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Lifestyle as a risk factor for endocrine diseases: does gender matter? A cross-sectional study

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Summary. *Introduction.* Gender-related risk factors have not been sufficiently investigated in the endocrine setting. This study aimed to evaluate gender difference in the determinants of health and their impact on endocrine diseases. *Methods.* A one-year cross-sectional study, enrolling all patients referring for the first time to our Oncological Endocrinology Unit. We collected data on diseases and gender-related health determinants. *Results.* We enrolled 1,107 consecutive patients (mean age, 56.8 ± 15.0 years; 77% females). Women had a higher socio-cultural level and followed a healthier lifestyle: alcohol and tobacco consumption were lower in females, and women had lower BMI. BMI was a risk factor for endocrine cancer [OR = 1.07 (95% CI:1.02-1.12) p = 0.003], while physical activity was a protective factor [OR = 0.45 (95% CI: 0.24-0.84) p = 0.013]. A gender-stratified analysis demonstrated that a higher BMI was a risk factor in women and physical activity was a protective factor in men. Smoking and alcohol were not risk factors for endocrine malignancies, while tobacco consumption was a risk factor for non-endocrine cancers [OR = 1.29 (95% CI: 1.01-1.64) p = 0.041]. *Discussion.* Gender is a health determinant, able to affect lifestyle and habits. Physical activity and BMI seem to be additional risk factors for endocrine malignancies, with a different impact according to gender, which should be considered in lifestyle interventions and patients' global assessment.

Keywords. Gender, lifestyle, endocrine system diseases, social determinants of health, risk factors.

Introduction

Gender medicine deals with the biological, psychological and socio-cultural differences between men and women, which can affect health status and disease development.[1,2] Gender medicine therefore aims to achieve a 'healthy' condition by paying attention not only to the disease itself, but also to the 'determinants of health', starting from lifestyle aspects – such as alcohol, smoking, physical activity, nutrition and body weight[3] – that depend on individual choices, but are also affected by the socio-cultural and environmental context, and therefore by gender.[4] These factors contribute to determining the health of women and men, and have an impact on the incidence of many chronic conditions, such as cardiovascular diseases and neoplasms.[5] However, while smoking, alcohol consumption, lack of physical activity and overweight/obesity are well-known risk factors for many malignancies, their role in the endocrine malignant diseases has not been established.

In addition, although the most widespread endocrine diseases have marked sex differences in term of prevalence, due to hormonal variations,[6] the impact of gender on the determinants of health has not yet been sufficiently investigated in this field.

The goals of this study were to:

- assess the gender difference in health determinants, such as area of origin, educational level, distance from the hospital, habits and lifestyle, in patients affected by endocrine diseases;
- evaluate the association between lifestyle and endocrine diseases in both genders, with the aim to establish if these elements could be possible risk factors for the development of endocrine diseases and if they have a different impact in women and men.

Materials and methods

This is a cross-sectional study, conducted in our Oncological Endocrinology Unit between January and December 2019.

All patients (age >18) referring for the first evaluation in the study timeframe were considered potentially eligible.

The following parameters were assessed during the first visit: sex, age, residence (to calculate the distance from the hospital), ethnicity and nationality, level of education (grade 8 or lower: elementary school and middle school; grade 12 or higher: high school, degree or higher qualification), body mass index (BMI), smoking status (3 groups: smokers, non-smokers or former smokers), alcohol consumption (classified as 'yes' in case of at least 0.5 UI alcohol units per day, or 'no'), physical activity (no, yes-moderate or yes-intense), endocrine and oncological diseases.

Each patient's data was collected using a standardized data collection form.

The study was conducted under the approval of the local Ethics Committee (reference number: 1370/20) and in accordance with the Helsinki Declaration of 1975, as revised in 2008. All patients give their written informed consent to their participation in the study.

This study followed the STROBE guidelines for observational studies.

