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ORIGINAL ARTICLE

Impact of body mass index on cancer development

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Summary

Purpose: *To determine the impact of body mass index (BMI) on cancer in a hospital-based Turkish population.*

Patients and methods: *The study group consisted of 2015 (1172 females: 423 pre- and 749 postmenopausal; and 843 males) patients with histologically proven cancer who applied to Marmara University Medical School, Medical Oncology Clinic. The control group included 305 healthy caregivers (192 females: 110 pre- and 82 postmenopausal; and 113 males).*

Results: *Mean BMI of the patients with breast, ovarian and cervical carcinoma was significantly higher than that of the healthy female controls ($p<0.001$, 0.003, <0.001, respectively). Postmenopausal breast cancer patients had significantly higher BMI than postmenopausal female controls (odds ratio [OR] 1.3; 95% confidence interval [CI], 1.06-1.6; $p=0.012$), while this was not seen in premenopausal patients. When compared with controls obese postmenopausal female patients had 3.26-fold (95% CI 1.54-6.90) increased risk for breast cancer ($p=0.002$). Mean BMI of lung, stomach, esophagus, pancreas and head and neck carcinoma patients was significantly lower than that of the healthy controls. Female patients with lung and colorectal carcinoma had higher BMI than female controls.*

Conclusion: *Elevated BMI might be a risk factor for breast cancer in postmenopausal women. Case-control studies may not show the actual association between BMI and cancers that present with pre-diagnosis weight loss and advanced stage.*

Key words: body mass index, breast cancer, malignant neoplasms, obesity

Introduction

Obesity constitutes a growing global epidemic, accompanied by a vast range of disorders. Epidemiological studies have shown obesity to be a significant risk factor for type 2 diabetes and cardiovascular disease, but its role in oncogenesis is less understood. The most widely used index of body weight for these assumptions is the BMI which is calculated by dividing the body weight in kilograms by the square of the person's height in meters (kg/m^2). A BMI of 18.5-24.9 is considered normal weight, 25-29.9 overweight and ≥30 obese [1].

There is growing evidence that excess body weight increases the risk of cancer at several sites. Large prospective studies show a significant association with obesity for several cancers, and the International Agency for Research on Cancer has classified the evidence of a causal link as "sufficient" for cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), prostate, gallbladder and esophagus (adenocarcinoma) [2-4].

During the past several years there is an increased interest on cancer risk, survival and obesity [5]. However, very limited information exists for populations outside the North America and Europe [6-10]. Recently, data from Asia has been published [11].

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The aim of the present study was to determine the impact of BMI on cancer development in a university outpatient oncology clinic-based Turkish population. We reviewed the BMI of cancer patients and compared the patients' BMI levels with a control group of healthy caregivers in order to see for any relationship of BMI with some specific types of cancer.

Patients and methods

A case-control study was conducted on 2015 patients (1172 females: 423 pre- and 749 postmenopausal; and 843 males, aged >19 years) with histologically proven cancer who applied to Marmara University Medical School, Medical Oncology Clinic, between October 1997-October 2004. The control group consisted of 305 consecutive healthy caregivers or relatives (192 females: 110 pre- and 82 postmenopausal; and 113 males, aged >19 years) of the cancer patients, without history of cancer or any wasting disease. Pregnant women were excluded. Body weight and height were measured while subjects were wearing light clothing without shoes. BMI was calculated by dividing the body weight in kilograms by the square of the person's height in meters (kg/m^2). A BMI <18.5 was considered underweight, 18.5-24.9 normal, 25.0-29.9 overweight, and ≥30 obese.

Statistical analysis

The SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL) statistical analysis program was used in all analyses. Comparisons between groups in the study population were performed using logistic regression and independent sample t-tests. The level of significance (alpha) was set to 0.05 for all tests and confidence intervals.

Results

Median BMI of controls was 24.8 (range 14.9-45.2) and median age was 42 years (range 20-81). Twelve (4%) controls were underweight, 145 (47.5%) were normal, 119 (39%) were overweight and 29 (9.5%) were obese.

Median BMI of patients was 24.8 (range 14.4-54) and median age was 57 years (range 20-84). Seventy-nine (4%) patients were underweight, 949 (47%) were normal, 666 (33%) were overweight and 321 (16%) were obese.

The mean BMI of the women with breast, ovarian and cervical cancer was significantly higher than that of the healthy female controls ($p<0.001$, $p=0.003$ and $p<0.001$, respectively) (Tables 1 and 2).

There was a significant positive association between BMI and breast cancer risk among postmenopausal women (OR 1.3, 95% CI 1.06-1.60, $p=0.012$). When compared with controls obese postmenopausal females had 3.26-fold (95% CI 1.54-6.90; $p=0.002$) increased risk for breast cancer. In premenopausal women BMI did not have any significant impact on breast cancer risk. Age showed a significant positive association with breast cancer among both premenopausal and postmenopausal women (OR 1.19, 95% CI 1.14-1.24; $p<0.001$ and OR 1.07, 95% CI 1.04-1.10; $p<0.001$, respectively).

