Thiruvananthapuram.

Selection of cases

Cases were defined as adult patients of ≥ 18 years who had undergone total thyroidectomy in the medical college hospital, Thiruvananthapuram and their histopathological examination confirmed of thyroid cancer. Controls were defined as adult patients of ≥ 18 years who had undergone total thyroidectomy during the same periods like cases in the Medical college hospital, Thiruvananthapuram and histopathological examination confirmed with no thyroid cancer. Since the cases were taken from the hospital, it was a hospital-based case-control study. The participants who came for first follow up after total thyroidectomy (two weeks after total thyroidectomy) with histopathology report positive for thyroid cancer were selected from the surgical outpatient department of Medical college hospital, Thiruvananthapuram.

Selection of controls

The control in this study were adults of ≥ 18 years who had undergone total thyroidectomy during the same period in the Medical college hospital, Thiruvananthapuram and histopathological examination confirmed with no thyroid cancer.

Both cases and controls were taken from the surgical outpatient departments. Since thyroid cancer is a rare disease and case-control ratio is 1:2 after selecting two controls for each case, the investigator had to wait for the next case before selecting another control. Patients who were critically ill were excluded from the study.

Purposive sampling technique was used to select the sample. The sample size was calculated in the statistical software Epi info using the percentage of exposure in controls, odds ratio (OR), type 1 error, $Z\alpha$ at 95% and power $(1-\beta)$ at 80% and case-control ratio 1:2. Among the estimated sample, maximum samples were chosen.

Sample size was calculated based on the formula: $n=pq$

$(1+1/c) \times (Z\alpha + Z(1-\beta))^2 / (p_1 - p_0)^2$ Total sample size for this study were: Cases: control =1:2 i.e. Cases: 86 and controls 172. The study was carried out after taking approvals from the Institutional Research committee, Institutional Ethics committee and permission from Medical college hospital, Thiruvananthapuram. Written informed consent was taken from the participants.

Data collection process

Data were collected from 01 August 2016 to 01 August 2017. The participants who met the inclusion and exclusion criteria and who came for first follow up after total thyroidectomy were selected from the surgical outpatient department of Medical college hospital, Thiruvananthapuram. The purpose of the study was explained to each subject and informed consent was obtained. Cases and controls were selected based on histopathological examination reports. Cases were those whose histopathological examination reports were positive for thyroid cancer and controls were those whose histopathological examination reports were negative for thyroid cancer.

Data related to the socio-demographic factors and reproductive risk factors related to thyroid cancer were collected by a structured interview schedule for both cases and controls. The reproductive factors included in this study were the age at menarche, menstrual irregularity, history of pregnancy, delivery, breastfeeding, duration of breastfeeding, attainment of menopause and process of attainment of menopause were assessed. Socio-demographic variables were analyzed using frequency and percentage. The association between thyroid cancer and selected risk factors were identified by Pearson Chi-square test. Crude odds ratios and their confidence intervals were calculated for the associations. The effect of different exposure variables on the outcome was assessed by logistic regression analysis.

Results

Among 258 females, 86 were cases and 172 were controls based on 1:2 for cases and controls. Regarding the age of the participants, it was found that 51% were

Table 1:
Association of socio-demographic and reproductive factors of thyroid cancer

Sl No.	Variable	Reproductive factors		Chi square (P value)	OR	95% CI
		Control n (%)	Case n (%)			
1	Age at menarche					
	Normal menarche (12-14 years)	48 (18.6%)	23 (8.9%)	.142 (0.931)	1.00	
	Early menarche (10-11)	102 (39.5%)	53 (20.5%)		1.072	0.589-1.953
	Late menarche (15-16)	22 (8.5%)	10 (3.9%)		0.929	0.378-2.281
2	Menstrual irregularities					
	No	91 (35.3%)	26 (10.2%)	11.894 ^a (0.001)	1.00	
	Yes	81 (31.2%)	60 (23.4%)		2.593	1.497-4.489
3	No. of pregnancies					
	0	23 (8.5)	17 (6.6%)		1.00	
	<=3	143 (55.8%)	55 (21.3%)	16.851 ^a (0.001)	.494	0.244-1.00
	>3	6 (2.3%)	14 (5.4%)		3.020	0.959-9.506
4	No. of deliveries					
	No delivery	22 (8.5%)	17 (6.6%)	4.063 ^a (0.131)	1.00	
	1-3 deliveries	28 (10.9%)	19 (7.4%)		.878	0.372-2.076
	>3 deliveries	122 (47.3%)	50 (19.5%)		.539	0.264-1.101
5	Abortion					
	No	142 (55%)	50 (19.4%)	17.957 ^a (0.001)		
	Yes	30 (11.6%)	36 (14.0%)		3.408	1.904-6.099
6	No. of abortions					

