Excess body weight, weight gain, and obesity-related cancer risk in women in Norway: the Norwegian Women and Cancer study

Running title: Weight and obesity-related cancer in women

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Abstract

Background

Excess body weight and weight gain have been reported to independently increase the risk of several cancers. There are few published studies in nationally representative populations of women on specific, "obesity-related" cancers in relation to prior weight change and relevant confounders.

Methods

Based on self-reported anthropometry, we prospectively assessed body mass index (BMI), weight change over 6 years, and subsequent obesity-related cancer risk in the Norwegian Women and Cancer study. We used multivariable Cox proportional hazard models to calculate hazard ratios.

Results

Excess body weight increased the risk of overall obesity-related cancer, postmenopausal breast, colorectal, colon, endometrial, and kidney cancer, with endometrial cancer showing the highest risk estimate. High weight gain (≥10 kg) increased the risk of overall obesity-related cancer, postmenopausal breast, endometrial, and pancreatic cancer. Pancreatic cancer showed the strongest association with high weight gain, with a 91% increased risk.

Conclusions

Maintaining stable weight in middle adulthood, irrespective of BMI category at baseline, as well as avoiding excess body weight, are likely important in the prevention of several obesity-related cancer in women. Our finding of increased risk of pancreatic cancer in women with moderate and high weight gain is novel.

Background

The prevalence of overweight and obesity has been increasing continuously worldwide over the past four decades, and today it is among the top five risk factors that contribute to the disease burden in both high and middle-income countries.[1, 2] Although excess body weight is a modifiable risk factor, attempts to halt the global obesity epidemic worldwide have failed. Obesity and weight gain are independently associated with increased risk of cardiovascular disease, diabetes, and several cancers, which highlights the public health implications of the increasing prevalence of obesity.[3-8] Thirteen cancer types have been defined as obesity-related, with sufficient evidence of a positive association with overweight/obesity (also referred to as excess body weight).[9] Although the biological mechanisms that explain the role of excess body weight in cancer development are not completely understood, three hypotheses have been postulated: (i) altered circulating levels of sex hormones in individuals with obesity could increase the risk of breast, endometrial, and ovarian cancer; (ii) increased insulin levels and higher bioavailability of insulin-like growth factor could promote tumour development in individuals with obesity; and (iii) increased concentrations of adipokines in individuals with obesity could promote tumour development alone and/or through inflammatory mediators.[10] In accordance with global trends, there are indications of increased obesity prevalence in Norway. The latest regional health examination from Nord-Trøndelag (HUNT), carried out in 2006-2008, reported a prevalence of obesity of 23.1% in women. This represented a 10-percentage-point increase from a previous HUNT report covering the period 1984-1986.[11] In addition, Statistics Norway conduct a survey on living conditions every 3 years in a representative sample of inhabitants in Norway aged 16 years or older.[12] Since 1998, the self-reported prevalence of obesity has increased in both women and men and reached 11% in women in 2015. There are differences in obesity prevalence according to age groups, region, rural/urban settlements and reporting method (self-report or examination), however, there is little doubt that increasing body weight is a public health

concern also in Norway. Moreover, three of the five most commonly diagnosed cancers among women in Norway are obesity-related (breast, colon, and endometrial cancer).[13]

In this study, we assessed the impact of adult body mass index (BMI) and weight change in relation to a larger number of obesity-related cancer, using data from the Norwegian Women and Cancer (NOWAC) study.

Materials and Methods

Study design, participants, and subcohorts

The NOWAC study is a nationally representative, population-based cohort study that was initiated in 1991, with the aim of investigating the aetiology of cancer among women in Norway. Women aged 30-70 years were randomly sampled from the Norwegian Central Population Register, which includes all Norwegian inhabitants, and invited to participate in the study during three separate waves of recruitment: 1991-1992, 1996-1997, and 2003-2005. Those who agreed to participate completed an enrolment questionnaire (Q1) and were invited to complete a follow-up questionnaire (Q2) 5-8 years after Q1. The unique personal identity number assigned to every resident of Norway allowed for linkages to national registers for complete follow-up. The response rate in the NOWAC study varied between 48% and 57% at enrolment, and was 81% at follow-up.[14] Details on the design, materials, and procedures of the NOWAC study have been described elsewhere.[15]

In the present study, 145 658 women who returned Q1 between 1991 and 2005 were considered eligible for inclusion. We excluded women who had emigrated or died before Q1 was registered in the study database (n=30), women who were diagnosed with cancer (other than non-melanoma skin cancer) prior to Q1 (n=5 112), and women with missing weight in both Q1 and Q2 (n=1 678). Women who reported implausible weight values (<30 or >200 kg), height values (<100 or >230 cm) (n=4), or age at menopause (<25 or >60 years) (n=88) in either questionnaire were also excluded. Thus,

our final analytical study sample consisted of 138 746 women: 40% enrolled in 1991-1992, 31% enrolled in 1996-1997, and 29% enrolled in 2003-2005.

