Impact of smoking and excess body weight on overall and site-specific cancer mortality risk

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Abstract

Background
Smoking and excess body weight are major preventable risk factors for premature death. This study aimed at analysing their single and combined association with site-specific cancer mortality.

Methods
Our study population comprised 35,784 men and women aged 14-99 years, who participated in population-based health surveys conducted 1977-1993 in Switzerland and were followed-up for mortality until 2008. Multivariable Cox proportional hazards models were calculated for different cancer sites, and population attributable fractions were derived.

Results
The hazard ratio of dying from cancer (all sites) was 2.32 [95% CI: 2.04, 2.63] for heavy smokers (vs. never smokers) and 1.15 [1.01, 1.32] for obese (body mass index (BMI) ≥ 30 kg/m²) vs. normal weight individuals. Heavy smoking (≥ 20 cigarettes/day) was associated with increased mortality due to cancer of the lung, upper aero-digestive tract, pancreas, bladder, liver, and the total of remaining sites. Obesity was associated with higher risk of dying from cancer of the liver and the female genital tract (essentially corpus or cervix uteri and ovary). More than 20% of all cancer deaths in our population were attributable to ever smoking and overweight (BMI ≥ 25 kg/m²).

Conclusions
Smoking was a much stronger risk factor for cancer than excess body weight. For lung, liver and pancreatic cancer the combination of excess body weight and smoking lead to cumulated higher risks.

Impact
Our findings support recommendations for obese persons to quit smoking despite potential post-cessation weight gain.

Abbreviations:
BMI: body mass index
NRP 1A: National Research Program 1A
SOMIPOPS: SOcio-Medical Indicators for the POPulation of Switzerland
MONICA: MONItoring of trends and determinants in CArdiovascular disease

SHS: Swiss Health Survey

CI: confidence interval

SNC: Swiss National Cohort

UADT: upper aero-digestive tract

ICD: International Classification of Diseases

HR: hazard ratio

AIC: Akaike’s information criterion

PAF: population attributable fraction

SD: standard deviation

PA: physical activity
Introduction

In Switzerland, as in other developed countries, age-standardized mortality due to cancer is declining, however less than that due to other causes of death. As a consequence of population ageing, case counts are still increasing. Even more unfavorable are the figures for cancer incidence (1), underlining the importance of prevention. Smoking and obesity are two major risk factors for premature death in western populations (2–4). Their prevalence is still high in many countries. While smoking has slowly decreased over the past decades (particularly in men), it is unclear whether the obesity epidemic has reached its peak (5). In Switzerland, recent trends suggest a continuation of the increase of the obesity prevalence over time in adults (6). Individuals, who accumulate these two risk factors, i.e. smoking plus obesity, may have a particularly high risk of dying from cancer. Statistics from 2012 indicate that of the adult male and female permanent resident population of Switzerland, 49% and 29% had excess body weight (body mass index (BMI) ≥ 25 kg/m²), 29% and 22% smoked, and 13% and 6% had excess body weight and smoked, respectively (7).

The few studies looking at this co-occurrence provided, however, conflicting results (2,8,9). Freedman et al. (2) reported the cancer mortality risk to be higher in obese than in normal weight current smokers, but for older individuals (age ≥ 65 years) the association between obesity and cancer mortality was more apparent in never than in former or current smokers. In contrast, Kitsantas et al. (8) reported that younger women (41-50 years) who smoked had a higher cancer mortality risk if they were underweight. Hjellvik (9) et al. examined middle age death risk and observed the combination of obesity and heavy smoking to increase the risk by the factor of 5.