Statistical analysis

Variables of interest were expressed as frequencies and percentage values, while continuous variables were expressed as mean ± standard deviation. Patients were divided into subgroups, according to gender and age. Associations among variables were tested with non-parametric Chi-square test. Univariate logistic regression models were applied to estimate odds ratios (ORs) and their relative 95% confidence intervals (95% CI) for selected factors. The presence of endocrine malignancies was considered as a dependent variable. A multivariate logistic regression model, including only the significant variables at univariate analysis, was performed using stepwise regression (forward selection). Enter limit and remove limit were set at p = 0.05 and p = 0.10, respectively. A p-value <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS software (SPSS version 21, SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics and diseases prevalence

In the study timeframe (one year), a total of 1180 patients referred to our endocrine Center for the first examination; 73 patients were excluded from the study due to missing data or refusal to participate, therefore a total of 1,107 patients were enrolled in the study: 854 patients were females (77%) and 253 males (23%). Total mean age was 56.8 ± 15.0, with a statistically significant difference between gender (male: 60 ± 16.6 years, female 56 ± 14.3 years, p <0.001) (Table 1).

Patients of both genders referred to our Center mainly for thyroid and bone diseases; many of them were also suffering from other non-endocrine oncological diseases (Table 2).

In our population, the majority of patients were affected by benign thyroid diseases, without gender difference (p = 0.517). In a subgroup analysis, the proportion of iatrogenic thyroid disorders (induced by amiodarone, tyrosine kinase inhibitors - TKI, immune checkpoint inhibitors, neck radiotherapy) was higher in males (10.6% vs 1.4% in females, p <0.001), while no statistically significant gender difference was found in the proportion of patients with thyroid nodules (70% males, 69.9% females, p = 0.77). Consequently, females had a higher prevalence of the remaining thyroid diseases (hypothyroidism and hyperthyroidism, thyroiditis; p = 0.016).

There was a statistically significant difference in the proportion of females and males (36.1% and 10.7%, respectively; p <0.001) affected by bone diseases, predominantly cancer treatment-induced bone loss. Likewise, adrenal and metabolic disease rates were higher in females (p = 0.002 and p = 0.024, respectively), while no gender difference was found in the prevalence of pituitary diseases (p = 0.288).

Considering the malignancies, a higher proportion of males referred for neuroendocrine neoplasms (4.0% vs 0.7%, p <0.001) and thyroid cancers (7.9% vs 4.7%, p = 0.047).

Gender-related determinants of health

Considering the lifestyle parameters, no difference in physical activities was found between males and females (p = 0.854), and this data was also confirmed by dividing patients in two age groups (under and over 45). Despite this, men had a statistically significant higher BMI than women (27.8 ± 5.0 vs 26.1 ± 5.5 kg/m^2, p <0.001).

A higher proportion of males were smokers or former smokers vs females (p <0.001); accordingly, 58% of women had never smoked in their life, vs only 42% of males. Once the study population was divided in two groups according to age, in younger people there was no statistically significant difference in smoking habits regarding to sex, while in people older than 45 there was a statistically significant gender difference in the proportion of smokers (p <0.001). Alcohol consumption too was higher in males than in females (49.2 vs 33.0%, p <0.001). As for smoking, a difference in alcohol habits was found only in older patients (p <0.001).

Among the other gender-related health determinants, women had a higher level of education than men (p = 0.024).

Considering nationality, 4.7% of the enrolled patients had a nationality other than Italian, with a significant higher proportion of females (p = 0.008). In addition, non-Italian people had more frequently a degree or a higher qualification than Italian patients (39.1% vs 23%, p = 0.02).

In the overall population, 32.4% of patients lived far from the hospital (distance from home >30 km), and the willingness of travelling longer distances did not vary with gender.

Gender-related determinants of health are summarized in Table 1.

Gender-related determinants of health as risk factors for endocrine diseases

We assessed the possible associations between the aforementioned health determinants and the diseases.

