



## Journal of Umm Al-Qura University for Medical Sciences

Journal homepage: <https://uqu.edu.sa/en/mj>

### Association of menstrual and reproductive factors with thyroid cancer in Saudi female patients

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#### ARTICLE INFO

##### Article History:

Submission date: 18/03/2021

Accepted date: 24/06/2021

##### Keywords:

Menstrual factors, Reproductive factors, Saudi female, Thyroid cancer.

#### ABSTRACT

**Introduction:** Thyroid cancer ranks the second highest cause of cancer among women in Saudi Arabia. Several risk factors have been reported as determinants of the onset of thyroid cancer. However, an association of menstrual and reproductive factors with thyroid cancer has not been completely explored in Saudi female patients with thyroid carcinoma.

**Objective:** This study was designed to investigate an association of menstrual and reproductive factors with thyroid cancer in Saudi female patients.

**Methods:** This is a case control study performed in Qassim University affiliated hospitals. The 90 Saudi females with thyroid cancer and 178 normal human controls of the same age groups were included. All participants were requested to complete a questionnaire based on their menstrual and reproductive history.

**Results:** The analysis showed no statistically significant association between variables of mean age of menarche, current status of menopause, pattern of menstrual cycles, mean duration of menstrual cycle, mean age at first pregnancy, mean number of pregnancies, mean number of deliveries, mean number of live births, family planning methods used (intrauterine devices, used injectable and used oral contraceptives) and thyroid cancer.

**Conclusions:** This is the first comprehensive study, to the best of our knowledge, from Qassim region of Saudi Arabia that demonstrates that menstrual and reproductive factors, have no significant association with the onset of thyroid cancer in Saudi females.

#### 1. Introduction

The prevalence of patients with thyroid cancer continues to rise and has now been reported to occur in about 2% of the world population. Its exponential growth has been reported in China, United States, and in several European nations [1,2]. The Cancer Incidence database in Five Continents revealed a worldwide increase in the incidence rates of thyroid cancer between 1960 and 2007 [3]. The incidence of thyroid cancer is higher among women, with a consistent female to male ratio of 3:1 [4]. Hussein et al (2013) observed that thyroid cancer increased exponentially between the years 2000 and 2010 with marked variation in the rates in respect to sex and geographic locality [5]. The incidence of thyroid cancer varies across countries and the differences are most likely due to ethnicity, environmental factors such as endemic background radiation and dietary habits [6]. Contradictory findings were reported in respect to reproductive factors and an excess risk of thyroid cancer. An association with irregular menstrual cycle, high parity and miscarriage and thyroid cancer was reported by Truong et al (2005) [7], whereas Akslen *et al.* did not observe a significant association between thyroid cancer and the reproductive variables of parity and age at first birth [8]. A meta-analysis of seventeen epidemiology studies reported a weak and equivocal association between risk factors associated with the hormonal status, menstrual cycle and thyroid cancer [9]. Another meta-analysis study based on twenty-five epidemiological studies found insignificant associations between the risk of onset of thyroid cancer with common hormonal abnormalities [10]. This study was undertaken to investigate an association of menstrual and reproductive factors with the onset of thyroid cancer in Saudi female patients. To the best of our knowledge, this is the first comprehensive study from Qassim that has examined

any relationship between menstrual or reproductive factors and the occurrence of thyroid cancer in Saudi females. Our findings demonstrated that the menstrual and reproductive factors have no significant association with the onset of thyroid cancer in Saudi females.

#### 2. Materials and Methods

This a case control study performed in Qassim University affiliated hospitals and also hospitals Qassim region of Saudi Arabia. The ninety female with thyroid cancer were included in the present study after their thorough clinical examination based on the histology of their cancer lesions. The inclusion and exclusion criteria of the patients selection were: only females patients with thyroid were selected; All females above 20 years of age were included; Patients with multiple disorders were excluded; Patients from other regions of Qassim province were also excluded. All patients were directly selected from their respective cancer clinics. Normal human healthy controls (n=178) of the same age groups were also included in the study. Ethical approval of this study was taken from the ethical committee of the University (Approval # QU19-2017). Written consents were also taken from all participants. The sample size has been computed using the Open Source Epidemiologic Statistics for Public Health (Open EPI, ver 3.5) considering a power of 80% and 95% level of confidence with a ratio of cases to controls of 1:2.

