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Weight change and cancer risk in a cohort of more than 65 000 adults in Austria

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Background: To investigate relations between weight loss or weight gain and the incidence of cancer.
Patients and methods: Weight change was assessed in a population-based cohort of >65 000 Austrian adults (28 711 men and 36 938 women) for a period of 7 years, after which participants were followed for incident cancers over 8 years on average. Incident cancers (other than nonmelanoma skin cancers) were ascertained by a population-based cancer registry (n = 3128). Cox proportional hazards models were used to estimate hazard rate ratios (HRs) stratified by age and adjusted for smoking, occupational group, blood glucose and body mass index at baseline.
Results: In both men and women, neither weight loss nor weight gain was clearly associated with the incidence of all cancers combined. Weight loss (>0.10 kg/m^2/year) was inversely associated with colon cancer in men [HR 0.50; 95% confidence interval (CI) 0.29–0.87], while high weight gain (≥0.50 kg/m^2/year) was inversely associated with prostate cancer (HR 0.43; 95% CI 0.24–0.76). Among women, high weight gain was positively associated with ovarian cancer (HR 2.48; 95% CI 1.05–5.85).
Conclusion: These findings indicate that recent weight change may influence the incidence of several types of cancer.
Key words: colon cancer, epidemiology, ovarian cancer, prostate cancer, weight change

introduction

Obesity is now an established risk factor for several types of cancer, including pancreatic, hepatocellular, gall-bladder and kidney cancer in men and women; endometrial cancer and postmenopausal breast cancer in women and colorectal cancer in men [1]. Although many studies have investigated associations between baseline weight and cancer [2–4], relatively few have examined the impact of weight change on cancer incidence, with the exception of breast cancer [5–10]. Most of these studies have assessed weight change over several decades on the basis of self-reported weight at the age of 18 or 20 years and self-reported adult weight, while only a few have assessed weight change over shorter periods of 10 years or less [3, 11–13]. Weight change over both long and short periods may be biologically relevant, but weight gain or loss over a shorter interval may represent a more meaningful time period for middle to older age adults who might be willing to change their eating behaviours in order to reduce their risk of cancer or other diseases.

We conducted a prospective investigation of associations between clinically measured weight change over 5–9 years and the incidence of specific cancers and all cancers combined (excluding nonmelanoma skin cancers) in a population-based cohort of >65 000 Austrian men and women. To our knowledge, a similar comprehensive evaluation of the impact of measured weight change on major cancer sites in both men and women has not been done before.

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methods

study population

The Vorarlberg Health Monitoring and Prevention Program (VHM&PP) is a population-based risk factor surveillance program in Vorarlberg, the westernmost province of Austria. It is carried out routinely by the Agency of Social and Preventive Medicine and covers all adults (aged ≥19 years) in the province. Enrolment is voluntary, and costs for one examination per year are covered by each participant's compulsory health insurance. The screening examinations take place in the practice of local physicians, and include a physical examination, fasting blood sample and consultation with the doctor. Most of the participants completed two or more registered visits, with varying times between visits.

From 1985 to 2003, 175 839 adult Vorarlberg men and women were enrolled in the VHM&PP Study Cohort after signing an informed consent to store and process personal data. The current analysis was restricted to individuals with at least two examinations over a 5- to 9-year interval, during which weight change from the first (baseline) visit was assessed. Participants were excluded if they had <1 year of follow-up after weight

change was assessed, or if they were diagnosed with an incident cancer before enrolment, during the weight change assessment period, or within the first year of follow-up ($n = 5356$). Participants who were underweight [Body mass index (BMI) < 18.5 kg/m^2] at baseline also were excluded ($n = 2228$) to reduce the likelihood of bias due to pre-existing disease. In addition, a sensitivity analysis with a 3-year exclusion criterion was carried out to further evaluate the potential influence of undiagnosed cancer on weight change. Complete data on height, weight, weight change, covariates and cancer incidence were available for 28 711 men and 36 938 women.