Moreover, it is unclear whether specific cancer sites are more affected than others by smoking, obesity or both, and which BMI levels, i.e., overweight and obesity vs. normal weight, are important. Our aim was to examine the significance of smoking and increased BMI on overall and site-specific cancer mortality in terms of relative risks and population attributable fractions (PAF). For this purpose, we used data from general population-based studies conducted in Switzerland between 1977 and 1993, which were linked with the Swiss National Cohort (SNC) for a mortality follow-up until the end of 2008.
Materials and Methods

Study population

Details about the study population were described previously (10). In brief, it consists of 35,784 participants aged 14-99 years at baseline who participated in one of four different population-based studies conducted between 1977 and 1993: NRP 1A (National Research Program 1A, 1977-79), SOMIPOPS (SOcio-Medical Indicators for the POPulation of Switzerland, 1982), Swiss MONICA (MONItoring of trends and determinants in CArdiovascular disease, three waves: I, 1984-86; II, 1988/89; III, 1992/93), and the first SHS (Swiss Health Survey, 1992/93). Cause-specific mortality follow-up until 2008 was obtained via anonymous record linkage with the Swiss National Cohort (SNC) (10,11).

After exclusion of 81 participants because of missing values in covariates used for the fully adjusted model, our study population comprised 35,703 participants with a mean and maximum follow-up time of 18.9 and 31.9 years, respectively. More details about the study population stratified by survey can be found in Supplementary Table S1.

Body Mass Index (BMI)

BMI was defined as weight (kg) divided by the square of height (m²) and classified into following categories: normal/underweight (reference category, BMI < 25.0 kg/m²), overweight (25.0 ≤ BMI < 30.0 kg/m²), and obesity (BMI ≥ 30.0 kg/m²). Only about 3.5% of the study population was underweight (BMI < 18.5 kg/m²). Moreover, this underweight population (irrespective of smoking status) had a similar cancer risk as normal weight persons (10). We therefore combined this category with normal weight in our analyses. In MONICA and NRP 1A, weight and height were measured at baseline, whereas in SOMIPOPS and SHS 92/93, they were reported by the participants (10).

Smoking

We defined the following smoking categories: never (reference category), former (reported having ever smoked for more than 6 months), current light (< 20 cigarette equivalents a day) and current heavy (≥ 20) smokers. Thereby, one pipe or cigarillo equals two, and one cigar equals four cigarette equivalents. Unfortunately, we only had fragmentary information on smoking duration and intensity in former smokers.
Covariates

Besides the covariates smoking and BMI we chose age (in years), sex (where appropriate), survey, years of education, marital status, nationality, frequency of physical activity (PA), alcohol consumption and a diet proxy variable for the fully adjusted model. For all covariates we used baseline information.

The covariate survey had 6 categories: NRP 1A, SOMIPOPS, MONICA I-III, SHS. Marital status had 4 categories: single, married, widowed, divorced. Nationality was binary: Swiss and other nationalities. For frequency of PA we used the categories daily, several times per week, once per week, and less. Alcohol was used as a binary variable and refers to the consumption the day before the interview (yes/no). As a proxy for a healthy diet a binary variable was defined: For MONICA, NRP 1A and SOMIPOPS as “regularly eating three main meals per day” and for SHS 92/93 as “eating fruits and vegetables at least once per day”.

Outcome variables

Causes of death were coded according to the International Classification of Diseases (ICD). Until the end of 1994 the 8th (ICD-8) and since 1995 the 10th (ICD-10) revision was used. For our cancer-specific analyses we aggregated them in the following 13 cancer groups: all cancers (ICD-8: 140-239; ICD-10: C00-C99, D00-D48), cancer of the lung (ICD-8: 162; ICD-10: C33-C34), colon or rectum (ICD-8: 153-154; ICD-10: C18-C21), upper aero-digestive tract (UADT, ICD-8: 140-150, 161; ICD-10: C0, C10-C15, C32), lymphatic and haematopoietic tissue (abbreviated as “blood cancer” in the following, ICD-8: 200-209; ICD-10: C81-C86, C88, C90-C96), pancreas (ICD-8: 157; ICD-10: C25), bladder (ICD-8: 188-189; ICD-10: C67-C68), liver (ICD-8: 155; ICD-10: C22), stomach (ICD-8: 151; ICD-10: C16), breast (ICD-8: 174; ICD-10: C50), female genital tract (ICD-8: 180-184; ICD-10: C51-C58), prostate (ICD-8: 185; ICD-10: C61), and the total of remaining cancer sites.