A previously well-established and validated questionnaire on menstrual and reproductive history of females was identified from the published literature [10]. All participated females were requested to complete this questionnaire which was administered during face-to-face interviews. The collected information from all patients and

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control participants were analyzed statistically by International Business Machines Corporation (IBM) SPSS version 21.0.

**3. Results**

Table 1 shows that the mean age of Saudi women who were suffering with thyroid cancer is 41.2 years and Saudi women who were disease free are 42.9 years. In table 2 the reproductive history of Saudi women and its association with thyroid cancer was assessed by comparing the responses between cases and controls, for the variables of mean age of menarche, current status of menopausal, pattern of menstrual cycle, mean duration of menstrual cycle, mean age at first pregnancy, mean number of pregnancies, mean number of deliveries, mean number of live births, used family planning method (intrauterine devices, injectable or oral contraceptives).

**Table.1:** Association between Socio-demographic characteristics of Saudi women and their Thyroid Cancer

Variables	Thyroid Cancer (n=90)		Controls (n=178)		Odds ratio(OR)	95% CI for OR	p value
	No.	%	No.	%			
Mean age (Mean±sd..)	41.2±12.4	--	42.9±10.7	--	1.01	0.99,1.03	>0.05
Marital status - Married	72	80.0	123	69.1	2.05	0.79,5.31	>0.05
Single	12	13.3	34	19.1	1.23	0.40,3.79	>0.05
Divorced & Widow	6	6.7	21	11.8	1.0(ref.)	--	>0.05

The analysis shows no statistically significant association between these variables thyroid cancer; that is, the distribution of responses for categorical variables are not significantly different between cases and controls. And the mean values of quantitative variables are not significantly different between cases and controls. The corresponding odds ratios are close to 1.0 which shows no association and its 95% confidence interval also indicates no statistically significant association as the intervals does include value of 1.0.

**Table 2:** Association between Reproductive History of Saudi Women and their Thyroid Cancer

Variables	Thyroid Cancer (n=90)		Controls (n=178)		Odds ratio (OR)	95% CI for OR	p value
	No.	%	No.	%			
Mean(sd) age of menarche	12.7(1.4)	--	13.1(1.5)	--	0.84	0.71,1.0	>0.05
Current status of menopausal - Pre-menopausal	65	72.2	3.31	73.6	0.93	.053,	>0.05
Post-menopausal	25	27.8	47	26.4	1.0(ref.)	--	
Pattern of menstrual cycle - Irregular	9	10.0	45	25.3	0.33	0.15,0.71	>0.05
- Regular	81	90.0	153	74.7	1.0(ref.)	--	
Mean (sd)duration of menstrual cycle	6.31(1.5)	--	6.65(2.8)	--	0.94	0.83,1.06	>0.05
Mean(sd) age at first pregnancy	21.6(4.2)	--	21.4(4.4)	--	1.01	0.94,1.08	>0.05
Mean (sd)number of pregnancies	7.1(3.2)	--	6.1(3.5)	--	1.08	0.99,1.18	>0.05
Mean(sd) number of deliveries	5.8(2.7)	--	5.1(3.0)	--	1.08	0.98,1.19	>0.05
Mean(sd) number of live births	5.7(2.7)	--	5.1(3.0)	--	1.08	0.98,1.19	>0.05
Used Family planning methods - Yes	55	61.1	96	53.9	0.74	0.44,1.25	>0.05
- No	35	38.9	82	46.1	1.0(ref.)	--	
Used Intrauterine devices - Yes	22	37.9	32	33.3	1.22	0.62,2.41	>0.05
- No	36	62.1	64	66.7	1.0(ref.)	--	
Used Injectable - Yes	2	3.4	8	8.3	.039	0.08,1.92	>0.05
- No	56	96.6	88	91.7	1.0(ref.)	--	
Used Oral contraceptives - Yes	53	91.4	87	89.7	1.22	0.39,3.76	>0.05
- No	5	8.6	10	10.3	1.0(ref.)	--	