Mean BMI of lung, gastric, esophagus, pancreatic and head and neck carcinoma patients was significantly lower than that of the healthy controls (Tables 1 and 2). Mean BMI of the patients with colon, nasopharyngeal, bladder, prostate carcinoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, melanoma, and soft tissue sarcomas was not significantly different from that of the healthy controls. Healthy controls were significantly younger than patients in all groups except Hodgkin's disease (Tables 1 and 2). Female patients with colorectal and lung cancer had significantly higher BMI than female controls ($p=0.007$ and <0.001,

Table 1. Comparison of BMI and age between patients and controls (logistic regression analysis)

Cancer type	*n*	*Mean BMI*	*p-value*	*Mean age (years)*	*p-value*
Controls	305	25.2±4.2		43.4±13.7	
Male controls	113	26.4±4.0		44.7±14.1	
Female controls	192	24.4±4.2		42.5±13.3	
Prem. controls	110	23.0±3.6		33.5±8	
Postm. controls	82	26.3±4.2		54.7±8.5	
Breast Ca	552	27.1±5.3	<0.001	52.5±11.7	<0.001
Prem. breast Ca	219	25.5±4.4	0.266	41.7±5.6	<0.001
Postm. breast Ca	333	28.2±5.5	0.012	59.7±8.8	<0.001
Colorectal Ca	354	25.7±4.4	0.065	60.4±12	<0.001
Lung Ca	338	24.3±3.9	<0.001	60.3±9.9	<0.001
NHL	84	25.3±5.7	0.634	56.6±17	<0.001

BMI: body mass index, Prem: premenopausal, Postm: postmenopausal, Ca: cancer, NHL: non-Hodgkin's lymphoma

Table 2. Comparison of BMI and age between patients and controls (independent sample t-test [2-tailed])

Cancer type	*n*	*Mean BMI*	*p-value*	*Mean age (years)*	*p-value*
Control	305	25.2±4.2		43.4±13.7	
Male controls	113	26.4±4.0		44.7±14.1	
Female controls	192	24.4±4.2		42.5±13.3	
Ovarian Ca	97	26.2±5.9	0.003	54.9±14.3	<0.001
Cervical Ca	38	27.8±5.1	<0.001	55.7±11.2	<0.001
Endometrial Ca	8	26.2±3.7	0.22	61±15.1	0.001
Gastric Ca	117	23.4±4.3	<0.001	56.6±4.3	<0.001
Pancreatic Ca	51	23.3±3.1	0.003	60.4±10.6	<0.001
Nasopharyngeal Ca	44	25.0±4.8	0.83	51.2±13.8	<0.001
Other Head & Neck Ca	52	22.9±3.6	<0.001	56.8±15	<0.001
Bladder Ca	23	25.5±3.6	0.68	68.4±8.4	<0.001
Hodgkin's disease	25	23.8±4.2	0.11	40.4±17.4	0.32
Soft tissue sarcomas	21	26.0±5.0	0.4	58.9±13.3	<0.001
Mesothelioma	14	24.7±3.4	0.67	54.9±14.6	0.004
Malignant melanoma	26	25.1±3.9	0.93	53.5±9.8	0.001
Prostate Ca	20	25.5±4.4	0.37	68.8±8.1	<0.001
Testicular Ca	8	24.7±4.0	0.25	32.4±11	0.02
Thyroid Ca	12	26.8±4.7	0.19	65.8±10	<0.001
Ca of unknown primary	20	23.9±4.9	0.21	58.6±11.6	<0.001
Renal cell Ca	9	23.3±4.5	0.19	60.89±7.9	<0.001
Esophageal Ca	17	21.8±3.9	0.002	61.3±7.8	<0.001

BMI: body mass index, Ca: cancer

respectively), while this was not seen in male patients with these cancer types. No gender difference was seen in other cancer types.

Discussion

The landmark study on the relationship between cancer and obesity was conducted by the American Cancer Society [7] over a 13-year period from 1959 to 1972. After adjusting for the effects of age and cigarette smoking, people whose body weight was 40% higher than the average had an overall increased risk of cancer death (33% increase in men and 55% in women). Overweight males experienced significantly higher rates of colorectal and prostate cancer, whereas overweight women experienced higher rates of gallbladder, breast, cervix, endometrium, uterus, and ovarian cancers.

Bergstrom et al. [6] reviewed the epidemiological literature and metaanalysed quantitatively the relationship between excess weight and the risk of developing cancer at 6 sites in the European Union (EU). Overall, excess body mass accounted for 5% of all cancers in the EU, 3% in men and 6% in women, corresponding to 27,000 male and 45,000 female cancer cases yearly. The highest attributable proportions were obtained for cancers of the endometrium (39%), kidney (25% in both sexes) and gallbladder (25% in men and 24% in women). Some 36,000 cases could be avoided by halving the prevalence of overweight and obese people in Europe.