Statistical analysis

For descriptive analyses, we stratified the population by sex and smoking status and calculated counts, means, standard deviation, and proportions. To reduce the number of missing values, we imputed (12) the covariates BMI (number of missing values (n) = 451), years of education (n = 577)
and frequency of physical activity (PA, n = 1,021). Multiple imputation was used for BMI and frequency of PA. As we had information on the education category (mandatory (modal value 9 years), further education (12 years), higher education (16 years), university (19 years)) for most of the missing values in the variable “years of education”, we used the modal value (was the same for women and men in all categories) for each category as imputation value. For all analyses, we excluded 81 observations that after imputation still contained missing values for one of the covariates required for the fully adjusted model.

To derive hazard ratios (HR) we calculated Cox proportional hazards models. We hereby used survival or censoring time from study entry as well as different cancer site-specific binary variables as outcomes. The models were calculated for both sexes separately and combined. Time to event or censoring was defined as time difference between study entry (date of baseline interview) and date of death from site-specific cancer, or the possible censoring dates of death from other causes, emigration, or end of the study (December 31, 2008), respectively. Model variables were selected according to Akaike’s information criterion (AIC). We calculated two Cox models for every cancer-specific outcome with different adjustment levels: Beside smoking and BMI, the basic model was adjusted for age, sex (where appropriate), and survey. The multivariable adjusted model additionally included years of education, marital status, nationality, frequency of PA, alcohol consumption and healthy diet. We also tested for a multiplicative interaction effect of smoking with BMI in the models. In order to calculate cumulative HRs for different risk combinations of BMI and smoking categories, we used linear combinations of the estimated HRs from the Cox models. The proportional hazards assumption was tested using Schönfeld residuals. The assumption was sufficiently fulfilled for all sex-specific models and not fulfilled for three out of ten sex-combined models, namely for all cancer deaths combined, lung cancer and the total of remaining cancer deaths.

To calculate population attributable fractions (PAFs) for smoking and BMI we used the punafcc STATA package by Newson (13). Smoking (ever including former vs. never smoking) and BMI (cut-off point at 25 kg/m²) were dichotomized for this analysis. This cut-off point for BMI was selected due to small case numbers for obese participants.

All analyses were conducted in STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).
Results

Baseline characteristics and figures for specific cancer sites are shown in Table 1. Heavy smokers exhibited higher proportions of persons being physically inactive and following a poor diet than individuals of the other smoking categories. The proportion of those who reported alcohol consumption on the previous day was lower in never smokers compared to all others. The mean age at baseline was lower for light and heavy smokers than for never and former smokers. Mean BMI was highest for former smokers. Sex-specific values are shown in Supplementary Table S2. Of the 7,383 persons who died in 676,312 person-years, 2,379 died of cancer. The proportion was higher in ever smokers (35.9%) than in never smokers (28.3%). This was mainly due to lung cancer and - to a smaller extent - to UADT cancer. In heavy smokers, about 41% and 10% of cancer deaths were from lung and UADT cancers as opposed to 8% and 3% in never smokers, respectively. On the other hand, deaths from other cancers, such as colorectal, were less frequent in heavy smokers compared to the other smoking categories.

