Research Article

Impact of Smoking and Excess Body Weight on Overall and Site-Specific Cancer Mortality Risk

Julia Meyer, Sabine Rohrmann, Matthias Bopp, and David Faeh, for the Swiss National Cohort Study Group

Abstract

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

Methods: Our study population comprised 35,784 men and women of ages 14 to 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% confidence interval, 2.04–2.63) for heavy smokers (vs. never smokers) and 1.15 (1.01–1.32) for obese [body mass index (BMI) $\geq$ 30 kg/m^2] vs. normal weight individuals. Heavy smoking ($\geq$ 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 $\geq$ 25 kg/m^2).

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 postcessation weight gain. *Cancer Epidemiol Biomarkers Prev; 24(10); 1516–22. ©2015 AACR.*

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 aging, 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. Although 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, that is, 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) $\geq$ 25 kg/m^2], 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 and colleagues (2) reported the cancer mortality risk to be higher in obese than in normal weight current smokers, but for older individuals (age $\geq$ 65 years) the association between obesity and cancer mortality was more apparent in never than in former or current smokers. In contrast, Kitsantas and colleagues (8) reported that younger women (41–50 years) who smoked had a higher cancer mortality risk if they were underweight. Hjellvik and colleagues (9) 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, that is, 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 of ages 14 to 99 years at baseline who participated in one of four different

Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland.

Corresponding Author: David Faeh, Division of Chronic Disease Epidemiology, Hirschengraben 84, Zurich 8001, Switzerland. Phone: 41-44-634-46-16; Fax: 41-44-634-49-86; E-mail: david.faeh@uzh.ch

AACR

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 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 was defined as weight (kg) divided by the square of height (m^2) and classified into following categories: normal/underweight (reference category, BMI < 25.0 kg/m^2), overweight (25.0 ≤ BMI < 30.0 kg/m^2), and obesity (BMI ≥ 30.0 kg/m^2). Only about 3.5% of the study population was underweight (BMI < 18.5 kg/m^2). 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 six categories: NRP 1A, SOMIPOPS, MONICA I-III, and SHS. Marital status had four categories: single, married, widowed, and 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 of 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 hematopoietic 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 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; besides 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 10 sex-combined models, namely for all cancer deaths combined, lung cancer, and the total of remaining cancer deaths.

To calculate PAFs for smoking and BMI, we used the punafcc STATA package by Newson (13). Smoking (ever including former vs. never smoking) and BMI (cutoff point at 25 kg/m^2) were dichotomized for this analysis. This cutoff point for BMI was selected because of small case numbers for obese participants.

All analyses were conducted in STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. 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

Table 1. Baseline characteristics of the study population and figures of cancer mortality for specific cancer sites stratified by smoking status