**4. Discussion**

This case-control study shows no statistically significant association between the menstrual and reproductive history of Saudi women and thyroid cancer. The variables of the reproductive history include age of menarche, current status of menopause, pattern of menstrual cycle, duration of menstrual cycle, age at first pregnancy, number of pregnancies, number of deliveries, number of live births, used family planning methods (intrauterine devices, injectable and oral contraceptives). These findings on Saudi females with thyroid cancer are fully supported by the several other studies performed in females with other population of the world [11,12]. This finding is consistent with the report from a case-control study where they observe no association between thyroid cancer and reproductive factors [11,12]. The meta-analysis of 25 epidemiological studies performed by Cao et al [11] reported the absence of a significant association between the risk of thyroid cancer in relation to common hormonal factors including oral contraceptive and hormone replacement therapy. Furthermore, these studies are also supported by another well performed study by Galanti et al [12] performed on Northern Norway and Central Sweden female populations, again they reported similar observation that menstrual and reproductive factors such as number of live births, number of pregnancies, a history of incomplete pregnancies, or the use of oral contraceptives or hormonal replacement therapy have no clear association with thyroid cancer [12]. However, a study conducted by Sakoda and Horn-Ross on the San Francisco Bay Area reported an unclear picture of the relation of risk factor based on reproductive history and thyroid carcinogenesis [13]. In contract, there are several studies that have shown an association between reproductive history with thyroid cancer. As an example, an excess risk of thyroid cancer in association with irregular menstrual cycle, high parity and miscarriage was reported by Truong et al [7]. Furthermore, a cohort study conducted in California found, among women whose age at menarche was above 14 years, there was an associated increased risk of papillary thyroid cancer (RR=1.88, 95% CI: 1.13–3.13); the risk also was increased in younger women with long duration of menstrual cycle (>30 days) (RR=1.78, 95% CI: 1.01–3.14) [13]. A case-control study in the France has reported a significant association between thyroid cancer and increasing number of pregnancies, early age of menarche [15]. A case-control study in California, reported that the risk of thyroid cancer increased when the number of pregnancy increased to three pregnancies or more (RR=3) and the risk of thyroid cancer increased if a miscarriage was the outcome of the first pregnancy (RR=11.5) [16]. Importantly, combining the conclusions of these studies gave us a contradictory judgement with no clear outputs on the relation of menstrual or reproductive factors with thyroid carcinogenesis, therefore further studies on a larger scale is needed to clear the unsolved facts on this important relation. This study has few limitations, and the most obvious limitation is the lower sample size and the study was restricted to only one region of Saudi Arabia. Therefore, we recommend a large-scale study on thyroid cancer patients and the study should involve female patients from all regions over Saudi Arabia. In short, this study found no direct association of menstrual or reproductive factors with the risk of onset of thyroid cancer in Saudi females.

**5. Conclusion and Recommendation**

This is the first comprehensive study to the best for our knowledge from Qassim region of Saudi Arabia that reported the menstrual and reproductive factors were not significantly associated with the onset of thyroid cancer in Saudi females. Our findings fully support the literature, that it is unclear if menstrual and reproductive factors influence thyroid carcinogenesis, and these relationships warrant further investigation.

**Authors' contributions:** All authors involved in conceptualization, study design, searching of literature, and preparation of the manuscript. Both authors have read and approved the final article.

**Disclosure statement:** None

**Funding statement:** None

**Ethical Consideration:** Ethical clearance was obtained from the College of Medicine, Qassim University, KSA. Written consents were also obtained from all subjects participated.

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