Reproductive factors						
Sl No.	Variable	Control n (%)	Case n (%)	Chi square (P value)	OR	95% CI
	0	142 (55.0%)	50 (19.4%)	17.957 ^a	3.408	1.832-6.341
	1	25 (9.7%)	30 (11.6%)	(0.001)	3.408	0.996-11.657
	2	5 (1.9%)	6 (2.3%)			
6	Breastfeeding					
	Yes	150 (58.1%)	69 (26.7%)	2.175 ^a	1.00	
	No child, no breastfeeding	22 (8.5%)	17 (6.6%)	(0.151)	1.680	0.839-3.369
7	Duration of breastfeeding					
	>24 months	48 (18.6%)	14 (5.4%)	4.998 ^a	1.00	
	12-24 months	101 (39.1%)	55 (21.3%)	(0.082)	1.867	0.946-3.685
	No breastfeeding	23 (8.9%)	17 (6.6%)		2.534	1.068-6.016
8	Attainment of menopause					
	Yes	83 (32.2%)	19 (7.4%)	16.417 ^a	1.00	
	No	89 (34.5%)	67 (26.0%)	(0.001)	3.289	1.822-5.937
9	Process of attainment of menopause					
	Naturally	62 (24.0%)	12 (4.7%)	16.589	1.00	
	Artificially	20 (7.8%)	7 (2.7%)	(0.0001)	1.808	0.627-5.218
	Not achieved	90 (34.8%)	67 (26.0%)		3.846	1.921-7.702

Univariate analysis showed that menstrual irregularities, history of abortion, duration of breastfeeding and not attained menopause were risk factors of thyroid cancer.

Table 2:

Logistic regression of significant variables

Variables	B	S. E.	Wald	df	Sig.	Exp (B)	95% C.I.
Menstrual irregularities	0.505	0.317	2.536	1	0.111	1.657	0.890-3.085
No. of pregnancies>3	0.968	0.715	1.833	1	0.176	2.632	0.648-10.686
Not attained menopause	1.123	0.346	10.534	1	0.001*	3.075	1.560-6.060
Abortion	1.030	0.355	8.406	1	0.004*	2.801	1.396-5.619

Abbreviations: C.I.= Confidence Interval; *P<0.01

aged less than 40 years. Univariate analysis showed menstrual irregularities, history of abortion, duration of breastfeeding, and attainment of menopause had a significant association with thyroid cancer. Multivariate analysis showed that attained menopause and abortion were not associated with reproductive risk factors of thyroid cancer.

Multivariate analysis was carried out to find out the effect of different exposure variables on the outcome. Not attained menopause and abortion were associated with reproductive risk factors of thyroid cancer. Multivariate analysis showed that not attained menopause and abortion were reproductive risk factors associated with thyroid cancer. (Table 2)

Discussion

In this study, reproductive risk factors were collected from 258 participants. The study found that menopausal status was significantly associated with thyroid cancer. Those who had not attained menopause had 3.08 times (OR 3.08; 95% CI 1.56-6.06) higher risk for thyroid cancer than those who attained menopause. Those who had a history of abortion had 2.8 times (OR 2.8; 95% CI 1.396-5.619) higher risk for thyroid cancer than those who had no history of abortion. Early and late age at menarche, menstrual irregularities and duration of breastfeeding did not find the association with thyroid cancer. These findings were congruent with other studies. All the participants did not use contraceptive pills.