assessment of weight change

Height and weight were measured by medical staff at every screening examination. BMI was calculated as weight (kg)/height (m^2). The number of examinations and the time between examinations differed among participants. We chose a 5- to 9-year period (mean 6.9 years) to assess weight change in order to balance the length of the assessment period against the length of the follow-up time for incident cancers (mean 8.0 years), which began after weight change was determined. Specifically, the weight change assessment period ended at the study visit that occurred closest to 7 years after baseline (±2 years). All measurements obtained during the period of weight change assessment were used to construct linear regression models for each participant to calculate the slope of the trend in BMI against time as an indicator of their individual trend for weight change. In addition, total weight change over the assessment period was categorized as weight loss (<−0.10 kg/m^2/year), stable weight (−0.10 to <0.1 kg/m^2/year) and small (0.10 to <0.30 kg/m^2/year), moderate (0.30 to <0.50 kg/m^2/year) and high weight gain (≥0.50 kg/m^2/year), with stable weight serving as the reference category. For example, high weight gain in a person 1.75 m tall would correspond to an increase of at least 10.7 kg over ∼7 years time.

covariates

Baseline BMI was classified according to World Health Organisation guidelines as normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (class I, II and III combined, ≥30.0 kg/m^2). Participants were classified as current, former or never smokers. Participants who never smoked could not be distinguished from those who did not respond to questions about smoking at baseline, but baseline smoking status was verified for all study participants on the basis of information provided at subsequent examinations. Fasting blood glucose was dichotomised as normal (<6.1 mmol/l) or impaired fasting glycaemia and diabetes (≥6.1 mmol/l) according to baseline values and was included in models since there is evidence that hyperglycaemia is a risk factor for several types of cancer [14]. Occupational group (blue collar, white collar or self employed) was determined by each participant's insurance number at baseline, and was included in models as a surrogate measure of socio-economic status. Participants who were retired at baseline were classified according to their former occupation, and housewives were classified according to their husband's profession.

outcomes

The end of the weight change assessment period marked the start of follow-up. Participants with <1 year of follow-up were excluded from the study, as previously noted. Incident cancers that occurred during the follow-up period (after weight change was assessed) were identified by the Vorarlberg cancer registry, which has been accepted for the International Agency for Research on Cancer publication since 1993 [15]. The proportion of cancers ascertained by death certificate only (DCO, an indicator of the completeness of cancer registry ascertainment) was 7% for men and 9% for women during 1993–1997 [16], and 5% for both sexes in 1998–2002 (W. Oberaigner, personal communication; Cancer Registry of Tyrol), consistent with expected DCO rates of 5%–10% for registries in developed countries. All cancers were histologically verified and coded according to the 10th revision of the International Classification of Diseases (ICD-10). In addition, cohort data were linked with the Vorarlberg Death Index to ascertain deaths and calculate person-years at risk.

statistical analysis

Cox proportional hazards analyses were used to calculate hazard rate ratios (HRs) and 95% confidence intervals (CIs). Models included age (in single years) in the strata statement and were adjusted for smoking status, fasting blood glucose and occupational group at baseline. Gender-specific associations were estimated for all cancers combined (excluding nonmelanoma skin cancers) and for individual cancers with at least 50 cases in a gender group. Analyses with large case numbers (all cancers combined, prostate cancer and breast cancer) were additionally stratified by BMI at enrolment to investigate potential interactions between baseline weight and weight change on cancer incidence. Tests of linear trend were carried out by scoring the categories of weight change, entering the median value for slope of BMI within each interval in a regression model and testing the significance of the term by the Wald chi-square test. Participants with weight loss were not considered when calculating tests of linear trend. For

Table 1. Characteristics of the Vorarlberg Health Monitoring and Promotion Program Study Cohort

