

# Influence of body mass index on prognosis in gynecological malignancies

Karsten Münstedt · Mathias Wagner ·  
Uwe Kullmer · Andreas Hackethal ·  
Folker E. Franke

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## Abstract

**Objective** To evaluate the effect of obesity on the presentation and course of disease in patients with gynecological cancers.

**Study design** Records of patients with endometrial ( $n = 1180$ ), cervical ( $n = 738$ ), and ovarian cancer ( $n = 824$ ) treated between 1986 and 2005 were reviewed. Body mass index (BMI) was analyzed in relation to tumor stage, tumor grading, and prognosis. Steroid hormone receptor status and growth fraction (MIB1; Ki-67-antigen) of tumors in relation to BMI were analyzed in subgroups with endometrial ( $n = 183$ ) and advanced ovarian ( $n = 221$ ) cancers. In the latter subgroup, tumor vascularization (CD31) and expression of bcl-2, c-erb-B2, fibronectin, and tumor markers (CA-125, CA15-3, CEA) were also evaluated. Statistical analyses included bivariate correlation, cross-tabulation, Kaplan-Meier-survival analyses, and multifactorial residual survival analyses.

**Results** Obese patients with endometrial carcinoma were significantly younger ( $p < 0.001$ ) and their tumors were less advanced at diagnosis ( $p = 0.001$ ) and were better differentiated ( $p = 0.010$ ). In the subgroups, neither steroid hormone receptor status nor MIB1-determined growth

fraction correlated with BMI. For both endometrial and cervical carcinomas, a high BMI influenced overall survival favorably ( $p_{\text{endometrial}} = 0.004$  and  $p_{\text{cervical}} = 0.026$ ). In ovarian cancer, there was a trend toward improved survival in more obese patients ( $p = 0.053$ ). Immunohistochemistry revealed that c-erb-B2 expression was slightly lower in tumors of obese patients ( $r = -0.142$ ;  $p = 0.039$ ), but BMI did not influence any other factor.

**Conclusions** Although obesity increases the incidence of cancer, a high BMI does not seem to adversely influence the prognosis in patients with the mentioned gynecological malignancies.

**Keywords** Body mass index · Endometrial cancer · Cervical cancer · Ovarian cancer · Prognosis · Tumor biology

## Introduction

Tumorigenesis is generally considered to be a multistep procedure modulated by risk factors as well as protective factors. Obesity is of current interest in tumorigenesis since the percentage of overweight people is increasing steadily in the western world [1, 2]. Overweight has long been recognized as a risk factor for diabetes and cardiovascular diseases [3]. More recently, it has become clear that overeating and obesity may be the largest avoidable causes of cancer in nonsmokers, accounting for one in seven cancer deaths in men and one in five in women in the USA [4]. This relationship seems to hold true for many gynecologic cancers—in particular, ovarian and endometrial cancer [5, 6]. However, the role of obesity in cervical carcinomas is still undefined. Apart from that, obese women are less likely to participate in screening measures,

K. Münstedt (✉) · M. Wagner · A. Hackethal  
Department of Obstetrics and Gynecology, Clinic of the  
Universities Giessen and Marburg, Klinikstrasse 32,  
35385 Giessen, Germany  
e-mail: karsten.muenstedt@gyn.med.uni-giessen.de

U. Kullmer  
Department of Obstetrics and Gynecology, Asklepios Clinic,  
Lich, Germany

F. E. Franke  
Institute of Pathology, Clinic of the Universities Giessen  
and Marburg, Giessen, Germany

to have more problems related to surgery, higher mortality from causes other than endometrial cancer, and experience more cutaneous but less gastrointestinal toxicity when receiving adjuvant radiation therapy [7–9].

Although recent studies have shown the influence of a high body mass index (BMI) on the biology of endometrial cancers [10–13], results for ovarian cancer are conflicting [14, 15]. In this study, we have endeavored to clarify the relationship between BMI and gynecological cancers by analyzing data from all patients with endometrial, cervical, and ovarian cancers who were treated at our clinic in the past 20 years.