BMI and weight change analyses were carried out in subcohorts of the final analytical study sample. In the BMI analysis, we excluded women with less than 2 years of follow-up after Q1 to reduce the possible influence of reverse causality from the effects of pre-clinical cancer on weight (n=1 565), and women with missing weight or height in Q1 (n=1 473). In the weight change analysis, we excluded women who did not return Q2 (n=51 637). Women who returned Q2 were younger, had lower body weight, and were less likely to use hormone therapy (HT) compared to women who completed only Q1. Furthermore, we excluded women who emigrated or died before Q2 was registered in the study database (n=8). Women who had been diagnosed with cancer (other than non-melanoma skin cancer) prior to Q2 (n=2 030), had less than 2 years of follow-up after Q2 (n=1 174), or had missing information on weight in Q1 or Q2 were also excluded (n=2 967) (Figure 1). In site-specific analyses, we excluded premenopausal women from the postmenopausal breast cancer analysis, women who reported hysterectomy from the endometrial cancer analysis, and women who reported bilateral oophorectomy from the ovarian cancer analysis.

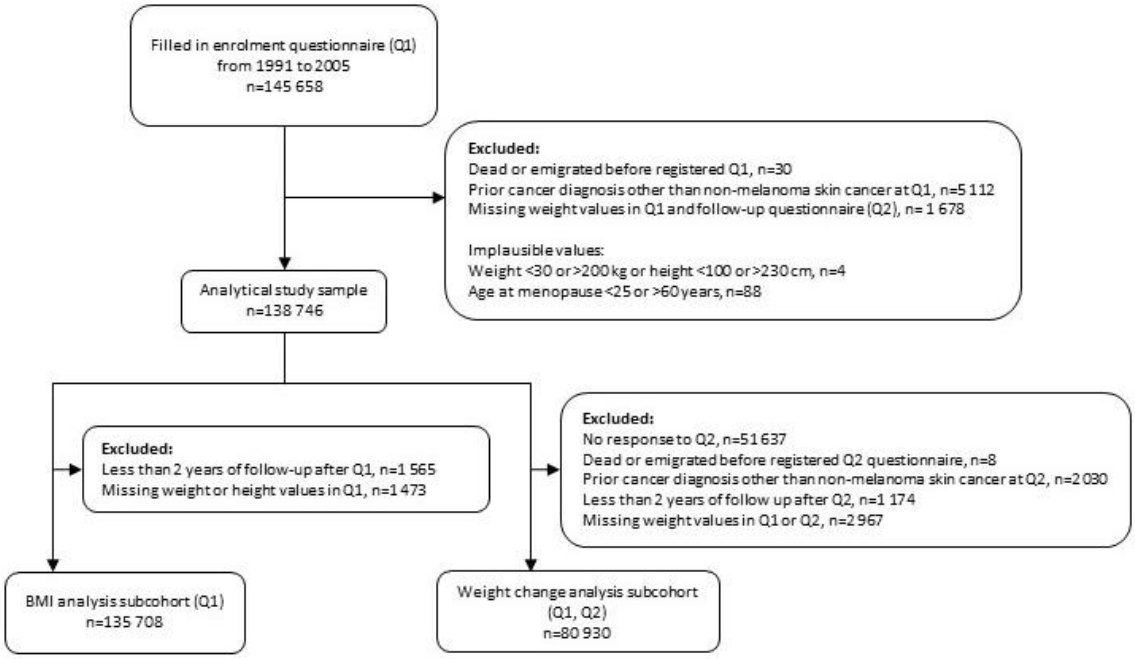

Figure 1. Flowchart of study participants

Follow-up and identification of cancer cases

Follow-up began at Q1 for the BMI analysis and at Q2 for the weight change analysis. Women were followed-up until cancer diagnosis, death, emigration, or the end of follow-up (31 December 2014), whichever occurred first. Incidence of cancer, death, and emigration were identified through linkage to the Norwegian Cancer Registry, the Cause of Death Registry, and the Norwegian Central Population Register, respectively. The outcome of interest was first primary invasive cancer, for which evidence of a positive association with excess body weight is considered sufficient, [9] hereafter referred to as "obesity-related cancer". These cancers were assessed as one combined outcome (overall obesity-related cancer) and as site-specific outcomes, and were classified according to the International Classification of Diseases, 10th Revision. They included cancer of the breast (postmenopausal) (C50), colon-rectum (C18-20), endometrium (C54), ovary (C56), pancreas (C25), kidney (C64), gallbladder (C23-24), gastric cardia