Most of the studies reported no significant associations between age at menarche and thyroid cancer risk (Xhaard et al., 2014; Horn-Ross et al., 2011a; Zhou et al., 2015). A pooled analysis of thyroid cancer case-control studies showed the OR per year of later menarche was 1.04 (95% CI 1.0-1.1). The study conducted among women of the San Francisco Bay area reported that either early or late age at menarche was at about 50% increased risk for papillary thyroid cancer (Sakoda & Horn-Ross, 2002) suggesting that the etiology of thyroid cancer may be related to female sex hormones and reproductive function. However, the results from epidemiological studies have been mixed. To assess this hypothesis, data on menstrual history, pregnancy history, and exogenous hormone use were analyzed from a population-based, case-control study conducted in the San Francisco Bay Area. Of 817 incident thyroid cancer patients (cases). Asian women with later menarche were at increased risk of papillary thyroid cancer, whereas among white women, early age conferred some elevation in risk (Takezaki et al., 1996) we conducted a hospital-based case-referent study at Aichi Cancer Center Hospital (ACCH).

A history of irregular menstrual cycles has been reported to confer a higher risk of thyroid cancer. Age at menopause and type of menopause failed to find consistent associations (Sakoda & Horn-Ross, 2002) suggesting that the etiology of thyroid cancer may be related to female sex hormones and reproductive function. However, the results from epidemiological studies have been mixed. To assess this hypothesis, data on menstrual history, pregnancy history, and exogenous hormone use were analyzed from a population-based, case-control study conducted in the San Francisco Bay Area. Of 817 incident thyroid cancer patients (cases (Memon, et al., 2002) we conducted a population-based case-control interview study among 238 women diagnosed with thyroid cancer and a similar number of individually matched controls in Kuwait. Among the demographic variables, women with 12+ years of education had a significantly reduced risk of thyroid cancer (OR = 0.4; 95% CI: 0.2-0.8; p-trend <0.05. Compared to pre-menopausal women, the OR was 1.3 for women with natural menopause and 1.8 for

those with artificial menopause (Negri et al., 1999) and hence menstrual and reproductive factors, play a role in thyroid cancer etiology. Epidemiological data, however, are limited and inconsistent, partly because of the small number of cases included in each study. To clarify the etiology of thyroid cancer, we conducted a pooled analysis of original data from 14 case-control studies, 4 from the United States, 2 from Asia, and 8 from Europe. **METHODS** This analysis included a total of 2,247 female cases of thyroid cancer (80% papillary(116). A case-control study from Kuwait found that events such as age at menarche, pregnancy, menopausal status and age at menopause were not associated with thyroid cancer (Memon, et al., 2002) we conducted a population-based case-control interview study among 238 women diagnosed with thyroid cancer and a similar number of individually matched controls in Kuwait. Among the demographic variables, women with 12+ years of education had a significantly reduced risk of thyroid cancer (OR = 0.4; 95% CI: 0.2-0.8; p-trend <0.05.

In a nested case-control study among Swedish women, a weak association between parity and risk of thyroid cancer (OR 1.1, 95% CI 1.0–1.3) was found (Negri et al., 1999) and hence menstrual and reproductive factors, play a role in thyroid cancer etiology. In a cohort study conducted in Europe, no significant associations were observed between thyroid cancer risk and the number of pregnancies, breastfeeding, menopausal status, and age at menarche and at menopause (Zhou et al., 2015).

Conclusion

The findings of this study suggest that menstrual irregularities, history of abortion, duration of breastfeeding and not attained menopause were risk factors of thyroid cancer. However, these findings should be studied as larger epidemiological studies or prospective studies to generate evidence. This research is limited to the study of reproductive risk factors. Identification of risk factors related to thyroid cancer help in planning an appropriate intervention to prevent thyroid cancer.

Source of support: None

Conflict of interest: None declared

Source of support in the form of grants: None

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