## Patients and methods

### Cases

Clinical records of 1,180 patients with endometrial cancer, 738 with cervical cancer, and 824 with ovarian cancer were identified from the university's cancer registry. These records were re-evaluated for BMI and common prognostic factors such as the patients' age, tumor stage (FIGO), histological tumor grading, and for survival status or causes of death (cancer-associated versus cancer-independent) at the time of last routine follow-up (December 2006). (In our cancer centre, survival status of all patients is assessed once every two years. On average, we had complete follow-up of 93.6% of our patients across the disease groups. By calling up the patients' family physicians or gynecologists, we investigated the survival status of those patients who did not attend our outpatient department for gynecological oncological aftercare. The system used for the management of patient data was the Giessen Tumor Dokumentation System, GTDS).

All patients referred to, treated, and followed up at the Department of Obstetrics and Gynecology of the Justus-Liebig-University Giessen between 1986 and 2005 were included in the analyses. There were no other criteria for inclusion than histological proof of the particular malignant tumor type. Patients' characteristics are shown in Table 1. BMI was categorized according to the Deutsche Gesellschaft für Ernährung e.V. (German Society for Nutrition) as shown in Table 1. For the calculation of the BMI, we used the preoperative weight at diagnosis. When information on grading, tumor stage, etc. was not exactly reported, unclear, or conflicting, the data were classified as unknown or unclear.

### Endometrial cancer

Most patients with endometrial carcinoma underwent primary surgery. Only patients with severe comorbidity

received primary radiotherapy, which was followed by control curettage three months later. Patients with tumor stages Ia and Ib received vaginal high-dose-rate afterloading radiotherapy, while those with more advanced tumor stages were treated with combined abdominal fields and intravaginal afterloading radiotherapy. Afterloading radiotherapy was carried out using iridium-192 as a source (high-dose-rate afterloading). In cases of primary radiotherapy, a one-tube applicator was chosen. We used hystero-graphy with an indwelling applicator to exclude patients with uterine cavities that were unsuitable for this type of treatment. Postoperative radiotherapy was administered using an ovoid-shaped applicator. Low-risk cases ( $\leq$ stage Ib, tumor grading  $\leq 2$ , and absence of lymphangiosis carcinomatosa) received intravaginal afterloading radiotherapy ( $4 \times 10$  Gy or  $5 \times 8$  Gy) only. All other patients underwent combined brachytherapy and teletherapy. A detailed overview of the therapeutic strategies used in our clinic has been published previously [16].

The histological types of endometrial cancer in these patients were as follows: adenocarcinoma, 59.4% ( $n = 701$ ); serous papillary carcinoma, 14.7% ( $n = 174$ ); adenosquamous carcinoma, 9.9% ( $n = 128$ ); squamous cell carcinoma, 0.4% ( $n = 5$ ); missing or unclear data 14.6% ( $n = 172$ ).

In a subset of 183 patients with endometrial cancer in whom the estrogen and progesterone receptor expression and the growth fraction of tumor cells (MIB1, Ki-67 antigen) had already been determined by immunohistochemistry [17], these data were also correlated with the BMI. In this subgroup, a detailed histological workup was done.

### Cervical cancer

Patients with cervical carcinomas who were initially seen at our department were evaluated critically for operability. The results of clinical examination and histological report determined whether they were managed by primary surgery or by radiotherapy. After 1998, radiotherapy was generally combined with platinum-containing chemotherapy. Patients who had been treated inadvertently by simple hysterectomy received secondary radiotherapy [18].

The general treatment plan for cervical carcinoma at this institution consisted of combined brachytherapy-teletherapy as follows:  $2 \times 10$  Gy (surface dose) high-dose-rate afterloading to vaginal wall and 45 (–51) Gy by biaxial cobalt-60 pendulum irradiation ( $3 \times 3$  Gy/week) to the B-Line (parametria) or 46 Gy abdominal opposing fields ( $5 \times 1.8$ – $2$  Gy/week), vaginal 50%-shield with or without paraortic chimney field by 18 MV beam. In some patients who showed a poor response to radiotherapy, the dose was increased to 60 Gy by opposing pelvic fields. Single doses were 2 Gy until the end of 1993; thereafter, they were reduced to 1.8 Gy. The histological types of carcinoma in