Table 2 shows HRs with 95% confidence intervals (CI) of BMI and smoking categories based on the fully adjusted Cox model for both sexes combined. Results from the basic model differed only marginally (data not shown). The risk for dying of any cancer was 15% [95%-CI: 1%-32%] higher for obese compared to normal-weight persons and 132% [104%-164%] higher for heavy compared to never smokers. Heavy smoking was also associated with an increased risk of dying from lung, UADT, pancreas, bladder, and liver cancer as well as a cancer of the remainder group. Former and light smoking were associated with increased risk to die of any site, lung and UADT cancer. Moreover, former smoking was associated with a higher risk for liver cancer. The significant association of former smoking with lung cancer (HR=2.29 [1.64, 3.20]) was only due to the association in men (HR=2.22 [1.46,3.38]; women: HR=1.05 [0.47, 2.34]). Sex-specific results of the fully adjusted model are shown in Supplementary Table S3. As a sensitivity analysis, we categorized smokers exclusively based on the number of cigarettes smoked per day (i.e. not considering cigars, cigarillos and pipes). The classification was the same for 96.4% and 97.8% of light and heavy smokers, respectively. The results of the Cox models remained virtually unchanged, with respect to both, the magnitude and the statistical significance.
Obese participants had an elevated risk of dying from cancers of the liver and female genital tract compared to normal weight persons whereas in overweight individuals, only prostate cancer reached statistical significance. We did not detect a significant association of overweight or obesity with breast cancer mortality in our data when looking at the entire age span. Inclusion of a smoking BMI interaction term did not significantly improve our models for all 13 cancer sites. In a sensitivity analysis, we calculated the Cox models in participants with measured BMI (NRP1A, MONICA I-III). The associations with all sites combined and liver cancer mortality were very similar. However, the association between obesity and pancreas cancer was statistically significant (HR = 2.37, 95% CI = [1.25, 4.48]) despite fewer mortality cases (77 vs. 127).

As shown in Figure 1, there is a suggestive cumulative association of BMI and smoking with specific cancer sites, such as pancreas or liver. For the other cancer sites, there was no significant cumulative association seen. Exact figures for the cumulative HRs including 95% CIs are shown in the Supplementary Material in Table S4 for all specific cancer sites.

The proportions of selected site-specific and total cancer deaths attributable to ever (including former) smoking and BMI ≥ 25 kg/m² are shown in Figure 2. Exact values of the PAFs including 95% CIs, also for other relevant cancer sites and sex-specific, are shown in Supplementary Table S5. About 22% of prostate cancer deaths were attributable to BMI ≥ 25 kg/m². For total, lung and liver cancer, 13%, 61% and 39% of deaths were attributable to ever smoking, respectively. Of all deaths deaths due to liver, pancreatic and prostate cancer 50%, 29% and 29% were attributable to ever smoking and overweight combined, respectively.
Discussion

Our results show that smoking was more strongly associated with cancer mortality than obesity. Heavy smokers had higher risks of dying from total, lung, UADT, pancreatic, bladder and liver cancer compared to never smokers. Moreover, former and light smokers had an increased risk of dying from any cancer, mainly due to lung and UADT cancer. Being obese compared to normal weight was associated with a small increased overall cancer risk and an elevated site-specific risk for cancer of the liver, the female genital tract as well as pancreatic cancer (only in participants with measured BMI). We did not observe a significant interaction between increased BMI and smoking on cancer mortality risk, which speaks against a substantial cumulative association with smoking and BMI. When calculating the PAF of ever smoking and overweight combined there was a suggestive cumulative association with cancer mortality risk for some cancer sites. More than 20% of all cancer deaths, in particular about 50%, 29% and 29% of liver, pancreatic and prostate cancer mortality cases were attributable to ever smoking and excess weight (BMI ≥ 25 kg/m²), respectively.

Based on previous reviews (14–17) on cancer incidence, regarding the sites analysed in this study, an association with smoking has been reported for lung, stomach, pancreatic, bladder, UADT, and liver cancer. In our analysis, we confirmed all these associations except for stomach cancer, which could be due to the relatively small number of cases (n=74). However, the results from the basic model showed a significantly increased stomach cancer risk in heavy smoking men (HR=2.69 [1.08, 6.73], n=10). Based on the same reviews, for colorectal, breast and prostate cancer, an association with smoking is uncertain or unlikely. This is in line with our results. A more recent review, however, has shown that current smoking is related to progression in prostate cancer leading to more aggressive and fatal cases (18). For incidence and mortality of colorectal cancer smoking was reported to be a risk factor (14,19). In previous studies, an association with smoking was shown for myeloid but not for lymphatic leukaemia (15). We did not account for this difference in our analysis and did indeed not see an association with smoking on overall blood cancer risk. For cancer of the female genital tract, we did not detect any association with smoking. Our definition of this site is a mix of different female cancers. Others suggested that smoking has no association with ovarian (15), an inverse association with endometrial (15,20), and doubles the risk for cervical cancer (15).