Smoking status		Never	Former	Light[a]	Heavy[b]	Total
Observations, n		16,786	6,426	7,320	5,171	35,703
Observations, %		47.0	18.0	20.5	14.5	100
Deaths from all causes, n		3,476	1,438	1,367	1,102	7,383
% Deaths from all causes[c]		20.7	22.4	18.7	21.3	100
Person-years		319,345	115,414	144,589	96,961	676,309
Mean (SD) follow-up in years		19.0 (7.3)	18.0 (7.0)	19.8 (7.6)	18.8 (7.3)	18.9 (7.3)
Mean (SD) age in years		47.1 (16.7)	48.7 (14.8)	42.6 (14.7)	41.4 (12.2)	45.6 (15.6)
Mean (SD) BMI in kg/m^2		24.2 (4.0)	25.0 (3.9)	23.9 (3.8)	24.3 (3.8)	24.3 (3.9)
BMI categories, %						
BMI < 25		63.4	53.5	65.2	61.2	61.6
25 ≤ BMI < 30		28.4	36.8	28.6	31.9	30.5
BMI ≥ 30		8.2	9.7	6.2	7.0	7.9
Marital status, %						
Single		21.5	12.4	24.1	22.8	20.6
Married		64.5	75.9	64.9	63.8	66.5
Widowed		9.1	5.3	3.9	2.5	6.4
Divorced		4.8	6.4	7.1	11.0	6.5
Frequency of PA, %						
Daily		6.5	6.5	5.9	4.8	6.1
Several times per week		22.5	25.3	22.6	17.8	22.4
Once per week		22.1	21.4	22.9	17.8	21.5
Less than once per week		48.9	46.8	48.6	59.6	50.0
Other covariates						
Alcohol (% yes)		56.9	74.6	71.0	76.5	65.8
Healthy diet[d] (% yes)		73.0	67.7	63.0	48.2	66.6
Mean (SD) years of education		11.5 (3.2)	12.2 (3.2)	12.0 (3.2)	11.8 (3.1)	11.8 (3.2)
Nationality (% Swiss)		85.1	83.7	81.6	79.0	83.2
Cancer mortality						
All cancer sites	n	985	494	467	433	2,379
	%[e]	28.3	34.4	34.2	39.3	32.2
Lung cancer	n	76	79	93	178	426
	%[f]	7.7	16.0	19.9	41.1	17.9
Colorectal cancer	n	125	61	44	20	250
	%[f]	12.7	12.3	9.4	4.6	10.5
UADT cancer	n	27	24	31	43	125
	%[f]	2.7	4.9	6.6	9.9	5.3
Blood cancer	n	120	53	45	28	246
	%[f]	12.2	10.7	9.6	6.5	10.3
Pancreatic cancer	n	56	28	26	17	127
	%[f]	5.7	5.7	5.6	3.9	5.3
Bladder cancer	n	36	15	16	18	85
	%[f]	3.7	3.0	3.4	4.2	3.6
Liver cancer	n	24	22	16	19	81
	%[f]	2.4	4.5	3.4	4.4	3.4
Stomach cancer	n	37	19	8	10	74
	%[f]	3.8	3.9	1.7	2.3	3.1
Breast cancer[g]	n	141	20	24	19	204
	%[f]	14.3	4.1	5.1	4.4	8.6
Cancer of female genitals[g]	n	86	15	24	7	132
	%[f]	8.7	3.0	5.1	1.6	5.6
Prostate cancer[h]	n	49	57	52	12	170
	%[f]	5.0	11.5	11.1	2.8	7.2
Remaining cancer cases	n	208	102	89	63	462
	%[f]	21.1	20.6	19.1	14.6	19.4

NOTE: Sex-specific results can be found in Supplementary Table S2.
[a]Current light smokers: smoking less than 20 cigarette equivalents a day. One pipe or cigarillo correspondents 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.

Table 2. HRs with 95% CIs for different BMI and smoking categories resulting from the fully adjusted model (statistically significant values are indicated in bold)

Cancer site	Deaths (n)	BMI[a]		Smoking[b] (cigarette equivalents per day)		
		≥ 25–< 30	≥ 30	Former	Light (< 20)	Heavy (≥ 20)
All sites	2,379	1.01 (0.92–1.10)	**1.15 (1.01–1.32)**	**1.31 (1.16–1.47)**	**1.37 (1.22–1.53)**	**2.32 (2.04–2.63)**
Lung	426	0.95 (0.77–1.17)	0.80 (0.57–1.14)	**2.29 (1.64–3.20)**	**3.11 (2.26–4.26)**	**9.86 (7.29–13.33)**
Colon or rectum	250	1.11 (0.84–1.46)	1.30 (0.87–1.95)	1.13 (0.80–1.58)	0.99 (0.69–1.42)	0.87 (0.53–1.45)
UADT[c]	125	0.71 (0.48–1.05)	0.78 (0.42–1.43)	**1.84 (1.03–3.29)**	**2.62 (1.53–4.49)**	**5.45 (3.18–9.34)**
Blood	246	1.02 (0.77–1.35)	1.13 (0.74–1.74)	1.14 (0.80–1.62)	1.00 (0.70–1.43)	1.16 (0.74–1.81)
Pancreas	127	1.20 (0.81–1.78)	1.60 (0.93–2.75)	1.46 (0.89–2.40)	1.46 (0.89–2.39)	**1.84 (1.01–3.37)**
Bladder	85	0.62 (0.38–1.02)	1.16 (0.62–2.18)	1.01 (0.53–1.95)	1.22 (0.65–2.29)	**2.57 (1.33–4.93)**
Liver	81	1.28 (0.77–2.12)	**2.21 (1.18–4.15)**	**2.14 (1.14–4.01)**	1.76 (0.91–3.42)	**3.41 (1.74–6.70)**
Stomach	74	1.19 (0.72–1.98)	1.45 (0.71–2.95)	1.23 (0.66–2.27)	0.60 (0.27–1.34)	1.34 (0.62–2.91)
Female breast	201	1.16 (0.84–1.60)	1.07 (0.64–1.79)	0.79 (0.49–1.29)	0.77 (0.49–1.21)	1.38 (0.82–2.33)
Female genitals[d]	132	1.31 (0.88–1.95)	**1.88 (1.10–3.20)**	1.21 (0.69–2.12)	1.48 (0.92–2.36)	1.16 (0.52–2.58)
Prostate	170	**1.45 (1.03–2.04)**	1.54 (0.93–2.55)	1.12 (0.76–1.66)	1.38 (0.93–2.05)	0.68 (0.35–1.29)
Remaining	462	0.89 (0.73–1.09)	1.08 (0.80–1.46)	1.22 (0.94–1.58)	1.18 (0.91–1.54)	**1.53 (1.12–2.09)**