**Table 1** Age, survival, tumor stage and grade (FIGO), and body mass index in our collectives of endometrial, ovarian, and cervical cancer (Value number (%))

Variable	Endometrial cancer ( <i>n</i> = 1180)	Cervical cancer ( <i>n</i> = 738)	Ovarian cancer (824)
Age (years)			
Median	67.9	58.6	60.5
Mean ± SD	68.0 ± 10.5	57.4 ± 16.8	60.9 ± 13.1
Overall survival of patients with tumor-associated death (years)			
Median	1.7	1.3	1.6
Mean ± SD	2.3 ± 2.3	2.2 ± 2.5	2.2 ± 2.0
Follow-up (Years)			
Median	6.2	3.4	5.13
Mean ± SD	6.7 ± 5.0	5.2 ± 4.9	3.1 ± 4.9
Tumor stage (FIGO)			
I	786 (66.6)	231 (31.3)	147 (17.8)
II	150 (12.7)	237 (32.1)	101 (12.3)
III	105 [8.9]	147 [19.9]	379 (46.0)
IV	27 [2.3]	48 [6.5]	29 (3.5)
Unknown/unclear	112 (9.5)	76 (10.3)	198 (24.0)
Tumor grading			
I	212 (18.0)	20 (2.7)	73 (8.9)
II	620 (52.5)	311 (42.1)	264 (32.0)
III	249 (21.1)	240 (32.5)	332 (40.3)
Unknown/unclear	99 (8.4)	168 (22.7)	155 (18.8)
Body mass index (kg/m <sup>2</sup> )			
≤20.0	30 (2.5)	78 (10.6)	84 (10.2)
20.1–25.0	242 (20.5)	258 (34.9)	330 (40.0)
25.1–30.0	328 (27.8)	202 (27.3)	258 (31.3)
30.1–40.0	322 (27.3)	111 (15.0)	118 (14.3)
>40.1	55 (4.7)	13 (1.8)	4 (0.5)
Unknown/unclear	203 (17.2)	77 (10.4)	30 (3.6)

this group of patients were as follows: squamous cell carcinoma 65.5% (*n* = 484), adenocarcinoma 11.5% (*n* = 85), carcinoma in situ 6.9% (*n* = 51), unclear or missing data 16.1% (*n* = 119).

#### Ovarian cancer

All patients with ovarian carcinomas underwent surgery. Patients with tumors limited to the ovary (FIGO stages Ia and Ib) and low tumor grading (grades 1 and 2) received no adjuvant treatment. Patients with early disease were treated with intraperitoneal radiotherapy, using either chronic phosphate (P<sup>32</sup>) or radioactive gold and/or chemotherapy. Until 1996, we mainly used the PEC regimen (cisplatin, 50 mg/m<sup>2</sup>; epirubicin, 60 mg/m<sup>2</sup>; and cyclophosphamide, 500 mg/m<sup>2</sup>; q28); thereafter, we used combined carboplatin and paclitaxel. Patients with advanced-stage disease underwent chemotherapy combined with radiotherapy by open-field technique (2 × 15 Gy) before 1998. The histological types of carcinoma in these patients were as follows:

serous papillary, 46.7% (*n* = 385); mucinous, 6.9% (*n* = 57); endometrioid, 7.5% (*n* = 62); clear cell, 1.2% (*n* = 10); others, missing, or unclear data, 37.6% (*n* = 310).

We also updated our data on an established group of 221 patients with invasive ovarian carcinomas. Their tumors were investigated immunohistochemically for various biological factors [19–22]. These factors included the following: the steroid hormone receptors of estrogen (ER) and progesterone (PR); the tumor markers, CA125, CA153, and CEA; angiogenesis by CD31; the tumor growth fraction by Ki-67 antigen/MIB1; the bcl-2 and c-erbB-2 oncoproteins and fibronectin. In this subgroup of patients, a detailed histological workup was undertaken.