	Men	Women	All
Number of participants[a]	28 711	36 938	65 649
Age at baseline, mean (SD)	42.0 (13.4)	42.5 (14.1)	42.3 (13.8)
Years of weight change assessment, mean (SD)	6.9 (0.9)	6.9 (0.9)	6.9 (0.9)
Years of follow-up, mean (SD)	7.7 (3.3)	8.2 (3.2)	8.0 (3.2)
Categories of weight change (%)			
<−0.1 kg/m^2/year	16.9	18.7	17.9
−0.1 to <0.1 kg/m^2/year	34.4	29.1	31.4
0.1 to <0.3 kg/m^2/year	30.2	28.4	29.2
0.3 to <0.5 kg/m^2/year	12.5	14.0	13.4
≥0.5 kg/m^2/year	6.0	9.7	8.1
BMI (%)			
18.5–25.0 kg/m^2	50.4	64.0	58.1
25.0–29.9 kg/m^2	41.4	25.9	32.7
≥30.0 kg/m^2	8.2	10.0	9.2
Smoking (%)			
Current	31.1	22.7	26.4
Former	17.2	6.4	11.1
Fasting blood glucose (%)			
≥6.1 mmol/l	7.9	6.7	7.2
Occupational group (%)			
Blue collar	30.8	36.8	34.2
White collar	59.1	56.3	57.5
Self employed	10.1	6.9	8.3
Number of incident cancers	1701	1427	3128
Age at cancer diagnosis, mean (SD)	66.3 (10.0)	64.0 (12.0)	65.2 (11.0)

[a]Eligible participants had complete baseline data for blood glucose, BMI, smoking and type of occupation; and had no history of malignant cancer before or within 1 year after baseline. Participants with nonmelanoma skin cancer were excluded.

SD, standard deviation; BMI, body mass index.

all tests of significance, $\alpha = 0.05$. All calculations were carried out with SAS version 9.1 software.

results

The final study cohort consisted of 28 711 men and 36 938 women with mean age at baseline of 42.3 years (Table 1). At baseline, the prevalence of overweight and obesity was 41.4% and 8.2% in men and 25.9% and 10.0% in women. Weight trends were classified as stable in 34.4% of men and in 29.1% of women over the period of weight change assessment. Moderate to high weight gain occurred more often in women than in men (23.7% versus 18.5%, respectively), and women also were somewhat more likely to loose weight during the assessment interval (18.7% versus 16.9%). A total of 3128 incident cancers (excluding nonmelanoma skin cancers) were ascertained during the follow-up interval (Table 1).

In men, there was an inverse association between high weight gain (versus stable weight) and all cancers combined (HR 0.76; 95% CI 0.57–1.02) (Table 2) which appeared to be driven by a strong inverse association between high weight gain and prostate cancer (HR for high weight gain and prostate cancer 0.43; 95% CI 0.24–0.76; HR for high weight gain and all cancers except prostate 1.00; 95% CI 0.71–1.40). Weight change was not associated with all cancers combined among women (Table 3).

Weight loss was inversely associated with colon cancer in men (HR 0.50; 95% CI 0.29–0.87), but not in women. Statistically non-significant associations ($\alpha = 0.05$) were observed between weight loss and several other cancers,

Table 2. Estimated HRs and 95% CIs for incident cancers diagnosed among male participants according to weight change

