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PART I. DISEASES AND PROBLEMS DISTINGUISHED BY WHO AND FAO
DZIAŁ I. CHOROBY I PROBLEMY WYRÓŻNIONE PRZEZ WHO I FAO

ASSOCIATION BETWEEN BODY MASS INDEX AND GASTRIC CANCER IN POMERANIAN MEN AND WOMEN

ZWIĄZEK POMIĘDZY WSKAŹNIKIEM MASY CIAŁA I WYSTĘPOWANIEM GRUCZOŁOWEGO RAKA ŻOŁĄDKA WŚRÓD MĘŻCZYZN I KOBIET W WOJEWÓDZTWIE POMORSKIM

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A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
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Summary

Background. Within the last few decades, the prevalence of obesity has increased rapidly throughout the world. Epidemiological studies indicate a relationship of several types of cancer with obesity. The study aimed was to analyse the relation between body mass index (BMI) and the risk of developing gastric cancer.
Material and methods. A multicenter case-control study was conducted between 2010 and 2015 in Poland. The study included 152 patients with gastric cancer and 152 patients with normal results of esophagogastroduodenoscopy performed in the same period and matched for age, education and sex. BMI was calculated by using patients' height and weight. An analysis of environmental factors associated with the risk of gastric cancer was performed.
Results. The group with the diagnosis of gastric cancer was characterised by significantly higher regular consumption of alcohol and was found to include a higher percentage of smokers compared to the control group. In a subgroup analysis, it was found that there was a significantly higher body mass index among both men and women diagnosed with gastric cancer. A relation between gastric cancer and both overweight (BMI 25.0-29.9 kg / m^2) and obesity (BMI≥30 kg / m^2) was established. In a multivariate analysis, this was an independent risk factor for gastric cancer.
Conclusions. We suggest that BMI should be considered as an independent risk factor for developing gastric adenocarcinoma, which should lead to further research leading to the development of recommendations for the prevention of gastric cancer for people with high BMI.

Keywords: gastric cancer, body mass index, public health, overweight

Streszczenie

Wprowadzenie. W ciągu ostatnich kilku dekad występowanie nadwagi i otyłości wzrasta gwałtownie. Badania epidemiologiczne wskazują na związek kilku typów nowotworów złośliwych z nadwagą i otyłością. Celem naszej pracy była analiza relacji pomiędzy wskaźnikiem masy ciała (BMI) a ryzykiem zachorowania na gruczołowego raka żołądka.
Materiał i metody. Wieloośrodkowe badanie kliniczno-kontrolne zostało przeprowadzone w latach 2010 do 2015 w województwie pomorskim w Polsce. Do badania włączono 152 pacjentów z rakiem żołądka i 152 pacjentów z prawidłowymi wynikami ezofagoduodendoskopii wykonywanymi w tym samym okresie. Przypadki zostały dopasowane pod względem wieku, wykształcenia i płci. BMI obliczano na podstawie wzrostu i wagi pacjenta. Dodatkowo przeprowadzono analizę czynników środowiskowych mogących mieć związek z ryzykiem zachorowania na gruczołowego raka żołądka.
Wyniki. W grupie z rozpoznaniem raka żołądka stwierdzano wyraźnie wyższą częstość regularnego spożywania alkoholu i wyższy odsetek osób palących w porównaniu do grupy kontrolnej. W analizie podgrup stwierdzono znacznie podwyższony wskaźnik masy ciała zarówno wśród mężczyzn jak i kobiet, u których zdiagnozowano raka żołądka w stosunku do grupy kontrolnej. Relacja pomiędzy występowaniem raka żołądka i nadwagi (BMI 25.0-29.9 kg / m^2) lub otyłości (BMI≥30 kg / m^2) była istotna statystycznie. W analizie wieloczynnikowej podwyższony BMI był niezależnym czynnikiem ryzyka rozwoju gruczołowego raka żołądka.
Wnioski. Sugerujemy, że BMI należy traktować jako niezależny czynnik ryzyka rozwoju gruczolakoraka żołądka, co powinno prowadzić do dalszych badań prowadzących do opracowania zaleceń dotyczących zapobieganiu i wczesnemu wykrywaniu raka żołądka u osób z wysokim BMI.

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Słowa kluczowe: rak żołądka, wskaźnik masy ciała, zdrowie publiczne, nadwaga

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Introdution

Over the past decades, there has been observed a continuous increase in the incidence of adenocarcinoma of the distal oesophagus, gastroesophageal junction and of the stomach (later in this paper, to simplify it, we will use the name: gastric adenocarcinoma) [1]. Despite the decreasing incidence of gastric cancer in recent decades all over the world, it remains the fourth most common cancer and the third leading cause of cancer-related deaths in men and the fifth leading cause of cancer-related deaths in women [2]. There is evidence that specific environmental factors increase the risk of gastric cancer, e.g. smoking, excessive alcohol intake, low intake of fruit and vegetables and high intake of smoked food [3-5]. Moreover, a relationship between the risk of gastric cancer and chronic Helicobacter pylori infection has been found [6]. Most of these data come from Asian countries. This is, however, consistent with the data presented in the report of the World Cancer Research Fund and the American Institute for Cancer Research (WCRF / AICR) in 2007, where the major causes of cancers are environmental factors and factors related to lifestyle, such as diet, insufficient physical activity, excessive alcohol consumption and smoking [7].

