Body mass index and the risk of male cancer mortality of various sites: 17-year follow-up of the Basel cohort study

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Questions under study: There is growing evidence for a link between body weight and cancer risk, but there is not a clear consensus yet.

Methods: We studied the association between body mass index (BMI) and overall, lung, prostate and colon cancer mortality. In 1971/73, weight and height were measured in 2974 men working in Basel, Switzerland. In 1990, the vital status of all participants was assessed.

Results: 290 men had died from cancer, 87 from lung, 30 from prostate, and 22 from colon cancer. In the predefined Cox Proportional Hazards Regression Models for survival analysis, a baseline hazard was modified multiplicatively by covariates, i.e. the untransformed continuous variable “BMI” was chosen as covariate. In addition it was assumed that the baseline hazard may be different for smokers, non-smokers and different age groups (age at entry into study). Thus, multiple strata, i.e. combinations of smoking status and age groups were allowed. With increasing BMI overall cancer mortality did not change. Accordingly, the relative risk (RR) per 1-unit increase of BMI (unit = 1 kg/m²) was 1.03 (95% CI: 0.99–1.07). In relation to lung cancer, mortality did neither increase nor decrease with increasing BMI (RR = 1.0; 95% CI 0.93–1.07). The results for prostate cancer mortality were similar, i.e. no correlation with BMI was observed (RR = 0.95; 95% CI: 0.93–1.18). The same was true for colon cancer mortality (RR = 1.09; 95% CI: 0.92–1.24).

Conclusions: This investigation provides little evidence of an association between BMI and mortality of all cancers combined, cancer of the lung, the prostate and the colon.

Key words: BMI; cancer mortality; cohort study; overall cancer; lung cancer; prostate cancer; colon cancer

Introduction

Body mass index (BMI), defined as a person’s weight in kilograms divided by the square of height in meters, is often used in epidemiologic studies as a proxy measure of overweight and obesity. It is widely accepted that a high BMI is associated with an increased risk to health, in particular with regard to hypertension, diabetes mellitus, and ischemic heart disease [1]. There is also growing evidence for a link between body weight and cancer risk [2–5]. Calle and co-workers for example showed a positive linear trend in death rates for all cancers with increasing BMI [5]. Among western men the three most common cancers in order of incidence are lung, prostate, and colon/rectum [2]. These cancers are all considered to be related to body weight, but there is not a clear consensus yet [4]. Obese men have been reported to be at higher risk of colorectal cancer in most but not all studies [3, 4]. Previous surveys on the relationship between incident prostate cancer and BMI have been controversial, predominantly no association, or a small increased risk among heavy men was found. The few mortality data, on the other hand, showed an increased risk more consistently [6]. Finally, an elevated risk of lung cancer associated with lower levels of BMI has been reported in a number of studies [7].

Evidence on body weight and cancer is not straightforward because the cancer process itself may cause loss of weight, even before the cancer is evident [2, 8–10]. Manson et al. 1987 [11] proposed several approaches to minimize this effect, i.e. careful screening of the patient population at baseline, exclusion of subjects experiencing substantial weight loss in the previous year, and to disregard mortality within the first few years of follow-up. On the other hand, analytic and simulation work by Allison et al. suggested that exclud-
ing subjects who died during the first few years of follow-up did not substantially decrease confounding by occult disease and under certain circumstances, did increase such bias [12, 13]. Moreover, smoking has to be considered as a potential confounding factor, because smokers on the one hand are at higher risk for cancer and, on the other hand are, on average, thinner than non-smokers.

The present report deals with cancer-related deaths (n = 290) during the 17-year follow-up (1971/73–1990) of 2974 men of the Basel Study. The hypothesis of an association between body mass index at baseline and cancer mortality risk was tested for all cancers combined and for cancer of the lung, prostate, and colon. No attempt was made to exclude mortality during the first few years of follow-up.