Weight change (kg/m^2/year)						
	<−0.1	−0.1 to <0.1	0.1 to <0.3	0.3 to <0.5	≥0.5	*P* for trend[a]
Number of persons	4865	9872	8680	3587	1707	
All cancers						
Incident cases	371	652	453	175	50	
HR (95% CI)[b]	1.00 (0.88–1.14)	1.00	0.95 (0.84–1.07)	1.10 (0.93–1.30)	0.76 (0.57–1.02)	0.49
All cancers other than prostate cancer						
Incident cases	207	335	222	103	38	
HR (95% CI)[b]	1.04 (0.87–1.24)	1.00	0.90 (0.76–1.06)	1.18 (0.94–1.48)	1.00 (0.71–1.40)	0.48
Stomach cancer (ICD-10 C16)						
Incident cases	11	25	20	10		
HR (95% CI)[b]	0.75 (0.36–1.54)	1.00	1.18 (0.65–2.13)	1.22 (0.58–2.59)	[c]	0.49
Colon cancer (ICD-10 C18)						
Incident cases	17	55	39	15		
HR (95% CI)[b]	**0.50 (0.29–0.87)**	1.00	0.97 (0.64–1.46)	0.84 (0.47–1.49)	[c]	0.58
Rectal cancer (ICD-10 C20)						
Incident cases	9	20	14	9		
HR (95% CI)[b]	0.82 (0.37–1.82)	1.00	1.01 (0.51–2.00)	1.44 (0.65–3.21)	[c]	0.50
Lung cancer (ICD-10 C34)						
Incident cases	47	58	30	19	7	
HR (95% CI)[b]	1.33 (0.90–1.97)	1.00	0.70 (0.45–1.09)	1.16 (0.69–1.95)	0.99 (0.45–2.19)	0.93
Melanoma (ICD-10 C43)						
Incident cases	14	19	11	9		
HR (95% CI)[b]	1.48 (0.73–3.02)	1.00	0.73 (0.35–1.54)	1.25 (0.56–2.81)	[c]	0.72
Prostate cancer (ICD-10 C61)						
Incident cases	164	317	231	72	12	
HR (95% CI)	0.96 (0.79–1.16)	1.00	1.00 (0.85–1.19)	1.01 (0.78–1.31)	**0.43 (0.24–0.76)**	0.06
Kidney cancer (ICD-10 C64)						
Incident cases	11	24	15	13		
HR (95% CI)[b]	0.79 (0.38–1.65)	1.00	0.83 (0.44–1.59)	1.41 (0.71–2.80)	[c]	0.33
Bladder cancer (ICD-10 C67)						
Incident cases	13	18	23			
HR (95% CI)[b]	1.10 (0.53–2.28)	1.00	1.22 (0.66–2.28)	[d]	[d]	

[a]Test for trend refers to stable weight or weight gain.

[b]Cox proportional hazards models were stratified according to age and adjusted for smoking status, blood glucose, occupational group and body mass index at baseline.

[c]Weight change categories (0.3 to <0.5 kg/m^2/year and ≥0.5 kg/m^2/year) were combined as needed to ensure >5 cases in each.

[d]Weight change categories (0.1 to <0.3 kg/m^2/year and 0.3 to <0.5 kg/m^2/year and ≥0.5 kg/m^2/year) were combined to ensure >5 cases in each.

HR, hazard rate ratio; CI, confidence interval; ICD, International Classification of Diseases.

Table 3. Estimated HRs and 95% CIs for incident cancers diagnosed among female participants according to weight change

Weight change (kg/m^2/year)						
	<−0.1	−0.1 to <0.1	0.1 to <0.3	0.3 to <0.5	≥0.5	*P* for trend[a]
Number of persons	6910	10 743	10 502	5184	3599	
All cancers						
Incident cases	306	419	412	178	112	
HR (95% CI)[b]	1.01 (0.87–1.18)	1.00	1.05 (0.91–1.20)	0.95 (0.80–1.14)	0.94 (0.76–1.16)	0.50
Stomach cancer (ICD-10 C16)						
Incident cases	19	12	19	9		
HR (95% CI)[b]	1.73 (0.82–3.63)	1.00	1.73 (0.84–3.57)	1.11 (0.46–2.65)	[c]	0.73
Colon cancer (ICD-10 C18)						
Incident cases	26	35	34	16	11	
HR (95% CI)[b]	0.97 (0.58–1.63)	1.00	1.11 (0.69–1.78)	1.14 (0.63–2.07)	1.31 (0.66–2.61)	0.46
Lung cancer (ICD-10 C34)						
Incident cases	20	17	13	15		
HR (95% CI)[b]	1.67 (0.87–3.23)	1.00	0.78 (0.38–1.61)	1.12 (0.55–2.27)	[c]	0.75
Melanoma (ICD-10 C43)						
Incident cases	13	22	21	8		
HR (95% CI)[b]	1.01 (0.50–2.04)	1.00	0.96 (0.53–1.75)	0.45 (0.20–1.02)	[c]	0.07
Breast cancer (ICD-10 C50)						
All incident cases	97	150	167	75	39	
HR (95% CI)[b]	0.95 (0.73–1.23)	1.00	1.15 (0.93–1.44)	1.08 (0.82–1.42)	0.87 (0.61–1.24)	0.63
Cancer of the uterine corpus (ICD-10 C54)						
Incident cases	16	36	29	11	8	
HR (95% CI)[b]	0.59 (0.32–1.07)	1.00	0.84 (0.51–1.37)	0.66 (0.33–1.29)	0.72 (0.33–1.57)	0.23
Ovarian cancer (ICD-10 C56)						
Incident cases	10	14	11	9	9	
HR (95% CI)[b]	1.00 (0.44–2.29)	1.00	0.88 (0.40–1.94)	1.59 (0.68–3.70)	**2.48 (1.05–5.85)**	**0.03**