Concerning incidence, the following of the cancer sites analysed in our study were shown to be positively associated with obesity: colon, postmenopausal breast, adenocarcinoma of the esophagus.
(included in our definition of UADT cancer), endometrium, pancreas, advanced-stage prostate, and liver (21). For the remaining sites, evidence is conflicting. Accordingly, we observed an association of obesity with liver cancer and in participants with measured BMI values with pancreatic cancer. For prostate cancer, we observed a statistically significant association with overweight but not obesity. A possible explanation is the low power, as our population comprised only 23 obese prostate cancer deaths. In our data, obesity was also positively associated with death due to cancer of the female genital tract. In the Million Women Study (UK), an association between elevated BMI and endometrial as well as ovarian but not cervical cancer incidence was observed (22). In contrast to our results, in the same study, an association between obesity and leukaemia was reported. Again there are discordant definitions and also the power might have been too low (14 blood cancer deaths among obese women). For breast cancer, we did not detect an association with BMI. Because of lack of information, we were unable to accurately classify deaths by menopausal status. Again, probably due to lack of statistical power, we could not confirm the association of obesity with pancreatic cancer (n=19). Furthermore, this association appears to be generally weak (23). We did see, however, that the mean BMI in female and male cases was significantly about 1.9 and 1.3 BMI units higher, than in non-cases, respectively. Moreover, there may be a cumulative association of smoking plus excess body weight with pancreatic cancer mortality risk (Figures 1 and 2).

Relatively few studies examined the interaction of these two cancer risk factors. Previous publications corroborate our findings of a stronger impact of smoking (vs. obesity) on cancer risk (2,3,8). This might be explained by residual confounding of unobserved lifestyle habits, as smokers tend to exhibit an unhealthier overall lifestyle (24,25). Besides, a lack of a general BMI-smoking interaction on mortality was reported previously (26,27). However, as suggested by our results, this joint association may depend on the respective cancer site. We could identify one study that also suggested a cumulative association of obesity and smoking with pancreatic cancer risk (28). In contrast to our results, Rauscher et al. (29) observed that obesity was associated with lung cancer risk in a non-smoking population. Furthermore, Luo et al. (30) observed that the association of smoking with breast cancer risk is modified by obesity in postmenopausal women, which was also not apparent in our population.
Our study comprised a large general population sample with a follow-up time of up to 32 years. The data stem from Switzerland, a country with a highly developed health care system allowing secure diagnoses. Our data also included a wide range of lifestyle factors allowing to account for potential confounding. Another strength of our study is that we were able to calculate the impact of smoking and BMI on specific cancer sites. Our study has several limitations. Firstly, we had data only on cancer mortality and no information on cancer incidence. However, Reeves et al. reported that the relationship between BMI and cancer mortality was similar to that of cancer incidence in women (22). Secondly, we only had baseline information on smoking and BMI. In light of the long follow-up time, participants might have changed their behavior over time. Thirdly, the PAFs were calculated only on the basis of our baseline and mortality data, which stem from up to 39 years ago. Therefore, the results should be interpreted with caution, as the prevalence e.g. of tobacco use or lung cancer mortality rates changed over the years. Fourthly, the exposure measurement in our study was crude and, for some variables, not uniform as we pooled different samples to obtain a sufficient number of specific cancer cases. For example, BMI was partly measured and partly self-reported and the definitions for healthy diet were different. The different BMI measurements, however, should not have a substantial impact on the relative mortality risks as shown previously by our group (10). In this publication the same pooled dataset was used to analyze all-cause mortality and a sensitivity analysis using a mixed effects Cox model with random effects for survey was performed. The results of that sensitivity analysis showed that adjusting for survey sufficed. Accordingly, we adjusted for survey in all our Cox models to compensate for heterogeneity. Finally, our study population is presumably healthier than the general population, which might influence prevalence rates (31). However, in the same study there was no difference in cancer mortality risk between the MONICA sample and the general population detected. We would expect that this applies also to the other samples included in our study.