#### Statistical analysis

SPSS software for Windows™, release 14.01, was used for data management and statistical analyses (bivariate correlation, cross-tabulation, Kaplan-Meier survival analyses, Kaplan-Meier multifactorial residual survival analyses, and

Cox regression). A probability of error less than 5% was regarded as significant.

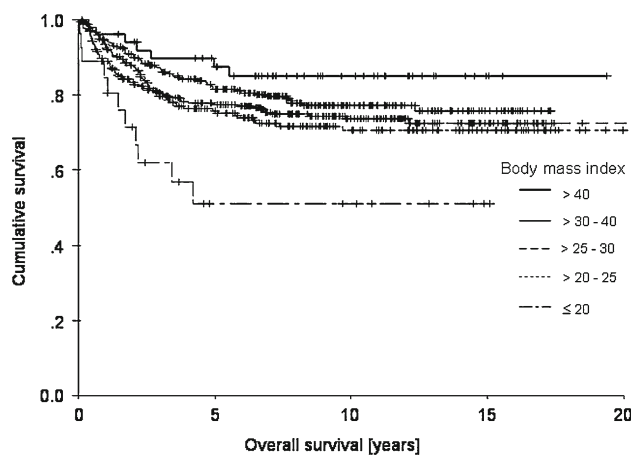
Ethical approval

The project was approved by the ethics committee of the Justus-Liebig-University, Giessen, on May 22nd, 2007 (application number 79/07).

Results

Endometrial cancer

The strength of the established prognostic factors, tumor stage and histological grading, were confirmed (log rank<sub>stage</sub> = 221.2, df = 9,  $p < 0.001$ ; log rank<sub>grading</sub> = 70.6, df = 2,  $p < 0.001$ ). Bivariate correlations showed that obese patients were likely to be younger ( $r_{age} = -0.152$ ,  $p < 0.001$ ), to be diagnosed when their tumors were less advanced ( $r_{stage} = -0.111$ ,  $p = 0.001$ ), and to have tumors that were well differentiated ( $r_{grading} = -0.072$ ,  $p = 0.010$ ). Kaplan-Meier survival analysis showed that a high BMI had a favorable influence on overall survival (log rank = 15.3, df = 4,  $p = 0.004$ ; Fig. 1). Kaplan-Meier multifactorial residual survival analysis incorporating age,



BMI category [kg/m <sup>2</sup> ]	Median survival time [years]	Standard error
≤ 20	1.48	0.42
> 20 - 25	1.19	0.16
> 25 - 30	2.02	0.28
> 30 - 40	2.16	0.31
> 40	2.16	0.56

**Fig. 1** The influence of body mass index on overall survival of patients with endometrial cancer (Kaplan-Meier survival analysis, log rank = 15.3, df = 4,  $p = 0.004$ ). Mean survival time of patients who died from endometrial cancer is given below for the different BMI categories

tumor stage, and grading confirmed the independent prognostic value of BMI (log rank = 9.53, df = 4,  $p = 0.049$ ;  $p_{beta} < 0.001$ ;  $R = 0.497$ ; Fig. 2). The Cox Proportional Hazard model showed a strong trend (Table 2). A linear association between overall survival and BMI was found.

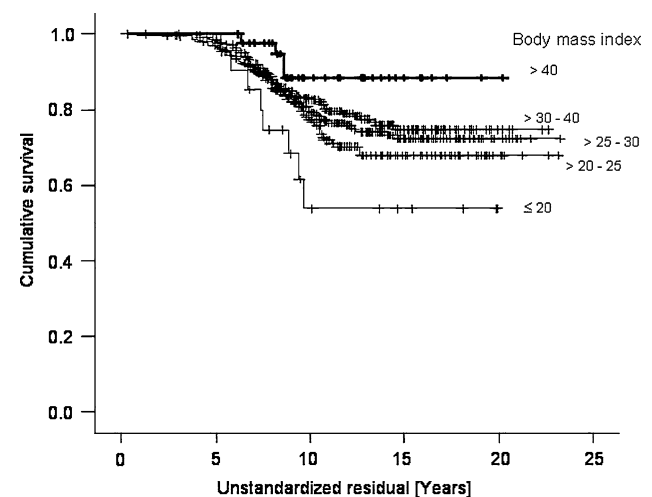
In the subset of 183 patients with endometrial cancer, we found no correlation between BMI and the expression of the estrogen and progesterone receptors or the tumor growth fraction.