[a]Test for trend refers to stable weight or weight gain.
[b]Cox proportional hazards models were stratified according to age and adjusted for smoking status, blood glucose, occupational group and body mass index at baseline.
[c]Weight change categories (0.3 to <0.5 kg/m^2/year and ≥0.5 kg/m^2/year) were combined as needed to ensure >5 cases in each.
HR, hazard rate ratio; CI, confidence interval; ICD, International Classification of Diseases.

including an inverse association with endometrial cancer in women and positive associations with malignant melanoma in men, stomach cancer in women and lung cancer in men and women (Tables 2 and 3).

With the exception of prostate cancer, weight gain was not clearly associated with specific cancers in men; however, kidney cancer was positively associated with weight gain on the basis of a small number of exposed cases. In women, weight gain was associated with an increased risk of ovarian cancer (HR 2.48; 95% CI 1.05–5.85 for high weight gain versus stable weight) and inversely associated with malignant melanoma. No association was observed between weight change and breast cancer in all women combined (Table 3).

Results did not change appreciably when cancers diagnosed during the first 3 years of follow-up (versus the first year of follow-up) were excluded (data not shown).

Estimates stratified by BMI at enrolment were imprecise due to small numbers of cases within exposure strata; however, estimated risks for prostate cancer and all cancers combined (without prostate cancer) appeared to be reduced in association with weight loss among obese men, but not among normal or overweight men (Table 4). In contrast, the inverse association between weight gain and prostate cancer appeared to be independent of BMI at enrolment. Weight loss in women did not appear to be associated with breast cancer or all cancers combined, regardless of BMI (Table 5); however, weight gain was inversely associated with all cancers and breast cancer among women who were obese at baseline, but not among women who were normal weight or overweight.

discussion

In this prospective cohort of middle-European men and women, we did not find an association between weight change and the incidence of all cancers combined. Very few studies have published data concerning weight change and the incidence of all cancers [3, 17, 18]; however, results of prior studies are consistent with our findings and with those of studies that analysed associations with overall cancer mortality instead of cancer incidence [19–21].

For some specific types of cancer, we observed associations between weight loss or weight gain and tumour incidence. In particular, we noted evidence of a reduced risk of colon cancer in men with weight loss. To our knowledge, evidence of a relation between weight loss and colon cancer has not been published before. To explore this further, we subdivided weight

Table 4. Estimated HRs and 95% CIs for incident cancers diagnosed among male participants according to weight change and BMI at enrolment

