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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Alcohol abuse as a risk factor for developing thyroid cancer

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SUMMARY

Introduction/Objective Alcohol abuse influence on developing thyroid cancer is controversial. While some studies consider it a protective factor, others deny any impact on thyroid cancer.
The objective of the paper was to establish a possible link between alcohol abuse and certain types of thyroid cancers.

Methods The retrospective study included 502 patients with thyroid cancer and a control group of 600 patients with benign forms of thyroid diseases (e.g. nodular, multinodular, and toxic nodular goiter). Thyroid cancer patients were divided into four groups: I – papillary, II – medullary, III – anaplastic, and IV – follicular carcinoma, and grouped by sex, age (< 30 years; > 30 years) and alcohol abuse, as defined by the World Health Organization.

Results Thyroid cancer patients were predominantly male of younger age. This distribution difference was statistically significant in groups I and II ($p < 0.001$). Of total 10 (0.9%) patients with chronic alcohol abuse, eight (1.6%) had thyroid cancer, while two (0.3%) belonged to the control group ($p < 0.001$). In thyroid cancer patients, chronic alcohol abuse was absent from groups III and IV. Distribution in groups I and II was six (1.6%) and two (2%), respectively ($p < 0.001$).

Conclusion Alcohol abuse deserves to be considered as a risk factor for papillary and medullary forms of thyroid cancer, while it does not stay the same for anaplastic and follicular thyroid cancers.

Keywords: thyroid cancer; papillary cancer; medullary cancer; anaplastic cancer; follicular cancer; alcohol abuse

INTRODUCTION

Apart from the social, mental, and behavioral disturbances, chronic alcohol abuse (CAA) causes and/or affects many serious somatic diseases, including cancer [1, 2]. Among the surgical patients, different drinking patterns may also affect specific features in the management of anesthesia, patient behavior, and different complications in the perioperative period [2, 3, 4].

Alcohol abuse was addressed as a possible cause or contributing factor for thyroid cancers and other non-cancerous thyroid diseases by many observational studies. The results of these studies are different, sometimes inconclusive, or even conflicting [5, 6]. Yet, the abundant evidence of the increasing incidence of thyroid cancers, attributed mainly to increased detection of papillary thyroid cancer, deserves a careful analysis of all possible risk factors, including CAA [7, 8].

We designed a retrospective, cross-sectional study to determine a possible influence of CAA on thyroid cancer incidence.

The objective of this study was to determine if CAA was a risk factor for thyroid cancer in general, as well as for different types of thyroid cancer (i.e. I – papillary, II – medullary, III – anaplastic, and IV – follicular carcinoma).

METHODS

A total of 1102 consecutive patients who underwent thyroid surgery at the Center for Endocrine Surgery, Clinical Center of Serbia, during three consecutive years were analyzed. The study group included 502 patients with different forms of thyroid cancer and the control group included 600 patients with benign or degenerative diseases of the thyroid gland. Thyroid cancer patients were divided according to histopathological findings into four groups: I – papillary carcinoma (380 patients, 75.7%), II – medullary carcinoma (102 patients, 20.3%), III – anaplastic carcinoma (10 patients, 2%), and IV – follicular carcinoma (10 patients, 2%). The control group consisted of patients with thyroid nodule (233 patients, 38.8%), multinodular goiter (337 patients, 56.2%), and toxic adenoma (30 patients, 5%) (Table 1). All patients with autoimmune thyroid diseases were excluded from the study.

Patients' records were used to collect demographic (age, sex) and clinical data (present and past diseases and surgeries) as well as socio-epidemiological questionary (exposures, habits, abuses) with a particular accent on CAA (type, dose, pattern), as defined by the World Health Organization [9]. For this study, CAA was

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defined at least as moderate alcohol intake and/or alcohol dependence. Accordingly, moderate alcohol intake implies daily consumption of 1–2 (women) or 3–4 (men) standard drinks. Standard drink implies 0.03 L of distilled beverage or 0.2 L of vine or 0.3 L of beer. Alcohol dependence is present if at least 3/7 criteria were present in the past year: craving, the irresistible need for alcohol; increased tolerance; loss of control; abstinence syndrome; use of the same or of related substances to relieve the withdrawal syndrome; progressive neglect of alternative pleasures (socializing, hobbies, sports, etc.) and specific drinking pattern.

All data were collected into an electronic database (IBM SPSS Statistics for Windows, Version 26.0; IBM Corp., Armonk, NY, USA) and presented in tables. Pearson's χ^2 test was used to compare the difference between categorical variables, and the p-value was set at < 0.05.

This study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade (decision No. 1575/7).

RESULTS

Papillary carcinoma was the most common form in thyroid cancer group (75.7%) while multinodular (56.2%) and nodular goiter (38.8%) made 95% of the control group pathologies (Table 1).

The mean age of patients was similar in the group with thyroid cancer (50.34 years) and the control group (50.88 years). Patients under the age of 30 were significantly more represented in the cancer than in the control group (13.3% *vs.* 6.8%, p < 0.001). The same is true for the male sex distribution (19.7% *vs.* 11.7%, p < 0.001) (Table 2).