Cervical cancer

The established prognostic factors, tumor stage and histological grading, were confirmed (log rank<sub>stage</sub> = 180.9, df = 10,  $p = 0.001$ ; log rank<sub>grading</sub> = 10.4, df = 2,  $p = 0.006$ ). Bivariate correlations showed that obese patients were likely to be older ( $r = 0.168$ ,  $p < 0.001$ ). BMI had no influence on tumor stage, tumor grading, or histological type. Kaplan-Meier survival analysis showed that patients with a higher BMI had a better prognosis (Fig. 3; log rank = 11.1, df = 4,  $p = 0.026$ ). Kaplan-Meier multifactorial residual survival analyses incorporating tumor stage and grading showed only a trend toward improved survival of obese patients and confirmed the prognostic value of BMI ( $p = 0.088$ ; function of the regression model  $p_{beta} < 0.001$ ;  $R = 0.345$ ). However, in the Cox Proportional Hazard model a significant favorable influence was found (Table 3).

Ovarian cancer

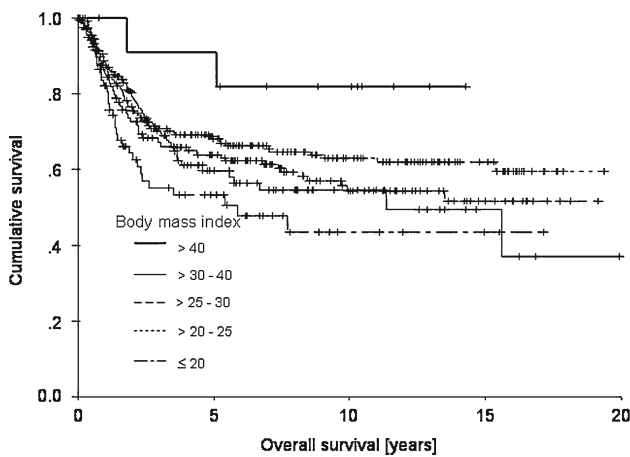
In the group of 824 ovarian carcinoma patients, the established prognostic factors, tumor stage and tumor



**Fig. 2** The influence of body mass index on overall survival of patients with endometrial cancer (multifactorial Kaplan-Meier residual survival analysis considering age, tumor stage and grading; log rank = 9.53, df = 4,  $p = 0.049$ )

**Table 2** Hazard function of Cox Proportional Hazard function for endometrial cancer ( $\chi^2 = 189.53$ ,  $df = 4$ ,  $p < 0.001$ ). Variables in the equation

	B	SE	Wald	df	Significance	Exp(B)	95.0% confidence interval for Exp(B)	
							Lower	Upper
Age	0.035	0.008	18.595	1	0.000	1.036	1.019	1.053
Grading	0.457	0.124	13.596	1	0.000	1.579	1.239	2.013
Stage	0.261	0.027	93.391	1	0.000	1.298	1.231	1.368
BMI	-0.023	0.014	2.921	1	0.087	0.977	0.951	1.003



BMI category [kg/m <sup>2</sup> ]	Median survival time [years]	Standard error
≤ 20	1.14	0.17
> 20 - 25	1.68	0.25
> 25 - 30	1.66	0.23
> 30 - 40	1.36	0.24
> 40	1.79	0.27

**Fig. 3** The influence of body mass index on overall survival of patients with cervical cancer (Kaplan-Meier survival analysis,  $\log \text{rank} = 11.1$ ,  $df = 4$ ,  $p = 0.026$ ). Mean survival time of patients who died from cervical cancer is given below for the different BMI categories

grading, proved to be highly significant ( $\log \text{rank}_{\text{stage}} = 214.3$ ,  $df = 9$ ,  $p < 0.0001$ ;  $\log \text{rank}_{\text{grading}} = 59.9$ ,  $df = 2$ ,  $p < 0.001$ ). Correlations between BMI and the patients' age, tumor stage, tumor grading, and histological type showed only a weak relationship between BMI and the patients' age at diagnosis ( $r = 0.095$ ,  $p = 0.007$ ). Cross-tabulation showed no influence of BMI on the histological