Weight change (kg/m^2/year)						
BMI at enrolment	<−0.1	−0.1 to <0.1	0.1 to <0.3	0.3 to <0.5	≥0.5	*P* for trend[a]
All cancers other than prostate cancer						
>18.5 kg/m^2 (all men)						
Incident cases	207	335	222	103	38	0.48
HR (95% CI)[b]	1.04 (0.87–1.24)	1.00	0.90 (0.76–1.06)	1.18 (0.94–1.48)	1.00 (0.71–1.40)	
18.5–25.0 kg/m^2						
Incident cases	67	139	87	45	17	
HR (95% CI)[b]	1.23 (0.92–1.66)	1.00	0.86 (0.66–1.13)	**1.46 (1.04–2.05)**	1.10 (0.66–1.83)	0.16
25.0–29.9 kg/m^2						
Incident cases	106	166	111	41	13	
HR (95% CI)[b]	1.03 (0.80–1.31)	1.00	0.90 (0.70–1.14)	0.96 (0.68–1.36)	0.83 (0.47–1.47)	0.54
≥30.0 kg/m^2						
Incident cases	34	30	24	17	8	
HR (95% CI)[b]	0.69 (0.41–1.16)	1.00	0.93 (0.54–1.63)	1.31 (0.71–2.42)	1.26 (0.56–2.82)	0.41
Prostate cancer						
>18.5 kg/m^2 (all men)						
Incident cases	164	317	231	72	12	0.06
HR (95% CI)[b]	0.96 (0.79–1.16)	1.00	1.00 (0.85–1.19)	1.01 (0.78–1.31)	0.43 (0.24–0.76)	
18.5–25.0 kg/m^2						
Incident cases	52	134	106	36	6	
HR (95% CI)[b]	1.00 (0.73–1.39)	1.00	1.14 (0.88–1.48)	1.35 (0.93–1.96)	0.52 (0.23–1.18)	0.95
25.0–29.9 kg/m^2						
Incident cases	97	160	108	28	6	
HR (95% CI)[b]	1.00 (0.77–1.29)	1.00	0.92 (0.72–1.17)	0.76 (0.51–1.14)	0.49 (0.22–1.11)	0.07
≥30.0 kg/m^2						
Incident cases	15	23	17	8		
HR (95% CI)[b]	0.53 (0.27–1.05)	1.00	0.89 (0.46–1.70)	0.56 (0.25–1.28)	[c]	0.25

[a]Test for trend refers to stable weight or weight gain.

[b]Cox proportional hazards models were stratified according to age and adjusted for smoking status, blood glucose and occupational group.

[c]Weight change categories (0.3 to <0.5 kg/m^2/year and ≥0.5 kg/m^2/year) were combined as needed to ensure >5 cases in each.

HR, hazard rate ratio; CI, confidence interval; BMI, body mass index.

loss in two categories (<−0.3 and −0.30 to <−0.10 kg/m^2/year) and found similar inverse associations with colon cancer, without evidence of a linear trend in the dose–response relation. Weight loss was not associated with colon cancer in women; however, gender differences in the relationship between baseline BMI and colon cancer are well known [1]. Therefore, a different influence of weight change on cancer incidence between men and women may be plausible.

Growth-promoting effects of insulin and insulin-like growth factor-I have been proposed as a causal link between obesity and colon cancer and both parameters can be lowered by caloric restriction [22].

We were not able to differentiate between intentional and unintentional weight loss. Therefore, reverse causation is a potential concern. To avoid an influence of undiagnosed cancer on weight change, we excluded cases that occurred during the first year of follow-up. Furthermore, we carried out additional analyses excluding cases that occurred during the first 3 years of follow-up. In these sensitivity analyses, the association between weight loss and colon cancer among men remained virtually unchanged (HR 0.49; 95% CI 0.25–0.94).

In men, high weight gain was associated with a reduced risk of incident prostate cancer. This is consistent with two large prospective studies [11, 23] that assessed weight gain over comparable time periods. In contrast, a third study that assessed weight change >30 or more years did not show an association between weight gain and prostate cancer incidence [23].