Table 1. Patients' characteristics and determinants of health

		Males N. = 253 (23%)	Females N. = 854 (77%)	p value
Age	Mean ± sd	60.0 ± 16.6	56.0 ± 14.3	<0.001*
	Age ≤45years	50 (19.9%)	202 (23.7%)	0.209#
	Age >45 years	201 (80.1)	650 (73.6%)	
Ethnicity	Caucasian n. (%)	250 (98.8%)	839 (98.6%)	1.0#
	Other n. (%)	3 (1.2%)	12 (1.4%)	
Nationality	Italian	249 (98.4%)	806 (94.4%)	0.008*#
	Others	4 (1.6%)	48 (5.6%)	
Menopausal status	No	-	349 (40.9%)	-
	Yes	-	505 (59.1%)	
Level of education	Grade 8 or lower	86 (38.2%)	239 (30.3%)	0.024*#
	Grade 12 or higher	139 (61.8%)	551 (69.7%)	
Distance from the hospital	≤10 km	51 (20.2%)	189 (22.1%)	0.229#
	10-20 km	79 (31.2%)	223 (26.1%)	
	20-30 km	39 (15.4%)	169 (19.8%)	
	>30 km	84 (33.2%)	272 (31.9%)	
BMI	Mean ± sd	27.8 ± 5.0	26.1 ± 5.5	<0.001*
Smoking status	Non smokers	101 (40.2%)	492 (58.0%)	<0.001*#
	Smokers or ex-smokers	150 (59.8%)	356 (42.0%)	
Alcohol consumption	No	125 (50.8%)	559 (67.0%)	<0.001*#
	Yes	121 (49.2%)	275 (33.0%)	
Physical activity	No	139 (65.0%)	468 (63.8%)	0.854#
	Yes, moderate	69 (32.2%)	240 (32.7%)	
	Yes, intense	6 (2.8%)	26 (3.5%)	

*Statistically significant differences between groups, #chi-square test, sd: standard deviation.

Considering only patients affected by endocrine malignancies and comparing them to patients affected by benign endocrine diseases, without any other concomitant oncological disease, BMI was a risk factor for the development of endocrine cancer [OR = 1.07 (95% CI: 1.02-1.12) p = 0.003]; conversely, physical activity was a protective factor [OR = 0.45 (95% CI: 0.24-0.84) p = 0.013]. Smoking and alcohol were not risk factors for endocrine malignancies.

On the contrary, as expected, among people with any malignancies (both endocrine and non-endocrine), the proportion of smokers or former smokers was higher compared to the group without malignancies [OR = 1.29 (95% CI: 1.01-1.64) p = 0.041], while no difference in proportion was found regarding physical activity, alcohol consumption and BMI.

Gender-stratified analyses revealed that BMI was the only significant risk factor in female gender [OR = 1.08 (95% CI: 1.02-1.14) p = 0.05], while in males physical activity was a protective factor for endocrine malignancies [OR = 0.30 (95% CI: 0.10-0.90) p = 0.032].

An age-stratified analysis of risk factors which divided patients in two age groups (≤45 and >45) confirmed that BMI and physical activity were a risk and a protective factor, respectively, for the development of endocrine malignancies only in the group of older patients, even if the low number of malignancies (19) in the younger group could have affected this result.

Table 2. Diseases prevalence. This table takes in consideration all patients' diseases.

	Males N. = 253 (23%)	Females N. = 854 (77%)
Benign thyroid diseases	160 (63.2%)	559 (65.5%)
Thyroid cancers	20 (7.9%)	40 (4.7%)
Bone diseases*	27 (10.7%)	308 (36.1%)
Adrenal diseases	23 (9.1%)	35 (4.1%)
Pituitary diseases	9 (3.6%)	20 (2.3%)
Neuroendocrine neoplasms	10 (4.0%)	6 (0.7%)
Diabetes mellitus and metabolic diseases	27 (10.7%)	55 (6.4%)
Andrological diseases	9 (3.6%)	NA
Other	7 (2.8%)	19 (2.2%)
Oncological comorbidities	115 (45.5%)	474 (55.5%)

Values are expressed as number of patients (percentage). NA: not applicable. *Including cancer treatment-induced bone loss, post-menopausal osteoporosis and osteopenia, hyperparathyroidism and hypercalcemia.

Table 3. Odds ratios. This table shows the odds ratios for determinants of health for endocrine malignancies and for thyroid cancers in the overall population, or in the population stratified for gender. Control groups were endocrine benign diseases (without any other malignancies) and thyroid benign diseases, respectively.