### Materials and methods

#### Study population

In 1971–1973, 2974 men were recruited for a cohort study in Basel, Switzerland. These were healthy volunteers of relatively high and homogenous socioeconomic status, most of them working in the former three major chemical/pharmaceutical companies in Basel. The age range of study participants was from 20 to 79 years. At recruitment all participants had a clinical examination (including height and weight measurements), underwent laboratory investigations, and completed a questionnaire. Body height and weight were measured in light indoor clothing without shoes.

The analysis was stratified according to the potential confounders “age” and “smoking” (see below). It is well known that age is a major risk factor for all cancer sites considered and that BMI increases with age in the general population. As shown in table 2 of the present study, cancer cases of all considered sites were on average older than survivors. Furthermore, BMI increased with advancing age (data not shown). Smoking is a known major risk factor for lung cancer. For prostate and colorectal cancer evidence is not conclusive, but results of recent studies are promising. Furthermore, smokers were on average thinner than non-smokers (mean BMI 25.1 and 25.8 respectively). At baseline no information was collected on past smoking, duration, age at which smoking started, and depth of inhalation. Moreover, no further information on socioeconomic status and recent weight loss was assessed and no screening for cancer was done.

In 1990 the vital status was assessed for the entire cohort of the 2974 men. Information about death was provided by employers, relatives, and local authorities. Death certificates were used to identify causes of deaths. A total of 801 men died during the 17 years of follow-up, including 290 from cancer (International classification of Diseases, Injuries, and Causes of Death, eight Revision (ICD-8), codes 140-239). For the present analyses, the malignancies grouped into all cancer (n = 290), lung cancer (n = 87, ICD-8 code 162), prostate cancer (n = 30, ICD-8 code 185), and colon cancer (n = 22, ICD-8 code 153).

#### Statistical analysis

**Descriptive analysis**

Group means and standard deviations of BMI, age, as well as number and percentages of smokers at baseline are provided for cancer deaths, all deaths and survivors.

In order to display the relationship of BMI graphically for each endpoint survival curves, where the BMI was categorized into quartiles (figures 1–4), were plotted for smokers and non-smokers. Concrete values for BMI-quartiles were:

<table>
<thead>
<tr>
<th>min</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.37</td>
<td>23.51</td>
<td>25.31</td>
<td>27.44</td>
<td>42.92</td>
</tr>
</tbody>
</table>

**Risk analysis**

Inferential analysis of the explanatory variables was based on Cox Proportional Hazards Regression Model for survival analysis [14, 15]. The time for each endpoint was coded as “time in study” (in days) for the cases. The 30th of June 1990 was set as the final date for the study. Survivors up to this date and subjects dying from another cause than the specific endpoint (all cancers, lung cancer, colon cancer, prostate cancer) were considered as right-censored (with respect to the corresponding endpoint).

In Cox models, a baseline hazard is modified multiplicatively by covariates. In our case, the untransformed continuous variable “BMI” was chosen as covariate in order to look for association between survival and baseline BMI. It was assumed that the baseline hazard may be different for smokers and non-smokers as well as for different age groups (age at entry into study). So, we allowed for multiple strata, i.e. combinations of smoking status (smokers, non-smokers) and age group. The age groups were chosen as ≤50 y, >50 y–65 y and >65 y for the endpoint ‘all cancers’ and ≤60 y as well as >60 y for the other endpoints due to the limited number of cases. Tables 1a and 1b show the number of cases for each stratum and endpoint.

The linearity of BMI was checked by plotting the martingale residuals from a model with BMI removed versus BMI. For all endpoints, the relation looked linear. The correlation coefficient between transformed survival time and the scaled Schoenfeld residuals was tested in order to check the proportional hazard assumption [16]. In this analysis we did not check for competing risks, i.e. the possibility that censoring did not occur completely at random but by other deaths with possible dependencies to the endpoints under consideration. All statistical analyses were performed using S-Plus version 6.1 for Windows [17].