Serum testosterone levels decrease with increasing obesity [24] and there is a long-standing suspicion that testosterone contributes to the growth and progression of prostate cancer [25]. Substantial weight gain over a relatively short period may therefore influence the risk of prostate cancer by reducing circulating androgen levels. In recent years, an increasing proportion of prostate cancers have been detected in the Vorarlberg study area by prostate-specific antigen (PSA) screening; however, we had no information about PSA screening on an individual level, so could not account for potential confounding by screening. In a sensitivity analysis, we used the number of screening examinations within the VHM&PP during the period of weight change assessment as a surrogate of individual screening behaviour. Adjustment by this variable did not attenuate the observed association (data not shown). To determine whether weight change is relevant to clinically significant prostate cancers (versus asymptomatic cancers with little risk of progression), additional studies of

Table 5. Estimated HRs and 95% CIs for incident cancers diagnosed among female participants according to weight change and BMI at enrolment

Weight change (kg/m^2/year)						
BMI at enrolment	<−0.1	−0.1 to <0.1	0.1 to <0.3	0.3 to <0.5	≥0.5	*P* for trend[a]
All cancers						
>18.5 kg/m^2 (all women)						
Incident cases	306	419	412	178	112	0.50
HR (95% CI)[b]	1.01 (0.87–1.18)	1.00	1.05 (0.91–1.20)	0.95 (0.80–1.14)	0.94 (0.76–1.16)	
18.5–25.0 kg/m^2						
Incident cases	116	249	242	96	45	
HR (95% CI)[b]	0.96 (0.77–1.21)	1.00	1.05 (0.88–1.25)	0.95 (0.75–1.20)	0.87 (0.63–1.20)	0.42
25.0–29.9 kg/m^2						
Incident cases	106	113	122	65	49	
HR (95% CI)[b]	1.10 (0.84–1.44)	1.00	1.13 (0.87–1.46)	1.18 (0.86–1.60)	1.26 (0.90–1.78)	0.14
≥30.0 kg/m^2						
Incident cases	84	57	48	17	18	
HR (95% CI)[b]	0.97 (0.68–1.37)	1.00	0.99 (0.67–1.47)	0.59 (0.34–1.02)	0.65 (0.37–1.12)	**0.05**
Breast cancer						
>18.5 kg/m^2 (all women)						
Incident cases	97	150	167	75	39	
HR (95% CI)[b]	0.95 (0.73–1.23)	1.00	1.15 (0.93–1.44)	1.08 (0.82–1.42)	0.87 (0.61–1.24)	0.63
18.5–25.0 kg/m^2						
Incident cases	31	92	102	45	19	
HR (95% CI)[b]	0.78 (0.52–1.18)	1.00	1.16 (0.87–1.53)	1.13 (0.79–1.62)	0.95 (0.58–1.56)	0.85
25.0–29.9 kg/m^2						
Incident cases	37	38	44	25	17	
HR (95% CI)[b]	1.17 (0.74–1.86)	1.00	1.20 (0.77–1.85)	1.33 (0.80–2.22)	1.25 (0.69–2.24)	0.45
≥30.0 kg/m^2						
Incident cases	29	20	21	8		
HR (95% CI)[b]	0.89 (0.50–1.59)	1.00	1.15 (0.62–2.15)	**0.39 (0.17–0.89)**	[c]	**0.02**

[a]Test for trend refers to stable weight or weight gain.

[b]Cox proportional hazards models were stratified according to age and adjusted for smoking status, blood glucose and occupational group.

[b]Weight change categories (0.3 to <0.5 kg/m^2/year and ≥0.5 kg/m^2/year) were combined as needed to ensure >5 cases in each.

HR, hazard rate ratio; CI, confidence interval; BMI, body mass index.

high grade or advanced stage prostate cancers, or of prostate cancer recurrence and mortality, are warranted.