The prevalence of overweight and obesity has been increasing worldwide in recent decades. It is well known that obesity leads to many adverse health effects, including increased risk of cancer. Many studies support the hypothesis that elevated BMI is associated with an increased risk of certain cancers, e.g. there is a well-demonstrated association between obesity and an increased risk of developing colorectal cancer, pancreatic cancer, and kidney cancer [8-13]. On the other hand, there are reports in the literature of a reduced risk of developing lung cancer with increasing BMI [14-15]. In addition, no correlation has been established between BMI and the risk of prostate cancer [16-17], or rectal cancer [18-19]. Given the various effects BMI has on the incidence of various cancers, the question of obesity's influence on the long-term incidence of cancers is still open to debate.

In the case of gastric cancer, several studies have shown a correlation between body mass index (BMI) and an increased risk of gastric cancer, which was confirmed in the meta-analysis [20]. In some studies, however, this correlation remained inconclusive, dependent on sex, the type of obesity, or Helicobacter pylori infection [21-24]. The purpose of the study presented here was to investigate the relationship between BMI and the risk of gastric cancer in the Polish society (taking into consideration the family history and the infection of Helicobacter pylori in gastric cancer, against eating habits, alcohol consumption and smoking).

Material and methods

The study included a total of three hundred and four people who had esophagogastroduodenoscopy in the F. Ceynowa Specialist Hospital in Wejherowo and in the Regional Oncology Centre in Gdansk, Poland, from May 2010 to December 2015. During this period a total of 153 cases of gastric adenocarcinoma were diagnosed by histopathology. One person was excluded from the study due to incomplete survey data. The control group was selected and matched from healthy patients who had esophagogastroduodenoscopy at the same time. Each case was matched individually with a control according to certain characteristics such as age, education, and gender. All study participants had their case history taken by a gastroenterologist, a surgeon, or a clinical oncologist, including their medical history, family history of cancers, obstetric/gynecological history in women and the factors related to lifestyle, including smoking and alcohol consumption. In each patient, a test for the presence of Helicobacter pylori infection was performed. Anthropometric information (height and weight) were measured by a qualified treatment nurse. Body weight and height were measured according to standard protocols with an accuracy corresponding to 0.1 kg and 1.0 cm. The study was based on a retrospective analysis of documents and the clinical treatment history of patients. Before the analysis, a database was prepared, consisting of the following columns: age, sex, education, smoking, alcohol consumption, significant burdens and chronic diseases, family history of diseases, gynecological history, Helicobacter pylori infection, height, weight, BMI, the final diagnosis. A current smoker was defined as a person who had smoked an average of at least one cigarette per day during the preceding 12 months. A former smoker was defined as someone who did not meet this definition but had smoked before. People who had never smoked were considered non-smokers. Drinking alcohol was defined as consuming at least three alcoholic drinks of any kind per week. These data were obtained basing on patients' own reporting in a standard patient questionnaire. A positive family history of gastric cancer was defined as an occurrence of this disease in first and /or second-degree relatives. The presence of chronic diseases was defined as answering "yes" to the question: "Have you ever been diagnosed with the following chronic diseases?". All patients were weighed and measured by a treatment nurse. BMI was defined as the ratio of the body weight (expressed in kg) divided by the square of the body height (in meters) (weight [kg] / height [m2]). BMI ranges were adopted in accordance with the definitions from WHO criteria. BMI values were divided into four groups:

underweight (BMI of less than 18.5 kg / m2), normal BMI (from 18.5 to 24.99 kg / m2), overweight (from 25 to 29.99 kg / m2) and obesity (≥ 30.0 kg / m2) (Table 1).

Table 1. BMI by WHO

body mass index	classification
0–18.49	underweight
18.5–24.9	normal
25–29.9	overweight
30–34.9	obese
35–40 and above	morbidly obese

The project was approved by the Bioethics Commission at the Regional Medical Council in Gdansk and by the directors of both hospitals. The condition of consent was the preparation of a database with complete anonymity of the study group.

Statistical methods

To calculate the BMI, measurements of height and weight carried at the day of esophagogastroduodenoscopy (the body weight in kilograms divided by the square of the body height in meters) were used. Differences in epidemiological factors between the groups of patients with gastric adenocarcinoma and the control group were tested using the Student's t-test for continuous variables and the Chi-square test for categorical variables. All tests were two-tailed and a p-value less than 0.05 was considered statistically significant. For statistical calculations, programs: Microsoft Excel version 2003 and PQStat version 1.4. were used.