### Table 1a.

<table>
<thead>
<tr>
<th>Strata</th>
<th>Number of all cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker and age ≤50 years</td>
<td>25</td>
</tr>
<tr>
<td>Non-smoker and age &gt;50–65 years</td>
<td>77</td>
</tr>
<tr>
<td>Non-smoker and age &gt;65 years</td>
<td>30</td>
</tr>
<tr>
<td>Smoker and age ≤50 years</td>
<td>17</td>
</tr>
<tr>
<td>Smoker and age &gt;50–65 years</td>
<td>99</td>
</tr>
<tr>
<td>Smoker and age &gt;65 years</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
</tr>
</tbody>
</table>
Descriptive analysis

Baseline characteristics of male cancer deaths (n = 290), all deaths (n = 801) and survivors (n = 2,173) are given in table 2. Group means for BMI were slightly higher in the overall cancer group and in the groups of prostate and colon cancer deaths than in the survivors group. Mean BMI of lung cancer cases and survivors on the other hand did not differ. On average, cancer cases of all the considered sites were about 10 years older than survivors. As expected, a higher percentage of smokers was observed in the lung (75%) and all cancer (55%) groups than among survivors (40%). Slightly higher percentages were also seen in the prostate cancer and the all deaths groups, but not in the colon cancer group.

In order to display the relationship of BMI graphically for each endpoint, survivor curves, where the BMI was categorized into quartiles, were plotted for smokers and non-smokers (figures 1–4).

Risk analysis

In table 3 the results of the analyses based on the Cox Proportional Hazards Regression Models are summarized.

With increasing BMI overall cancer mortality did not change. Accordingly, the relative risk (RR)
Body mass index and the risk of cancer mortality

Figure 2.

Figure 3.

Figure 4.
Table 3. Relative risks (RR) and 95% confidence intervals (CI) for fatal cancer by 1-unit increase of BMI (unit = 1 kg/m²).

<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>RR* per unit increase of BMI</th>
<th>Lower 95% confidence limit</th>
<th>Upper 95% confidence limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers (n = 290)</td>
<td>1.03</td>
<td>0.99</td>
<td>1.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Lung cancer (n = 87)</td>
<td>1.0</td>
<td>0.93</td>
<td>1.07</td>
<td>0.96</td>
</tr>
<tr>
<td>Prostate cancer (n = 30)</td>
<td>0.95</td>
<td>0.93</td>
<td>1.18</td>
<td>0.42</td>
</tr>
<tr>
<td>Colon cancer (n = 22)</td>
<td>1.09</td>
<td>0.92</td>
<td>1.24</td>
<td>0.2</td>
</tr>
</tbody>
</table>

BMI, body mass index, which is calculated as weight in kilograms divided by the square of height in meters. * The risk is defined as exp(β), where β is the coefficient of BMI in the corresponding Cox regression model.

As in our study, Seidell et al. in their large Dutch cohort observed no clear association between total cancer mortality and BMI. The lowest mortality was seen in slightly overweight men. In non-smokers no association was found at all [18]. In the Health Professional Follow-up study neither the 65+ year olds nor the younger study participants showed any significant relation between BMI and mortality due to overall cancer [19]. In the American Cancer Society’s prospective study, conducted in 1960–1972, the mortality ratio in males was highest (1.33) among men who were 40% or more overweight and in those who were 20% or more underweight. In male nonsmokers, mortality ratio did not change much with increasing weight index [20]. A U-shaped association between BMI and cancer occurrence as well as cancer mortality was also seen in a Japanese cohort study [21]. Low BMI affected cancer occurrence more strongly among current smokers than in never-smokers. Calle et al. [5] revealed significant positive linear trends in death rates with increasing BMI for all cancers in men and women, with the exclusion of participants with a BMI of less than 18.5 from the analyses. Among those who had never smoked the positive association was of greater magnitude than in the total population. The heaviest men (those with a BMI of at least 30) had death rates from all cancers that were 52% higher than the rates in men of normal weight. In a Swedish cohort a comparable 33% excess incidence of cancer was seen in obese persons [22]; no results on lower BMI categories were presented. The divergent findings on the association between BMI and overall cancer risk may be attributable to the wider or narrower range of BMI-values between studies, to the BMI categorization, to bias introduced by reverse causality, i.e. by the effect of occult cancer on body weight, to bias due to the weight-lowering effect of smoking, and/or to the percentage of smoking-related cancers of the total group of cancer [5].