tumor type. Kaplan-Meier survival analysis using the BMI categories of the German Society for Nutrition did not reveal a significant result. When we split the collective at the BMI value of 25 kg/m<sup>2</sup>, we found a trend toward improved survival in obese patients ( $\log \text{rank}_{\text{stage}} = 3.74$ ,  $df = 1$ ,  $p = 0.053$ ; Fig. 4). Restricting this analysis to patients with serous histology reveals a similar Kaplan-Meier survival curve; however, the result is not statistically significant. When the analysis was restricted to patients with various tumor stages with and without postoperative tumor residuals or patients with and without evidence of disease after completion of primary treatment, no significant results were found. Overall survival of patients, independent of tumor-associated deaths (birth until death, diagnosis of ovarian cancer until death), also showed no significant influence of obesity.

In a more detailed analysis of the subgroup of 221 cases, we correlated patients' BMI with various molecular factors. Tumor growth fraction and angiogenesis, expression of ER, PR, bcl-2, c-erb-B2, and fibronectin as well as CA-125, CA15-3, and CEA showed no correlation with BMI, except for the expression of c-erb-B2 in tumor cells of obese patients, which was found less frequently ( $r = -0.142$ ;  $p = 0.039$ ). In this subgroup, multifactorial residual Kaplan-Meier analysis, incorporating all relevant prognostic factors including postoperative residual mass and treatment outcome, showed no adverse effect of obesity.

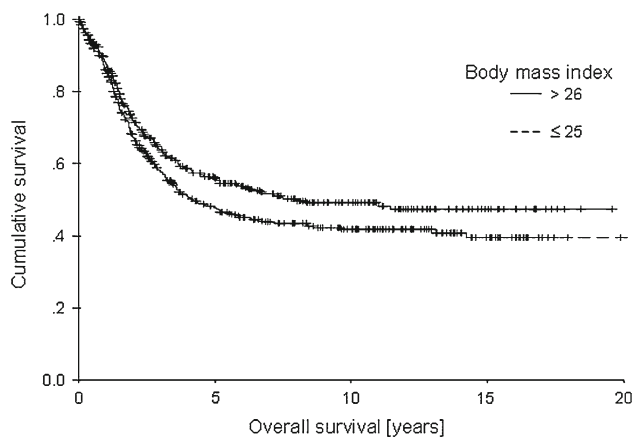
**Discussion**

Our analysis showed that the BMI has no adverse influence on poor prognostic factors or prognosis in patients with

**Table 3** Hazard function of Cox Proportional Hazard function for cervical cancer ( $\chi^2 = 141.30$ ,  $df = 4$ ,  $p < 0.001$ ). Variables in the equation

	B	SE	Wald	df	Significance	Exp (B)	95.0% confidence interval for Exp (B)	
							Lower	Upper
Grading	0.295	0.136	4.694	1	0.030	1.343	1.029	1.753
Stage	0.803	0.084	92.101	1	0.000	2.233	1.895	2.631
Age	0.019	0.005	14.413	1	0.000	1.019	1.009	1.029
BMI	-0.035	0.015	5.905	1	0.015	0.965	0.938	0.993





BMI category [kg/m <sup>2</sup> ]	Median survival time [years]	Standard error
≤ 20	1.62	0.28
> 20 - 25	1.69	0.14
> 25 - 30	1.48	0.08
> 30 - 40	1.92	0.35
> 40	3.44	0.09

**Fig. 4** The effect of body mass index on overall survival in the total patient group of patients with ovarian cancer (Kaplan-Meier survival analysis, log rank = 3.74; df = 1;  $p = 0.053$ ). Mean survival time of patients who died from ovarian cancer is given below for the different BMI categories

endometrial, cervical, and ovarian carcinomas. In contrast, it showed a weak but significant advantage in survival affects in obese patients. Interestingly, the impact of age, tumor stage, and grading differ in patients with endometrial and cervical cancer. While obese patients with endometrial cancers tend to be younger, the opposite seems to be true for those with cervical cancer. A comparison of the results shows that the favorable effects of obesity are more pronounced in patients with endometrial cancer and cervical but least evident in those with ovarian cancer.