Table 1. Distribution of patients by diseases

Disease	n (%)
Thyroid cancer group	
I – papillary cancer	380 (75.7)
II – medullary cancer	102 (20.3)
III – anaplastic cancer	10 (2)
IV – follicular cancer	10 (2)
Total	502 (100)
Control group	
Nodular goiter	233 (38.8)
Multinodular goiter	337 (56.2)
Toxic nodular goiter	30 (5)
Total	600 (100)

Table 2. Distribution of patients by age and sex

Characteristics	Thyroid cancer (n = 502) n (%)	Control group (n = 600) n (%)	p
Age			
≤ 30 years	67 (13.3)	41 (6.8)	< 0.001
> 30 years	435 (86.7)	559 (93.2)	n.s.
Sex			
Male	99 (19.7)	70 (11.7)	< 0.001
Female	403 (80.3)	530 (88.3)	n.s.

n.s. – non-significant

Group I (i.e. papillary carcinoma), compared with the control group, had significantly more patients under the age of 30 (14.5% *vs.* 6.8%, p = 0.000) and patients of male sex (18.7% *vs.* 11.7%, p = 0.002). Group II (i.e. medullary carcinoma) had no age difference but did show a significant male predominance, compared to control (26.5% *vs.* 11.7%, p = 0.000). All patients from group III (i.e. anaplastic carcinoma) were over the age of 30, but this fact provided no statistically significant difference to the control group (100% *vs.* 93.2%, p = 0.392). Group IV (i.e. follicular carcinoma) had no significant difference in age (p = 0.695) and sex (p = 0.251) distribution, compared with the control group, despite old age and female predominance (Table 3).

There was an overall significant difference in CAA distribution between the cancer and the control group (1.6%, 8/502 patients *vs.* 0.3%, 2/600 patients, p < 0.001). The presence of CAA was recorded only in groups I and II of thyroid cancer patients, with incidences significantly higher than the control group (1.6% and 2% *vs.* 0.3%, p = 0.034 and p = 0.044). There were no records of CAA in groups III and IV. The incidence in these groups was significantly lower than that of the control group (p = 0.001) (Table 4).

DISCUSSION

Almost 10% of men in Serbia had alcohol use disorders, compared to 2.1% of women [10]. Alcohol consumption is an attributable risk for 5.1% of all-cause deaths in our country [11]. There is epidemiological evidence that alcohol causes cancer at seven sites in the body (oropharynx, larynx, esophagus, liver, colon, rectum, and breast), although without exact and complete knowledge of underlying biological mechanisms [1]. Pandemic increase in thyroid cancer incidence over the past two decades resulted in significant efforts towards early detection and therapy, but also deeper analyses of possible toxic, environmental, and socio-economic causes [12].

Many studies, so far, have addressed alcohol abuse as a possible risk factor for thyroid cancer [6, 13, 14]. A recent and, so far, the most comprehensive meta-analysis of 33 observational studies which involved a total of 7725 thyroid cancer patients and 3,113,679 participants without cancer suggested that alcohol intake may decrease the risk of thyroid cancer. In a subgroup meta-analyses by geographic region, alcohol intake was associated with a decreased risk of thyroid cancer in the American, but not in the European or Asian regions [6]. Previous studies of risk factors for thyroid cancer published in Serbia also have not found any correlation with CAA [15, 16].

However, our study has shown that younger (under the age of 30 years) male patients with history of CAA were at a higher risk for overall and particularly for papillary (group I) and medullary (group II) forms of thyroid carcinoma, compared to the control group of non-cancerous thyroid patients.

Results of a study from South Korea, which has the highest incidence of thyroid cancers in the world, based on data collected from 12,276 individuals, among others, reveals CAA (OR: 1.89; 95% CI: 1.08–3.32) as a significant risk factor for thyroid cancer [14]. Data from the Thyroid

Table 3. Distribution of patients by age and sex according to the type of thyroid cancer

Parameter (p-value)	Control n = 600 n (%)	I – Papillary n = 380 n (%)	II – Medullary n = 102 n (%)	III – Anaplastic n = 10 n (%)	IV – Follicular n = 10 n (%)
Age					
≤30	41 (6.8)	55 (14.5)	11(10.8)	0 (0)	1 (10)
> 30	559 (93.2)	325 (85.5)	91 (89.2)	10 (100)	9 (90)
p		(0.000)	(0.159)	(0.392)	(0.695)
Sex					
Male	70 (11.7)	71 (18.7)	27 (26.5)	1 (10)	0 (0)
Female	530 (88.3)	309 (81.3)	75 (73.5)	9 (90)	10 (100)
p		(0.002)	(0.000)	(0.871)	(0.251)