To examine the relationship between BMI and the risk of gastric cancer, non-parametric logistic regression was used. For this purpose, following variables were used: age (continuous), smoking, alcohol consumption, family history of gastric cancer, chronic diseases (separately for patients with diabetes, chronic gastritis, and stomach ulcers), and Helicobacter pylori infection. In addition, for women, menopause was included in the logistic regression analysis.

Results

During the study (on average 66 months for both centres) 153 cases of gastric adenocarcinoma were found. Selected epidemiological data and the characteristics of the respondents are summarised in Table 2.

Table 2. Selected characteristics of 152 gastric cancer cases and 152 controls

variable	men					women				
	case (n = 109)		control (n = 109)		p	case (n = 43)		control (n = 43)		p
	n	%	n	%		n	%	n	%	
age (years, mean ± SD)	63.6 ± 9.3		63.3 ± 9.8		0.47	64.3 ± 8.7		64.0 ± 9.3		0.71
smoking	83	76.1	64	58.7	<0.01	25	58.1	11	25.5	<0.01
drinking alcohol	68	62.3	42	38.5	<0.01	12	27.9	7	16.2	<0.01
family history of gastric cancer	29	26.6	6	5.5	<0.01	9	20.9	1	2.3	<0.01
medical history										
diabetes mellitus	12	11.0	13	11.9	0.16	6	13.9	5	11.6	0.35
chronic gastritis	23	21.1	15	13.7	<0.01	7	16.2	8	18.6	0.41
helicobacter pylori infection	72	66.1	70	54.2	0.18	36	83.7	35	81.4	0.49
menopause						41	95.3	39	90.7	0.37
BMI Information (mean ± SD)										
BMI	27.3 ± 1.18		24.8 ± 1.22		<0.01	29,4 ± 1.73		26.3 ± 1.1		<0.01
height (cm)	173.5 ± 9.8		173.2 ± 9.4		0.24	165.8 ± 7.9		165.5 ± 8.4		0.29
weight (kg)	83.1 ± 11.4		75.5 ± 10.8		<0.01	81.2 ± 10.8		72.6 ± 7.7		<0.01

p value calculated by Chi-square test for categorical variables and t test for continuous variables

The mean age of the patients was 63.6 for men and 64.3 for women. The group of patients with gastric cancer was more likely to have a positive family history of gastric cancer than the control group (26.6% vs 5.5% for men and 20.9% vs. 2.3% for women respectively). In addition, the group with cancer included more smokers, both among men (76.1% vs 58.7%) and among women (58.1% vs 25.5%). Alcohol consumption was also more frequent in patients with gastric cancer, both in men (62.3% vs. 38.5%) and women (27.9% vs 16.2%). Moreover, in the case of men, there was a difference established in the incidence of chronic gastritis and peptic ulcers (21.1% vs 13.7%). In women, there was no difference of this kind (16.2% vs 18.6%). There was no statistically significant difference between groups, when it comes to the percentage of post-menopausal women (95.3% vs 90.7%). No effect of Helicobacter pylori infection on the increased risk of gastric adenocarcinoma was found.

Body weight was significantly higher in patients diagnosed with gastric cancer compared to the control group, both among men (88.1 ± 11.4 kg and 80.5 ± 10.8 kg respectively) and women (86.2 ± 10, 8 compared to 77.6 ± 7.7 kg).

The relation between BMI and the risk of gastric cancer is shown graphically in Fig. 1.

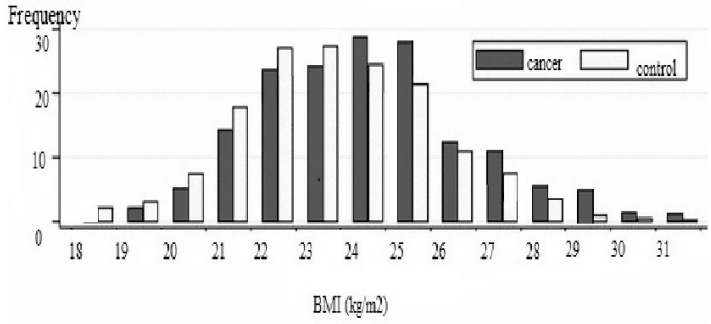

Figure 1. The association between BMI and gastric cancer risk

Taking BMI of 21.75 kg / m2 as an optimum, the risk of gastric cancer increases in men with BMI higher than or equal to 25.0 kg / m2, whereas in women, the risk increases in patients with BMI of 25.3 kg / m2 or more. The odds ratio is estimated at more than two in men with BMI over 28.7 kg / m2 and in women with BMI over 28.5 kg / m2.