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

Sex-specific results can be found in Supplementary Table S3.

[a]Reference: BMI < 25 kg/m^2.

[b]Reference: never smoking. One pipe or cigarillo correspondent to two and one cigar to four cigarette equivalents.

[c]Cancer of UADT: malignant growth of lips, oropharynx, nasopharynx, piriform sinus, laryngopharynx, oesophagus, and larynx.

[d]Cancer of female genitals: malignant growth of vulva, vagina, cervix uteri, corpus uteri, ovary, and placenta.

lower in never smokers compared with 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 with 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 with normal-weight persons and 132% (95% CI, 104%–164%) higher for heavy compared with 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 smoking 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; 95% CI, 1.64–3.20) was only due to the association in men (HR, 2.22; 95% CI, 1.46–3.38; women: HR, 1.05; 95% CI, 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 with 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 Fig. 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 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/m^2 are shown in Fig. 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/m^2. 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-related mortality than obesity. Heavy smokers had higher risks of dying from total, lung, UADT, pancreatic, bladder, and liver cancer compared with 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 with 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
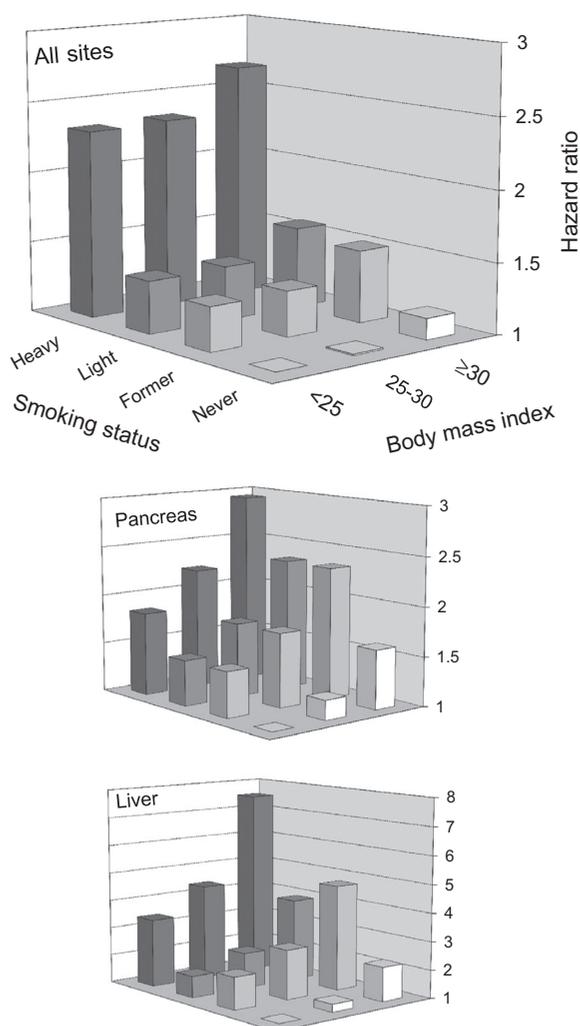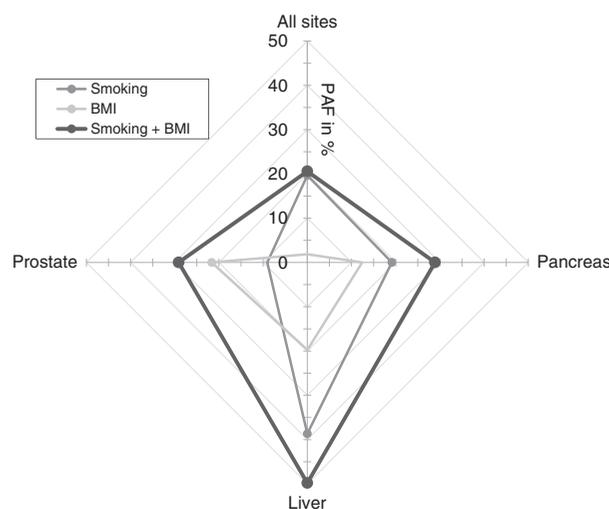
Figure 1.
Cumulative HRs of BMI and smoking on selected cancer sites, resulting from the full model adjusted for sex (where appropriate), age, survey, alcohol consumption, frequency of PA, civil status, years of education, nationality, and healthy diet. Note: Y-axis starts at HR = 1. Exact figures with CIs for all cancer sites are shown in Supplementary Table S4. Reading example: Heavy smokers, who are obese (BMI $\geq$ 30 kg/m^2), have a 2.9-fold risk to die of pancreatic cancer, compared with normal-weight (BMI < 25 kg/m^2) never smokers.