More recently Wolk et al. [8] have evaluated the relationship between obesity and the risks for various forms of cancer in a population-based cohort of 28,129 hospital patients (8,165 men and 19,964 women) in Sweden from 1965 to 1993. Cancer risk was estimated using the standardized incidence ratio (SIR, with 95% CI), which is the ratio of the observed number of cancers to the one expected. Overall, a 33% excess incidence of cancer was seen in obese persons, 25% in men and 37% in women. These data, and the rising worldwide trend in obesity, suggest that over-eating may be the largest avoidable cause of cancer in nonsmokers.

The mechanism of increased cancer risk in obese populations is unclear and data on this issue are still limited, but nutritional and dietary factors and sedentary lifestyle may have a role. The biologic mechanisms that are suggested to explain the links between obesity and cancer include steroid hormones, insulin, insulin-like growth factor (IGF) system and mechanical processes such as the association between abdominal obesity, gastroesophageal reflux and esophageal adenocarcinoma [12,13]. Leptin, IGF-1, vascular endothelial growth factor (VEGF) and adiponectin might be the

promoting factors in the transition from premalignant lesions to overt cancer, in tumor growth and invasiveness through the induction of tumor angiogenesis. The adipocytokines are biologically active polypeptides that are produced either exclusively or substantially by the adipocytes, and act by endocrine, paracrine, and autocrine mechanisms. Most have been associated with obesity, hyperinsulinaemia, type 2 diabetes, and chronic vascular disease; in addition, 6 adipocytokines (VEGF, hepatocyte growth factor, leptin, tumor necrosis factor-alpha, heparin-binding epidermal growth factor-like growth factor, and interleukin-6) promote angiogenesis while one, adiponectin, is an angiogenesis inhibitor. Obesity and insulin resistance have both been identified as risk factors for breast cancer and are associated with late-stage disease and poor prognosis. Angiogenesis is essential for breast cancer development and progression, and so it is plausible that obesity-related increase in adipocytokine production and a reduction in adiponectin may adversely affect breast cancer outcome by their angiogenesis-related activities. There is also experimental evidence that some adipocytokines can act directly on breast cancer cells to stimulate their proliferation and invasive capacity. Thus, adipocytokines may provide a biological mechanism by which obesity and insulin resistance are causally associated with breast cancer risk and poor prognosis [14]. These results suggest that the low serum adiponectin levels are significantly associated with an increased risk for breast cancer and that tumors arising in women with the low serum adiponectin levels are more likely to show a biologically aggressive phenotype. The association between obesity and breast cancer risk might be partly explained by adiponectin [15]. Both experimental and clinical studies are needed to develop this concept, and particularly in estrogen-independent breast cancers where preventive and therapeutic options are limited.

We have seen a positive correlation between increased BMI and postmenopausal breast cancer; especially obese patients had 3.26-fold increased risk for cancer. This had been postulated in previous studies [16]. On the contrary, obesity didn't have any impact on premenopausal breast cancer. In fact, it was shown that overweight had a protective effect from breast cancer in premenopausal women, as there was an increased number of anovulatory cycles [17].

Our results also differed from the relevant literature as all our patients with colorectal carcinoma and male patients with this disease had similar levels of BMI compared to controls. On the contrary, a positive correlation was seen in our study between obesity and colorectal carcinoma in the female patient population, which was also reported before [18-20]. In the Canadian National Breast Screening Study, Terry et al. [18] suggested that there was a 2-fold increased risk of colorectal cancer in obese premenopausal women, while this was not seen in postmenopausal women. When we studied the entire cohort we found a non-significant 8% increased risk of colorectal cancer in obese women. Although we did not subcategorize women with colorectal cancer according to their menopausal status in our study, our results didn't change with age (≤ 50 vs. > 50 years).

Patients with lung and head and neck carcinomas usually present with more advanced or metastatic disease and pronounced weight loss to medical oncology clinics. Our findings are compatible with some literature data as these cancer types are closely related with cigarette smoking, alcohol consumption and poor nutritional status [21]. We didn't find any significant association between obesity and esophageal or gastric carcinoma. Similarly to lung and head and neck cancers, these patients present with more advanced and metastatic disease to medical oncology clinics. We did not categorize esophageal and gastric cardia adenocarcinomas separately and, therefore, this might have biased our findings. Still, there are conflicting findings for esophageal and gastric cardia adenocarcinomas in the literature [13,22-25].

There were several limitations to our study. The most striking limitation was the age difference between patient population and the controls. Our patient population was older than controls because caregivers were chosen as controls in order to compare patients to a group coming from the same genetic background and nutritional status, living in the same environment and for some in the same house. These people were younger than the patients because most of the caregivers were the children of our patients. Another limitation of the study was that it was difficult to draw a firm conclusion for several other cancers which had been postulated to be related to obesity such as endometrial, testicular, renal, and thyroid cancers and mesothelioma, because of the very low numbers of patients with these malignancies (less than 15).

In summary elevated BMI increases the risk of breast cancer among postmenopausal women. Outpatient oncology clinic-based case-control studies may not show the actual association between obesity and some cancer types that present with a pre-cancer diagnosis weight loss or advanced disease. Although caregivers, relatives and household members were selected as healthy controls in order to neglect the bias of environmental and genetic differences between two study groups, our control group may not be the ideal population for our study. Large prospective cohort studies will show the link between cancer and obesity.

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