(C16), liver (C22), oesophagus (adenocarcinoma) (C15), meningioma (C70-72), thyroid (C73), and multiple myeloma (C90). In the overall obesity-related cancer analysis, women were considered to have postmenopausal breast cancer if they reported being postmenopausal in Q1, or if they gave an age at menopause that was earlier than their age at breast cancer diagnosis. Women with unknown menopausal status or missing information on age at menopause were considered to have postmenopausal breast cancer if they had reached 53 years of age at or before the time of breast cancer diagnosis. This age cut-off has been used previously to classify women as postmenopausal in the NOWAC study[16] and represents approximately 80% of the women in our study population who reached natural menopause. We did not perform site-specific analyses for cancer of the gallbladder, gastric cardia, liver, oesophagus, meningioma, thyroid, or multiple myeloma, due to the small number of incident cases for each of these sites.

Assessment of body mass index, weight change, and covariates

BMI was calculated as self-reported weight in kg divided by the square of self-reported height in meters and categorised according to the World Health Organisation definition [17]: underweight (BMI <18.5kg/m^2), normal weight (BMI 18.5-<25kg/m^2), overweight (BMI 25-<30kg/m^2), or obesity (BMI ≥30kg/m^2). We used self-reported weight from Q1 and Q2 to calculate weight change, which was categorised into five groups: weight loss (<-2kg), stable weight (-2 to <2kg), low weight gain (2 to <5kg), moderate weight gain (5 to <10kg), or high weight gain (≥10kg).

Information on covariates was extracted from Q1 for the BMI analysis, and Q1 or Q2 for the weight change analysis. An *a priori* selection of covariates was done, based on findings from previous studies on BMI or weight change and obesity-related cancer, as well as previous reports from the NOWAC study. Thus the covariates education (<10 years/10-12 years/>12 years), physical activity level (low/moderate/high), smoking status (never/former/current), and alcohol intake (≤median/>median g/day) were included in all analyses. In addition, we assessed smoking transition (cessation/restart/no

change) and physical activity change (increase/decrease/no change) in all weight change analyses. The outcome-specific covariates that were common for postmenopausal breast, ovarian and endometrial cancer were age at menarche (≤median/>median age), parity/age at first full-term pregnancy (nullipara/unipara <29 years/unipara ≥30/multipara <29/multipara ≥30), oral contraceptive (OC) use (never/ever), and HT use (never/former/current). For postmenopausal breast cancer, maternal history of breast cancer (yes/no) was also included in the model, and for endometrial and ovarian cancer, menopausal status was also included in the model. Diabetes (yes/no) was evaluated as a potential confounder for endometrial, colorectal, pancreatic, and kidney cancer; for colorectal cancer (as well as for colon and rectal cancer analysed separately) we assessed consumption of red and processed meat, fruits, vegetables, fibre, and calcium categorised into tertiles (low/medium/high).

Statistical analysis

Population characteristics by BMI and weight change category were assessed using chi-squared tests for categorical variables and one-way ANOVA or Kruskal-Wallis test for continuous variables. We used Cox proportional hazard regression models with age as the underlying time metric [18] to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of BMI and weight change with obesity-related cancer risk. The reference groups were 'normal weight' and 'stable weight'. To account for the calendar and birth cohort effect, we constructed a variable based on wave of enrolment and birth year (categorised into four groups) that was included in the Cox regression models, and allowed the baseline hazard function to vary between the groups but with equal coefficients across groups. The Cox models were built according to the 'purposeful selection' approach.[19] In brief, we performed univariable Cox models for each covariate and included those that were significant at a 20% level in a multivariable model (the full model). Thereafter, we used Wald statistics to exclude covariates that were no longer significant in the full model, or did not change the coefficients of the exposure variable more than 20%. Log-likelihood ratio tests were performed to compare goodness of fit between the reduced model and

the full model. Covariates that remained in the reduced final models are presented in the footnotes of Tables 2 and 3. Tests based on Schoenfeld residuals showed no evidence of violation of the proportional hazard assumptions.[20] We fitted two models per outcome; Model 1 controlled only for age (by time in the Cox regression) and Model 2 (main model) with adjustments by purposeful selection of covariates for each outcome separately. Test for linear trends were conducted by treating the median values within each exposure category as a continuous variable. We tested for interactions with log-likelihood ratio test, comparing reduced models with and without the interaction term. In all weight change analyses, we tested for interaction between BMI category and weight change category. In site-specific analyses where HT use or menopausal status was included as a covariate, we tested for interactions between these and each exposure. All statistical analyses were performed using STATA version 15.1 (Stata Corp., College Station, TX, USA).