**Conclusion**

In Switzerland, 19.7% of fatal cancer were attributable to ever smoking. When adding overweight this proportion increased slightly to 20.6%. In this country, as in other developed nations, cancer as cause of death is gaining relative significance. Therefore, the government, public health authorities and primary care providers need to intensify their efforts aimed at reducing the modifiable proportion
of cancer risk. Our results suggest that tobacco control is by far the most efficient measure to prevent cancer deaths. The overall impact of excess weight on cancer mortality risk was comparably small, which underlines the importance of recommendations for obese persons to quit smoking despite potential post-cessation weight gain.

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References


Table 1: Baseline characteristics of the study population and figures of cancer mortality for specific cancer sites stratified by smoking status. Sex-specific results can be found in Supplementary material Table S2.

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>never</th>
<th>former</th>
<th>light</th>
<th>Heavy</th>
<th>TOTAL</th>
</tr>
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<tbody>
<tr>
<td>n observations</td>
<td>16,786</td>
<td>6,426</td>
<td>7,320</td>
<td>5,171</td>
<td>35,703</td>
</tr>
<tr>
<td>% observations</td>
<td>47.0</td>
<td>18.0</td>
<td>20.5</td>
<td>14.5</td>
<td>100</td>
</tr>
<tr>
<td>n deaths from all causes</td>
<td>3,476</td>
<td>1,438</td>
<td>1,367</td>
<td>1,102</td>
<td>7,383</td>
</tr>
<tr>
<td>% deaths from all causes</td>
<td>20.7</td>
<td>22.4</td>
<td>18.7</td>
<td>21.3</td>
<td>100</td>
</tr>
<tr>
<td>Person-years</td>
<td>319,345</td>
<td>115,414</td>
<td>144,589</td>
<td>96,703</td>
<td>676,309</td>
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<tr>
<td>Mean (SD) follow-up in years</td>
<td>19.0 (7.3)</td>
<td>18.0 (7.0)</td>
<td>19.8 (7.6)</td>
<td>18.8 (7.3)</td>
<td>18.9 (7.3)</td>
</tr>
<tr>
<td>Mean (SD) age in years</td>
<td>47.1 (16.7)</td>
<td>48.7 (14.8)</td>
<td>42.6 (14.7)</td>
<td>41.4 (12.2)</td>
<td>45.6 (15.6)</td>
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<tr>
<td>Mean (SD) BMI in kg/m²</td>
<td>24.2 (4.0)</td>
<td>25.0 (3.9)</td>
<td>23.9 (3.8)</td>
<td>24.3 (3.8)</td>
<td>24.3 (3.9)</td>
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<tr>
<td>BMI categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>% BMI &lt; 25</td>
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<td>53.5</td>
<td>65.2</td>
<td>61.2</td>
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<td>% 25 ≤ BMI &lt; 30</td>
<td>28.4</td>
<td>36.8</td>
<td>28.6</td>
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<tr>
<td>% BMI ≥ 30</td>
<td>8.2</td>
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<td>6.2</td>
<td>7.0</td>
<td>7.5</td>
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<td>Marital status</td>
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<tr>
<td>% single</td>
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<td>12.4</td>
<td>24.1</td>
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<td>% married</td>
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<td>75.9</td>
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<tr>
<td>% widowed</td>
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<td>5.3</td>
<td>3.9</td>
<td>2.5</td>
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<td>% divorced</td>
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<td>6.4</td>
<td>7.1</td>
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<tr>
<td>Frequency of physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>% daily</td>
<td>6.5</td>
<td>6.5</td>
<td>5.9</td>
<td>4.8</td>
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<td>% several times per week</td>
<td>22.5</td>
<td>25.3</td>
<td>22.6</td>
<td>17.8</td>
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<tr>
<td>% once per week</td>
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<td>21.4</td>
<td>22.9</td>
<td>17.8</td>
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<td>% less than once per week</td>
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<td>46.8</td>
<td>48.6</td>
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<td>71.0</td>
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<td>48.2</td>
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<td>Mean (SD) years of education</td>
<td>11.5 (3.2)</td>
<td>12.2 (3.2)</td>
<td>12.0 (3.2)</td>
<td>11.8 (3.1)</td>
<td>11.8 (3.2)</td>
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<td>Nationality (% Swiss)</td>
<td>85.1</td>
<td>83.7</td>
<td>81.6</td>
<td>79.0</td>
<td>83.2</td>
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Cancer Mortality