	Overall		Females		Males	
Variables	OR (95% CI)	p value	OR (95%)	p value	OR (95%)	p value
Endocrine malignancies						
BMI, continuous	1.07 (1.02-1.12)	0.003*	1.08 (1.02-1.14)	0.050*	1.01 (0.93-1.11)	0.757
Physical activity Yes *vs* No	0.45 (0.24-0.84)	0.013*	0.52 (0.24-1.14)	0.104	0.30 (0.10-0.90)	0.032*
Smoking Yes/Ex *vs* No	1.52 (0.93-2.50)	0.095	1.19 (0.63-2.24)	0.590	1.69 (0.71-4.05)	0.240
Alcohol Yes *vs* No	0.91 (0.54-1.52)	0.703	0.55 (0.27-1.13)	0.101	1.50 (0.64-3.51)	0.353
Thyroid cancers						
BMI, continuous	1.06 (1.01-1.11)	0.017*	1.06 (1.01-1.13)	0.029*	1.03 (0.93-1.13)	0.625
Physical activity Yes *vs* No	0.60 (0.31-1.16)	0.126	0.62 (0.28-1.38)	0.239	0.52 (0.17-1.62)	0.257
Smoking Yes/Ex *vs* No	1.44 (0.83-2.48)	0.193	1.11 (0.57-2.19)	0.756	2.03 (0.71-5.78)	0.185
Alcohol Yes *vs* No	0.88 (0.50-1.56)	0.667	0.50 (0.23-1.09	0.081	2.12 (0.76-5.91)	0.151

OR: odds ratio, 95% CI: 95% confidence interval, *statistically significant differences between groups.

Since thyroid disease was one of the most common conditions in our population, we also evaluated the determinants of health in patients affected by thyroid cancer vs benign thyroid disorders (in patients without any other oncological diseases). BMI was the only risk factor for the development of thyroid cancer [OR = 1.06 [95% CI: 1.01-1.11] p = 0.017]; a subgroup analysis by gender confirmed BMI as a risk factor only in the female gender [OR = 1.06 (95% CI: 1.01-1.13) p = 0.029]. ORs are shown in Table 3.

Discussion

This cross-sectional study aimed to evaluate the role of gender and gender-related health determinants as risk factors for endocrine diseases. Many studies in the literature focused on the impact of gender on lifestyle.[7] Men seem more prone to consume alcohol and to develop alcohol-related diseases than women. Conversely, women usually drink less alcohol due to a lower tolerance, but also to cultural reasons, such as society's disapproval of drinking or the increased risk of physical and sexual assault.[8]

In our population, we confirmed a gender difference in alcohol consumption, which was lower in females. Interestingly, this difference was not statistically significant in younger people, testifying how younger women have a lifestyle more similar to the males', perhaps due to female emancipation, while in older people traditional gender differences are still more preserved. Likewise, in our study, a higher proportion of men vs women were smokers, in line with the literature.[9,10] Considering only patients aged 45 or younger (therefore born after the emancipation of Italian women), this gender-difference has not been confirmed, testifying to a change in lifestyle in new generations. Several factors should be considered in the relationship between smoking and female gender. Low socio-cultural and educational levels are known to be risk factors for the onset of tobacco consumption[11] and for the risk of cancer.[12] In the last years, the proportion of women who become smokers has increased, mainly due to women's earning power and to targeted marketing strategies by tobacco companies.[13]

Scientific research has also shown differences in food intake and the practice of physical activity in both sexes. For example, in modern Western societies, the male gender seems to prefer fatty meals and sweet foods, while healthier foods such as vegetables, fruit, fish and dairy products are mostly consumed by women.[14] These differences may depend on a dissimilar awareness of the relationship between food behavior and health and on a different attention to weight control or good physical shape, in line with modern society stereotypes.[15] This attitude is reflected in the nutritional pattern and BMI. Males had a higher BMI than females, probably mirroring their less healthy dietary habits. In our population, there were no differences in the physical activity level between males and females, unlike other studies published in the literature, which show, especially among younger people, a greater propensity to physical activities in males than in females.[16]

Taking all these aspects together, in our study population women seem to follow a healthier lifestyle. This data could depend on the influence of multiple factors. First, women pay greater attention to their health condition than men;[17] second, social conditioning leads women to maintain a good body shape in order to achieve beauty stereotypes; finally, the level of education of patients. It has been demonstrated that better educated people follow a healthier lifestyle, probably due to the increased awareness of the correlation between lifestyle and health.[18] This is consistent with our finding that, in the population observed, women had a higher level of education than men, which could have determined the healthier lifestyle of our female patients.

In our study, we evaluated the distance of the hospital from home, because this could theoretically indicate a gender-related discrepancy. However, our results did not confirm any gender-difference in this parameter, although this could be explained by the need by a relevant percentage of patients (32%) to reach a tertiary health care center, probably due to a lack of similar institutions in their geographical area.