participants with measured BMI). We did not observe a significant interaction between increased BMI and smoking on cancer-related 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-related mortality risk for some cancer sites. More than 20% of all cancer deaths, in particular 50%, 29%, and 29% of liver, pancreatic, and prostate cancer-related mortality cases were attributable to ever smoking and excess weight (BMI $\geq$ 25 kg/m^2).

On the basis of previous reviews (14–17) on cancer incidence, regarding the sites analyzed 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; 95% CI, 1.08–6.73; $n = 10$). On the basis of 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 leukemia (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 analyzed 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

Figure 2.
Population attributabe fractions (PAFs) of smoking (ever, including former), BMI $\geq$ 25 kg/m^2 and both factors combined in percent. PAFs that are significantly greater than zero are marked by a filled circle. Depicted are the results from the full model adjusted for sex (where appropriate), age, survey, alcohol consumption, frequency of PA, 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 $\geq$ 25 kg/m^2, ever smoking, or both risk factors combined, respectively.

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 leukemia 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 (Figs. 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 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 and colleagues (29) observed that obesity was associated with lung cancer risk in a nonsmoking population. Furthermore, Luo and colleagues (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 reliable 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. First, we had data only on cancer-related mortality and no information on cancer incidence. However, Reeves and colleagues (22) reported that the relationship between BMI and cancer mortality was similar to that of cancer incidence in women. Second, 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. Third, 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, for example, of tobacco use or lung cancer-related mortality rates changed over the years. Fourth, 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-related 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 cancers 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-related mortality risk was comparably small, which underlines the importance of recommendations for obese persons to quit smoking despite potential postcessation weight gain.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Rohrmann, M. Bopp, D. Faeh
Development of methodology: J. Meyer, S. Rohrmann, D. Faeh
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Bopp
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Meyer
Writing, review, and/or revision of the manuscript: J. Meyer, S. Rohrmann, M. Bopp, D. Faeh
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Bopp
Study supervision: M. Bopp, D. Faeh