<table>
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<tr>
<th>Cancer type</th>
<th>n</th>
<th>%</th>
<th>%a</th>
<th>%b</th>
<th>%c</th>
<th>%d</th>
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<tr>
<td>All cancer sites</td>
<td>985</td>
<td>494</td>
<td>467</td>
<td>433</td>
<td>2,379</td>
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<td>Lung cancer</td>
<td>76</td>
<td>79</td>
<td>93</td>
<td>178</td>
<td>426</td>
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<tr>
<td>Colorectal cancer</td>
<td>125</td>
<td>61</td>
<td>44</td>
<td>20</td>
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<tr>
<td>UADTcancer</td>
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<td>24</td>
<td>31</td>
<td>43</td>
<td>125</td>
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<tr>
<td>Blood cancer</td>
<td>120</td>
<td>53</td>
<td>45</td>
<td>28</td>
<td>246</td>
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<tr>
<td>Pancreatic cancer</td>
<td>56</td>
<td>28</td>
<td>26</td>
<td>17</td>
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<tr>
<td>Bladder cancer</td>
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<td>15</td>
<td>16</td>
<td>16</td>
<td>85</td>
<td></td>
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<tr>
<td>Liver cancer</td>
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<td>22</td>
<td>16</td>
<td>19</td>
<td>81</td>
<td></td>
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<tr>
<td>Stomach cancer</td>
<td>37</td>
<td>19</td>
<td>8</td>
<td>10</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>141</td>
<td>20</td>
<td>24</td>
<td>19</td>
<td>204</td>
<td></td>
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<tr>
<td>Cancer of female genitals</td>
<td>86</td>
<td>15</td>
<td>24</td>
<td>7</td>
<td>132</td>
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</tr>
<tr>
<td>Prostate cancer</td>
<td>49</td>
<td>57</td>
<td>52</td>
<td>12</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Remaining cancer cases</td>
<td>208</td>
<td>102</td>
<td>89</td>
<td>63</td>
<td>462</td>
<td></td>
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<tr>
<td>%</td>
<td>21.1</td>
<td>20.6</td>
<td>19.1</td>
<td>14.6</td>
<td>19.4</td>
<td></td>
</tr>
</tbody>
</table>