Evidence of an association between obesity and ovarian cancer has been inconclusive [1], though a recent meta-analysis demonstrated a weak positive relation [26]. Only a few studies investigated the influence of weight change on ovarian cancer. Two large prospective studies did not find an association between weight loss or weight gain over adult life and the incidence of ovarian cancer [27, 28]. A recent case–control study found weight gain to be positively related to ovarian cancer risk, but only in nulliparous women [29], and two additional case–control studies reported that ovarian cancer was most closely linked with body weight in the relatively recent past [13, 30]. Our investigation of recent weight change showed a positive dose–response relation between weight gain and the incidence of ovarian cancer; however, we could not evaluate potential effect modification by parity or estrogen replacement therapy, and the number of incident cancers was relatively small ($n = 53$). There is a growing body of data supporting the hypothesis that stimulation of ovarian epithelial cells by unopposed estrogens may increase the risk of ovarian cancer [31], and circulating levels of estrogen are higher in postmenopausal women who are obese versus normal weight [32].

We did not find an association between weight change and the incidence of breast cancer in all women combined. In obese women, we observed an inverse association between weight gain and breast cancer, but this result was on the basis of only eight observed cases among obese women in the highest weight gain category. These results are inconsistent with many prior studies that have reported weight gain to be a risk factor for breast cancer [5–10]; however, most of these studies assessed weight change from age 18, rather than recent weight change as in our study. In addition, several large studies observed an association only in women who had never used postmenopausal hormones [8–10]. Unfortunately, we had no information about the use of postmenopausal hormones.

Many studies, including a prior publication based on the VHM&PP cohort, have shown a close relation between baseline obesity and endometrial cancer [4, 33], and most studies investigating weight change also found weight gain to be positively related to endometrial cancer [12, 34, 35]. This is in contrast to our results; specifically, weight gain over 7 years was not associated with an increased risk of endometrial cancer, regardless of whether estimates were adjusted for BMI at baseline. Weight loss, however, was inversely associated with endometrial cancer, though the association did not reach statistical significance.

We are not aware of previous publications concerning the association between weight change and the incidence of malignant melanoma. Our finding of a reduced risk of malignant melanoma with increasing weight gain in women but not men may be confounded by frequency and intensity of sun exposure, which is the major environmental risk factor for this type of skin cancer [36]. The observed gender difference may be plausible if women are more likely than men to reduce intentional sun exposure after gaining weight; however, we cannot access sun exposure patterns in the study population, and estimates were on the basis of small numbers of observed cases.

To our knowledge, our study is the first to present analysis of weight change and cancer incidence for all major cancer sites among both men and women. Incident cancers were ascertained by an established population-based cancer registry, and nearly all cases were histologically confirmed; therefore, the likelihood of outcome misclassification was low. Despite the large number of study participants, however, some cancers of interest could not be evaluated at all due to small numbers of cases, and effect estimates for more common cancers were sometimes imprecise because of small numbers of cases in exposure strata. A further limitation is that we were unable to account for some factors that might have confounded or modified relations between weight change and specific cancers, such as parity and hormone replacement therapy in women or physical activity and diet in men and women. The potential influence of bias or chance should therefore be considered when interpreting individual effect estimates, regardless of the presence or absence of statistical significance.

In most previous cohort studies, the period of weight change assessment was determined by the difference between weight at a baseline examination and recalled weight from early adulthood. Thus, weight change has been typically assessed over several decades, and differences between our findings and previous studies may therefore reflect differences in the time interval over which weight change was determined. Weight gain over adult life and recent weight change are both likely to be biologically relevant, but associations on the basis of weight change over a shorter interval may be more relevant to potential dietary interventions to reduce cancer risk in middle-aged and older adults. In addition, in our study weight change was determined on the basis of measured values rather than self-reported recall of body weight in the past. Finally, we did not analyse absolute change in weight, but instead defined weight change based on the annual trend in relative body weight (BMI) to account for potential differences in the physiological impact of absolute weight change among persons with different body sizes.

In summary, we investigated associations between weight change for a period of ~7 years and incident cancers. Weight loss was inversely associated with colon cancer in men, but not in women, while weight gain of 0.5 mg/m^2 per year was inversely associated with prostate cancer in men, and positively associated with ovarian cancer in women.

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