We then proceeded to assess the impact of common gender-influenced risk factors in endocrine diseases. The two gender-related health determinants associated with endocrine malignancies were a high BMI and physical activity. These risk factors are understudied in endocrine malignancies, compared to other type of cancers. However, our findings are in agreement with some studies on neuroendocrine neoplasms, which have shown an association between waist circumference and other parameters of the metabolic syndrome and the development of these neoplasms[19] and some preliminary data about thyroid cancer, that suggest a potential role of obesity in thyroid cancer.[20]

In our population, neither tobacco use nor alcohol consumption were associated with the development malignant endocrine diseases (thyroid cancers and neuroendocrine neoplasms), in agreement with the awareness that these elements are less pathogenetic for thyroid cancer[21,22] than other risk factors, such as family history or previous radiation exposure.[23,24]

Interestingly, BMI would seem to have a greater role in females, while physical activity would seem protective in males: despite these two parameters being generally correlated, surprisingly our results would seem to indicate that they have a gender-based impact on the development of endocrine malignancies.

On the other hand, in patients with at least one tumor (of endocrine or non-endocrine origin), our data confirmed that the proportion of smokers and former smokers was higher than in patients without neoplasms, as expected.[5]

In our population, we found a different gender-related prevalence of endocrine diseases. Although there was no gender difference in the overall prevalence of benign thyroid diseases, a subgroup analysis found that the prevalence of iatrogenic thyroid diseases was higher in males, while hypothyroidism, hyperthyroidism and thyroiditis were higher in females, consistently with previously reported data.[25]

In our study, thyroid malignancies were more frequent in males than females. The risk of malignancy of the thyroid nodules is known to be greater in males,[23,26] as well as the fact that male gender is an independent prognostic factors in papillary thyroid carcinoma, which affects staging and the risk of recurrence.[27] These factors together could explain the propensity of male patients and general practitioners to refer to a national cancer center, overestimating the real prevalence of the disease in men.

One of the limitations of our study is the major prevalence of women in our population. This derives from the choice to enroll all consecutive patients referring to our Center during one year. The higher percentage of women could be explained by the more common prevalence of endocrine diseases in females,[25] but also by the higher attention paid to personal health status, typical of women, and their higher propensity to refer to health care centers and manage health problems.[1,17] Moreover, the impact of age difference between males and females on some results cannot be excluded, since the cross-sectional design of the study does not contemplate age-matching.

Further studies will be needed to confirm our observations, and extend the study also to other issues, such as gender differences in the propensity to carry out periodic follow-up visits and in the adherence to the treatment proposed by physician, with a possible impact on the progression and outcomes of the endocrine disorders.

Conclusions

The study highlights the importance of considering gender and gender-related health determinants as key factors for health, even in patients affected by endocrine diseases, in whom this approach has not been widely used.

This study confirms that some lifestyle aspects, such as smoking and alcohol, have a less pathogenetic impact on endocrine malignancies, unlike neoplasms of other origins, while reveals BMI and physical activity as possible risk and protective factor for thyroid cancers and neuroendocrine neoplasms, although they would seem to have a different impact on the two genders.

Although further studies are needed to corroborate these findings, in endocrine tumors we suggest evaluating also some aspects of lifestyle, as sedentariness and obesity, in addition to the most well-known risk factors, for the global assessment of patients' cancer risk, always considering, from a precision medicine perspective, the influence of gender in the pathogenetic impact of these risk factors.

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Key messages

- Gender medicine is receiving increasing attention, but some gender-related health determinants are understudied in the endocrine setting.
- Gender has a significant impact on common risk factors: in our population women followed a healthier lifestyle.
- Our study demonstrated that lifestyle and habits can be risk factors also for endocrine malignancies: BMI was a risk factor for endocrine cancer, while physical activity was a protective factor.
- The study revealed a gender difference in the role of these risk factors, demonstrating a higher impact of BMI in women and of physical activity in men.
- Gender difference should be considered in lifestyle interventions and in the global assessment of patients affected by endocrine malignancies.

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Ethics approval: this study was approved by Regina Elena National Cancer Institute Local Ethic Committee (reference number: 1370/20) and has been conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent: all patients give their written informed consent to their participation in the study and to the publication of their data.

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