a. Current light smokers: smoking less than 20 cigarette equivalents a day. One pipe or cigarillo corresponds to two and one cigar to four cigarette equivalents.
b. Current heavy smokers: smoking at least 20 cigarette equivalents a day.
c. Percent of all observations in this smoking category.
d. Defined as follows: MONICA, NRP 1A and SOMIPOPS: regularly eating three main meals per day; SHS 92/93: eating fruits and vegetables at least once per day.
e. Percent of all deaths in this smoking category.
f. Percent of all cancer deaths in this smoking category.
g. Only women, h. Only men, BMI= body mass index, SD= standard deviation.
Table 2: Hazard Ratios (HR) with 95% confidence intervals (CI) for different BMI and smoking categories resulting from the fully adjusted model. Sex-specific results can be found in Supplementary Table S3.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Deaths (n)</th>
<th>Body Mass Index</th>
<th>Smoking (cigarette equivalents per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 25 - &lt; 30</td>
<td>≥ ≥ 30</td>
</tr>
<tr>
<td>all sites</td>
<td>2,379</td>
<td>1.01</td>
<td>[0.92,1.10]</td>
</tr>
<tr>
<td>lung</td>
<td>426</td>
<td>0.95</td>
<td>[0.77,1.17]</td>
</tr>
<tr>
<td>colon or rectum</td>
<td>250</td>
<td>1.11</td>
<td>[0.84,1.46]</td>
</tr>
<tr>
<td>UADT c</td>
<td>125</td>
<td>0.71</td>
<td>[0.48,1.05]</td>
</tr>
<tr>
<td>blood</td>
<td>246</td>
<td>1.02</td>
<td>[0.77,1.35]</td>
</tr>
<tr>
<td>pancreas</td>
<td>127</td>
<td>1.28</td>
<td>[0.81,1.78]</td>
</tr>
<tr>
<td>bladder</td>
<td>85</td>
<td>1.28</td>
<td>[0.38,1.02]</td>
</tr>
<tr>
<td>liver</td>
<td>81</td>
<td>1.28</td>
<td>[0.72,1.98]</td>
</tr>
<tr>
<td>stomach</td>
<td>74</td>
<td>1.28</td>
<td>[0.72,1.98]</td>
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<tr>
<td>female breast</td>
<td>201</td>
<td>1.28</td>
<td>[0.81,1.60]</td>
</tr>
<tr>
<td>female genitals d</td>
<td>132</td>
<td>1.28</td>
<td>[0.88,1.95]</td>
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<tr>
<td>Prostate</td>
<td>170</td>
<td>1.28</td>
<td>[1.03,1.04]</td>
</tr>
<tr>
<td>remaining</td>
<td>462</td>
<td>1.28</td>
<td>[0.73,1.09]</td>
</tr>
</tbody>
</table>

Models are adjusted for sex (where appropriate), age, survey, alcohol consumption, frequency of physical activity, civil status, years of education, nationality, and healthy diet.

a Reference: BMI < 25 kg/m²
b Reference: never smoking. One pipe or cigarillo correspondent to two and one cigar to four cigarette equivalents.
c Cancer of upper Aero-digestive tract: malignant growth of lips, oropharynx, nasopharynx, piriform sinus, laryngopharynx, oesophagus, larynx
d Cancer of female genitals: malignant growth of vulva, vagina, cervix uteri, corpus uteri, ovary, placenta
Figure Legends

**Figure 1**: Cumulative hazard ratios (HR) of body mass index (BMI) and smoking on selected cancer sites.

*Caption*: Combined HRs resulting from the full model adjusted for sex (where appropriate), age, survey, alcohol consumption, frequency of physical activity, civil status, years of education, nationality, and healthy diet. Note: Y-Axis starts at HR=1. Exact figures with CIs for all cancer sites are shown in Supplementary Table S4.

Reading example: Heavy smokers, that are obese (BMI ≥ 30 kg/m²), have a 2.9-fold risk to die of pancreatic cancer, compared to normal-weight (BMI < 25 kg/m²) never smokers.

**Figure 2**: Population attributable fractions (PAF) of smoking (ever, including former), BMI ≥ 25 kg/m² and both factors combined in percent. PAFs that are significantly greater than zero are marked by a filled circle.

*Caption*: Depicted are the results from the full model adjusted for sex (where appropriate), age, survey, alcohol consumption, frequency of physical activity, civil status, years of education, nationality, and healthy diet. Exact results including 95% CIs are shown in Supplementary Table S5.

Reading example: Of all pancreas cancer deaths, 12% (not significant), 19% (sign.) or 29% (sign.) are attributable to a BMI ≥ 25 kg/m², ever smoking or both risk factors combined, respectively.
Figure 1

### All-sites

- **Smoking status**: heavy, light, former, never
- **Body Mass Index**: ≤25, 25-30, ≥30
- **Hazard ratio**

### Pancreas

- **Hazard ratio**

### Liver

- **Hazard ratio**
Impact of smoking and excess body weight on overall and site-specific cancer mortality risk


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