In our cohort study 87 of 290 cancer deaths were due to lung cancer. No significant association between BMI and lung cancer mortality was observed. Thus, our results provide no evidence for an elevated risk of lung cancer in association with lower levels of BMI. This was previously seen in all but one of five cohort and three case-control studies considered in a review of the International Agency for Research on Cancer (IARC) [4]. Since cigarette smoking is directly associated with lung cancer risk and inversely associated with BMI, the inverse association of BMI with lung cancer observed in most studies may be the result of incomplete adjustment for the effects of smoking. Accordingly, Rauscher et al. [23] found in their case-control study among former and never smokers that persons in the upper octile of BMI had a twofold greater risk of lung cancer. Obese persons are known to have higher circulating levels of insulin, which may act as a growth factor on cancer cells directly by activating its own receptor or the
receptor for IGF-I, a potent mediator of cell growth and survival [24].

Several cohort studies suggested that an inverse association between BMI and lung cancer risk was limited to those who developed lung cancer in the first years of follow-up [4]. Thus, the inverse association observed between BMI and lung cancer may also be explained by weight loss due to preclinical lung cancer. In the present study we did not attempt to control the effect of pre-existing cancer. No information on recent weight loss was available and no screening for cancer had been done at baseline. Furthermore, as Allison et al. pointed out, to the extent that the exclusion of the first few years of follow-up from the analyses has any effect, the observation of this reduction may be attributed to occult disease when in fact it could be the lowering of the overall age of subjects rather than the elimination of subjects with pre-existing occult disease [13].

As for lung cancer, our study did not observe a significant association between per unit increase of BMI and prostate cancer mortality. Previous studies on the relationship between incident prostate cancer and BMI have been inconsistent, finding no association particularly in case-control studies, a small increased risk (for references see [6, 25]) or even an inverse association [26, 27]. In contrast, an increased risk associated with obesity was suspected for prostate cancer mortality [6, 22, 28, 29]. Accordingly, Andersson et al. [28] found in their cohort study of prostate cancer incidence and mortality a stronger association between BMI and prostate cancer mortality (RR: 1.40) than was seen with incidence (RR: 1.13). Three other studies [30–32] assessed whether BMI predicted more advanced incidence prostate cancer, but the results were not consistent. Accordingly, the IARC [4] concluded that although the majority of the significant associations with body mass were found in studies which focused on fatal or more aggressive tumours, a clear pattern of a stronger association for the more clinically significant forms of the disease has not been consistently observed. BMI reflects both lean body mass and adipose tissue, and thus may not be an ideal measure for studies of an androgen-dependent tumour, such as prostate cancer, since lean body mass is related to androgen levels [4].

Although the relationship of BMI to colon cancer has been studied extensively, there does not appear to be a clear consensus [2, 3]. Obese men have been reported to be at higher risk of colorectal cancer, whereas data for women has been more inconsistent [for references see 2, 3, 4]. Even though our negative findings are in accordance with the results of a few other studies [33, 34], they are rather due to the small number of colon cancer deaths (n = 22) in the present study.

Overall, the associations between BMI and cancer mortality of various sites should be interpreted within the limitations of the present study. Strengths of our study include the completeness of follow-up of all study participants and the rather homogenous socioeconomic status of the 2974 men. A limitation of our study was that we had to rely on measured body weight at a single point in time. Furthermore, there was no information on (recent) weight loss and no screening for cancer had been done at baseline. In addition, at baseline no information was collected on past smoking, duration, age at which smoking started, and depth of inhalation.

In conclusion, our prospective data do not support an association between current body mass index and mortality of all cancers combined, and cancer of the lung prostate and colon.

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