Table 4. Alcohol abuse among thyroid cancer patients

Alcohol abuse	All cancers n = 502 n (%)	I – Papillary n = 380 n (%)	II – Medullary n = 102 n (%)	III – Anaplastic n = 10 n (%)	IV – Follicular n = 10 n (%)
Yes	8 (1.6)	6 (1.6)	2 (2)	0 (0)	0 (0)
No	494 (98.4)	374 (98.4)	100 (98)	10 (100)	10 (100)
p*	< 0.001	0.034	0.044	0.001	0.001

*Statistical significance was measured against the control group incidence of alcohol abuse;
bold – significantly higher incidence;
bold-italic – significantly lower incidence

Cancer Longitudinal Study on 2258 thyroid cancer patients and 22,580 healthy individuals showed that acute high-dose and chronic lifetime exposure (> 31 years) to alcohol are linked to an increased risk of developing thyroid cancer [13]. In addition to these findings, another study from the same country, comparing health behaviors of 942 thyroid cancer survivors with 9420 matched non-cancer controls, found that clustering of smoking, drinking, and physical inactivity is more often present in male thyroid cancer survivors [12].

Inconsistent reports from different studies of CAA and thyroid cancer are commonly based on a small number of patients with cancer involved (i.e. less than 500), restriction to certain patient sub-population (e.g. postmenopausal females), and failure to evaluate the effect modifiers (e.g. cigarette smoking, obesity, physical inactivity, etc.) [6, 12, 13, 14].

Rare studies have precisely defined thresholds of alcohol intake (i.e. amount, duration) in terms of thyroid cancer risk. Honnamurthy et al. [17] revealed a significant influence of alcohol consumption duration, but not alcohol dependence on thyroid function tests. Hwang et al. [13] report a reduction in thyroid cancer risk with decreased alcohol consumption (25 g or less) per event (i.e. mild to moderate consumption) and a drinking duration of less than 10 years, compared to never-drinkers. In contrast, acute heavy alcohol consumption (151 g or more per event), consumption of alcohol for 31 or more years, was associated with an increased risk for thyroid cancer in both men and women [13]. Our study has set the threshold of alcohol intake to moderate and higher levels, which may explain similar results in terms of a positive correlation between CAA and thyroid cancer.

The precise mechanism by which alcohol possibly induces thyroid oncogenicity remains unclear. It has not yet been firmly established whether the alcohol at certain blood levels and duration of exposure has a direct toxic effect on thyroid cells, but abnormal functioning of the hypothalamic–pituitary–thyroid axis has been observed in chronic alcoholics. Experimental data have shown that chronic ethanol exposure in rats elevated thyroid-releasing hormone messenger RNA in hypothalamic neurons. Whether this effect, in the long term, may produce hyperproliferation and/or cancerogenesis, remains unclear [18, 19, 20].

This study has several limitations. Being a retrospective cross-sectional study, its results necessitate further validation in a wider scope, prospective study, including a larger number of patients and variables to allow statistics that are more powerful.

CONCLUSION

The results of our study suggest that the CAA is positively correlated with the appearance of papillary and medullar forms of thyroid carcinoma, whereas in anaplastic and follicular forms this correlation was absent. Further prospective investigations are needed to confirm these findings.

Conflict of interest: None declared.

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Злоупотреба алкохола као фактор ризика за развој рака штитне жлезде

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САЖЕТАК

Увод/Циљ Утицај злоупотребе алкохола на развој рака штитне жлезде је контроверзан. Док неке студије то сматрају заштитним фактором, друге негирају икакав утицај на рак штитне жлезде.

Циљ рада је анализа могуће везе између хроничне злоупотребе алкохола и одређених врста рака штитне жлезде.

Методе Ретроспективна студија обухватила је 502 болесника оболела од рака штитне жлезде и контролну групу од 600 болесника са доброћудним облицима болести ове жлезде (нпр. нодуларна, мултинодуларна и токсична нодуларна струма). Оболели од рака штитне жлезде подељени су у четири групе: I – папиларни, II – медуларни, III – анапластични и IV – фоликуларни карцином и груписани по полу, узрасту (< 30 год.; > 30 год.) и злоупотреби алкохола, у складу са дефиницијом СЗО.

Резултати Оболели од рака штитне жлезде били су претежно мушкарци млађег узраста. Ова разлика у расподели је статистички значајна у групама I и II ($p < 0,001$). Од укупно 10 (0,9%) болесника са хроничном злоупотребом алкохола, 8 (1,6%) њих је имало рак штитне жлезде, док су 2 (0,3%) припадала контролној групи ($p < 0,001$). Код оболелих од рака штитне жлезде хронична злоупотреба алкохола није забележена у групама III и IV. Дистрибуција у групама I и II је била 6 (1,6%), односно 2 (2%) ($p < 0,001$).

Закључак Злоупотреба алкохола заслужује да буде размотрена као фактор ризика за папиларне и медуларне облике рака штитне жлезде, док то исто не важи за анапластични и фоликуларни рак штитне жлезде.

Кључне речи: рак штитњаче; папиларни рак; медуларни рак; анапластични рак; фоликуларни рак; злоупотреба алкохола