References

1. Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer Incidence in Five Continents, CI5plus [Internet]. Cancer Incid. Five Cont. Time Trends, IARC CancerBase No. 9. 2014 [cited 2015 Jan 22]. Available from: http://ci5.iarc.fr/CI5plus/.
2. Freedman DM, Sigurdson AJ, Rajaraman P, Doody MM, Linet MS, Ron E. The mortality risk of smoking and obesity combined. Am J Prev Med 2006;31:355–62.
3. Ma J, Jemal A, Flanders WD, Ward EM. Joint association of adiposity and smoking with mortality among U.S. adults. Prev Med 2013;56:178–84.
4. Chyou PH, Burchfiel CM, Yano K, Sharp DS, Rodriguez BL, Curb JD, et al. Obesity, alcohol consumption, smoking and mortality. Ann Epidemiol 1997;7:311–7.
5. OECD. Health at a glance 2013: OECD Indicators. OECD Publ. 2013.
6. Storni M, Kaeser M, Eichholzer M, Richard A, Favero K. [Schweizerische Gesundheitsbefragung 2012: Übergewicht und Adipositas]. BFS Aktuell 2014;14.
7. Bundesamt für Statistik (BFS). [Schweizerische Gesundheitsbefragung 2012]. Neuchâtel; 2013.
8. Kitsantas P, Wu H. Body mass index, smoking, age and cancer mortality among women: a classification tree analysis. J Obstet Gynaecol Res 2013;39:1330–8.
9. Hjellvik V, Selmer R, Gjessing HK, Tverdal A, Vollset SE. Body mass index, smoking, and risk of death between 40 and 70 years of age in a Norwegian cohort of 32,727 women and 33,475 men. Eur J Epidemiol 2013;28:35–43.
10. Roh L, Braun J, Chiolero A, Bopp M, Rohrmann S, Faeh D. Mortality risk associated with underweight: a census-linked cohort of 31,578 individuals with up to 32 years of follow-up. BMC Public Health 2014;14:371.
11. Bopp M, Spoerri A, Zwahlen M, Gutzwiller F, Paccaud F, Braun-Fahrländer C, et al. Cohort Profile: the Swiss National Cohort—a longitudinal study of 6.8 million people. Int J Epidemiol 2009;38:379–84.
12. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91.
13. Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. Stata J 2013;13:672–98.
14. Batty GD, Kivimaki M, Gray L, Smith GD, Marmot MG, Shipley MJ. Cigarette smoking and site-specific cancer mortality: testing uncertain associations using extended follow-up of the original Whitehall study. Ann Oncol 2008;19:996–1002.
15. Kuper H, Boffetta P, Adami H-O. Tobacco use and cancer causation: association by tumour type. J Intern Med 2002;252:206–24.
16. Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, et al. Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 2004;96:99–106.
17. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer 2004;2:3–9.
18. Zu K, Giovannucci E. Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. Cancer Causes Control 2009;20:1799–810.
19. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Ann Oncol 2014;26:1–10.
20. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med 2008;121:501–8.e3.
21. Pischon T, Nöthlings U, Boeing H. Obesity and cancer. Proc Nutr Soc 2008;67:128–45.
22. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. Br Med J 2007;335:1134.
23. Aune D, Greenwood DC, Chan DSM, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23:843–52.
24. Chiolero A, Wietlisbach V, Ruffieux C, Paccaud F, Cornuz J. Clustering of risk behaviors with cigarette consumption: a population-based survey. Prev Med 2006;42:348–53.
25. Schuit JA, van Loon JA, Tijhuis M, Ocké MC. Clustering of lifestyle risk factors in a general adult population. Prev Med 2002;35:219–24.
26. Durazo-Arvizu RA, Cooper RS. Issues related to modeling the body mass index-mortality association: the shape of the association and the effects of smoking status. Int J Obes 2008;32(Suppl 3):S52–5.
27. Neovius M, Rasmussen F, Sundstro J. Combined effects of overweight and smoking in late adolescence on subsequent mortality: nationwide cohort study. Br Med J 2009;338:b496.
28. Larsson SC, Permert J, Håkansson N, Näslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 2005;93:1310–5.
29. Rauscher GH, Mayne ST, Janerich DT. Relation between body mass index and lung cancer risk in men and women never and former smokers. Am J Epidemiol 2000;152:506–13.
30. Luo J, Horn K, Ockene JK, Simon MS, Stefanick ML, Tong E, et al. Interaction between smoking and obesity and the risk of developing breast cancer among postmenopausal women: the Women's Health Initiative Observational Study. Am J Epidemiol 2011;174:919–28.
31. Bopp M, Braun J, Faeh D. Variation in mortality patterns among the general population, study participants, and different types of nonparticipants: evidence from 25 years of follow-up. Am J Epidemiol 2014;180:1028–35.

BLOOD CANCER DISCOVERY

Impact of Smoking and Excess Body Weight on Overall and Site-Specific Cancer Mortality Risk

Julia Meyer, Sabine Rohrmann, Matthias Bopp, et al.

Updated version	Access the most recent version of this article at: doi: 10.1158/1055-9965.EPI-15-0415
Supplementary Material	Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2015/07/29/1055-9965.EPI-15-0415.DC1

Cited articles	This article cites 27 articles, 2 of which you can access for free at: http://cebp.aacrjournals.org/content/24/10/1516.full#ref-list-1
Citing articles	This article has been cited by 1 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/24/10/1516.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/24/10/1516. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.