Discussion

Over the past several decades we have seen a significant increase in the incidence of adenocarcinoma of the gastroesophageal junction in the populations of Western countries, in contrast to a decrease in the incidence of cancer of the distal stomach [25]. In the literature, there is a hypothesis that this trend is a result of an increasing rate of Helicobacter pylori eradication. This hypothesis may indicate that adenocarcinomas are not associated with Helicobacter pylori infection but with other environmental factors, such as diet, smoking, alcohol consumption and obesity. In our study, we analysed the relationship between BMI, smoking, alcohol consumption, and increased risk of gastric cancer, assuming that BMI is associated with an increased risk of gastric cancer. Our results indicate that the BMI is a substantial risk factor for developing gastric cancer. After excluding the impact of other known epidemiological risk factors for developing gastric cancer, high BMI has remained significantly related to the risk of gastric cancer (both in men and women).

There are at least a few mechanisms that may explain the relation between overweight and obesity and an increased risk of developing this type of cancer. First, the accumulation of body fat increases the concentration of endogenous hormones, such as insulin and the insulin-like growth factor-1, as well as steroids. The result of these hormones' influence is an increase in cell proliferation and the weakening of apoptosis, which, consequently, spurs the growth of malignant cells. Also, insulin resistance and chronic hyperinsulinemia, produced by the metabolic adaptation to increased levels of free fatty acids circulation from adipose tissue can be conducive to developing cancer [26]. Secondly, overweight and obesity can promote the formation of Barrett's oesophagus, which is a precancerous condition [27]. One possible mechanism is an increase of intra-abdominal pressure on the lower oesophageal sphincter [26, 28]. Thirdly, the level of estrogen, which is closely associated with obesity, may be associated with an increased risk of certain cancers [29]. Fourth, obesity increases the release of inflammatory mediators that can promote tumour growth [30]. It is also suggested that obese people have prolonged passage through the oesophagus, resulting in a longer contact time between the oesophageal mucosa and food (containing potentially carcinogenic ingredients) [31].

However, even these suggested mechanisms explaining the link between obesity and the development of cancer are not sufficient. Reflecting on other causes, one must mention population ageing. People live longer, and the incidence of cancer has been significantly associated with ageing [32]. In the present study, the risk of gastric cancer was related to age and was significantly higher in patients older than 60, in comparison with those under the age of 60.

Another well-known risk factor for cancer is tobacco smoke, containing many chemical carcinogens, which can operate through direct contact with gastric mucosa or indirectly by the flow of blood. The cause-effect relationship between smoking and gastric cancer has been the subject of controversy in the past 20 years. A meta-analysis published in 1997 showed, however, that such a relation exists [33]. Our study also shows an increased risk of gastric cancer among current smokers. This correlation has been observed in both men and women.

The risk of gastric cancer is increased in patients with a positive family history of this cancer [34]. The risk of gastric cancer increases from 1.5 to 3.5 times in the case of family history of the disease. Of course, this may be since relatives tend to be exposed to the same environmental risk factors, but the influence of genetic factors cannot be excluded. Our study confirms that the presence of gastric cancer in first- and second-degree relatives increases the risk of developing this type of cancer. In addition, the risk was independent of smoking tobacco, BMI, education, sex, and age in the multivariate analysis.

This study has, however, several potential limitations, which should be considered in the analysis. Firstly, our study has a potential bias. Patients were recruited from hospitals performing treatments for gastric cancer. Secondly, the control group was not completely healthy. These were patients who volunteered to perform esophagogastroduodenoscopy, due to gastroenterological symptoms. To overcome this problem, we have compared the cases of disease with a control group, which had the same demographic profile and comorbidities. In fact, there is no significant difference between the groups regarding education, age, and sex. These variables were equalised in the selection of the control group.

Recently, a meta-analysis based on prospective studies has demonstrated that BMI is a risk factor for developing gastric cancer [35]. However, half of the studies which were included were based on self-reports of anthropometric data, which could lead to an overestimation of the relative risk [36]. The advantage of our study is that the data on weight and height were collected by a qualified nurse. As for the history of smoking and alcohol consumption, the situation was different, and the amount of alcohol consumed was very imprecise. Besides, our study did not include other factors, such as diet, physical activity or the amount of non-steroidal anti-inflammatory drugs taken.

Conclusions

Although the study involved a small population, it revealed a positive relation between BMI and gastric cancer. In summary, this study provides additional information to previous studies on the effect of BMI on the risk of gastric cancer. The results of our study may shed light on public health, stressing the importance of weight control in the prevention of gastric cancer. We suggest that BMI should be considered as an independent risk factor for developing gastric adenocarcinoma, which should lead to further research leading to the development of recommendations for the prevention of gastric cancer for people with high BMI.

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