The retrospective design of this study has imposed some limitations. Not all cofactors (e.g., residual tumor mass in the case of ovarian cancer) could be analyzed in all cases in the groups. Furthermore, few lymphadenectomies were undertaken, especially in the older patients, and this could have led to an underestimation of tumor stages. However, our study has other important strengths. Our institution was the only one offering chemotherapy and radiotherapy in the region of Giessen for large parts of the study period; thus, selection bias was low. The follow-up of patients, which is crucial for Kaplan-Meier survival analyses, was done very thoroughly at our institution. In general, routine assessments of survival status were completed every year and these assessments also tried to ascertain the exact causes of death. It has also been shown that retrospective analyses may well be able to determine the extent and quality of treatment effects [23]. In addition, the present study is of

great interest since it is, to our knowledge, the first detailed analysis of the influence of BMI on tumor biology, and, in particular, on cervical cancer where we succeeded to prove that high BMI may also be an independent favorable prognostic factor.

Since the correlation coefficients with BMI are low, the better differentiation and lower stages of endometrial carcinomas may only partially explain the more favorable prognosis of obese patients. These findings agree with those in earlier studies [12, 13, 24]. However, we have shown that BMI is a prognostic factor that is independent of age, tumor stage and grading in one of two multifactorial analyses. Temkin et al. [13] did not succeed with this, but it may result from the fact that our study group is almost three times larger.

It seems that the at least partially hormonally responsive ovarian carcinomas do not differ from other tumor entities regarding the influence of obesity on survival that has previously been suggested in smaller and less comprehensive studies [15, 25]. Regarding the histological tumor type, our data agree with those of other workers, who found no relationship between tumor type and BMI or fat intake [26, 27]. When we analyzed various molecular factors in ovarian carcinomas, we found that only the tumor expression of c-erb-B2 was significantly less likely in obese patients. Since c-erb-B2 expression is associated with more advanced stages of ovarian cancer [28], obesity alone may not represent a negative prognostic factor.

In general, a higher BMI has proved to be a favorable prognostic factor in many tumor entities, including ovarian cancer, gastric cancer, esophageal cancer, and clear cell renal cell carcinoma [14, 29–31]. Apart from the possible influences of obesity on tumor biology, obese patients definitely have better nutritional resources to withstand longer the problems associated with metastatic disease and tumor cachexia [32]. This finding also corresponds well with the fact that early nutritional interventions and parenteral nutrition have a positive influence on the survival of cancer patients [33]. There are a few exceptions to this general rule, but these still need to be explained. For example, in breast cancer, some studies and our own unpublished data show that obese patients have a significantly poorer prognosis [34, 35]. However, underweight patients are known to have a poorer prognosis as well [36].

Obesity is associated with overproduction of steroid hormones that increases the incidence of ovarian and endometrial cancer. However, its role in the incidence of cervical cancer still remains to be defined. It has been shown that tumor-inducing factors may exert different roles in relation to tumor incidence and the course of disease. Examples of this are BRCA1 mutations, which lead to a higher incidence of ovarian cancer but are linked with a better prognosis [37, 38], and parity, which reduces the

incidence of ovarian cancers but worsens the patients' prognosis [39, 40]. This paradox has been explained by the threshold model, which suggests that under the influence of cancer-promoting factors the development of disease takes less time, fewer gene mutations and leads to more tumors. In the case of the tumor, however, it is probably more aggressive than that which develops in a regular situation and under the influence of protective factors [39].

In conclusion, obese patients do not seem to have a poorer prognosis than their nonobese counterparts in cases of carcinomas of the uterus or the ovary. We found some evidence that the opposite may be true, which raises the question of whether lean patients with gynecological cancers and advanced disease should be advised to gain some weight to improve their survival chances in case of recurrence. However, patients with a favorable prognosis are well advised to normalize their weight to avoid the well-known negative general consequences of obesity.

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