Results

In total, 135 708 women were included in the BMI analysis and 80 930 women who also responded to Q2 were included in the weight change analysis (Figure 1). In the BMI analysis, average follow-up time was 16.9 (standard deviation [SD]=5.8) years, during which 9 328 obesity-related cancers were diagnosed, with a mean age at diagnosis of 61.9 (SD=7.9) years. In the weight change analysis, average follow-up time was 13.1 (SD=4.2) years, during which 4 831 obesity-related cancers were diagnosed, with a mean age at diagnosis of 63.0 (SD=7.7) years. The average response time between Q1 and Q2 was 6.3 years (SD=0.9) and did not differ substantially across weight change categories.

Population characteristics

In the BMI analysis, the population mean (SD) age, weight, and BMI were 48.2 (8.6) years, 66.7 (11.4) kg, and 24.1 (3.9) kg/m^2, respectively. The majority of women were of normal weight (64.6%), followed by overweight (25.5%), obesity (7.7%) and underweight (2.2%). Compared to the other BMI categories, women with obesity were older, and had lower education, physical activity level, and alcohol intake.

They were more likely to be never or former smokers, report lower age at menarche, younger at first full-term pregnancy, have three or more children, less likely to use OC, more likely to be postmenopausal, and more likely to report former use of HT (Table 1).

In the weight change analysis, the population mean (SD) age, weight, and BMI in Q2 was 52.4 (8.5) years, 68.6 (11.5) kg, and 24.8 (3.9) kg/m^2, respectively. During the 6.3 years between Q1 and Q2, 9.7% of women lost weight, 29.3% had stable weight, 27.6% had low weight gain, 24.1% had moderate weight gain, and 9.3% had high weight gain. Population characteristics differed across these weight change categories (Supplementary Information, Table S1). Women with high weight gain were younger and reported lower physical activity at Q1 compared to women with stable weight. Moreover, between Q1 and Q2, women with high weight gain were more likely to have stopped smoking, decreased their physical activity level, and transitioned to menopause.

Table 1. Population characteristics by body mass index (BMI) category at enrolment. The Norwegian Women and Cancer study 1991-2005 (n=135 708)

		BMI category (kg/m)			
	N†	Underweight	Normal weight	Overweight	Obesity
Number of women. n (%)	135 708	3 022 (2.2)	87 595 (64.6)	34 656 (25.5)	10 435 (7.7)
Obesity-related cancer. n	9 328	173	5 689	2 603	863
Characteristics at enrolment*					
Age (y). mean (SD)	135 708	44.1 (8.4)	46.9 (8.4)	50.8 (8.4)	51.5 (8)
Weight (kg). mean (SD)	135 708	49.3 (3.9)	61.4 (6.1)	74.2 (6.3)	91.0 (11.7)
Height (cm). mean (SD)	135 708	166.6 (5.6)	166.5 (5.6)	165.9 (5.7)	165.3 (5.8)
Education (y). %	128 948				
<10		24.0	21.7	29.8	34.3
10-12		22.1	23.5	24.6	24.4
>12		53.9	54.9	45.6	41.3
Physical activity level. %	123 531				
Low		25.7	21.2	30.7	45.7
Moderate		37.5	42.2	42.6	37.0
High		36.8	36.7	26.7	17.4
Smoking status. %	135 231				
Never smoker		27.2	34.4	37.8	40.0
Former smoker		21.3	31.8	35.7	36.2
Current smoker		51.6	33.8	26.5	23.8

Alcohol intake (g/day). median	128 046	1.6	1.9	1.5	0.9
Age at menarche (y). mean (SD)	133 625	13.7 (1.4)	13.4 (1.4)	13.2 (1.4)	12.9 (1.4)
Age at first full-term pregnancy (y). mean (SD)	123 592	24.7 (4.7)	24.1 (4.4)	23.6 (4.3)	23.4 (4.4)
Parity. %	135 708				
Nulliparous		13.0	9.5	8.1	11.1
1-2 children		56.8	55.7	50.1	46.3
≥ 3 children		30.2	34.9	41.9	42.6
Oral contraceptive use. %	131 415				
Never		38.2	40.6	49.8	54.4
Ever		61.8	59.4	50.2	45.6
Menopausal status. %	135 708				
Premenopausal		64.0	55.3	37.1	31.6
Perimenopausal		4.2	4.8	5.6	6.6
Postmenopausal		25.9	32.9	50.1	54.7
Unknown		5.9	7.0	7.2	7.2
Age at menopause (y). mean (SD)	45 160	46.7 (5.9)	48.3 (4.8)	48.8 (4.7)	48.5 (5.2)
Hormone therapy use. %	126 669				
Never		85.7	79.6	72.7	73.7
Former		5.6	8.2	12.9	14.4
Current		8.7	12.2	14.4	11.9

*Overall differences between weight change categories were significant for all variables (p<0.001)

†N is the total amount of responses for the specific variable

Abbreviations: y: years, SD: standard deviation

BMI and obesity-related cancer risk

Compared to normal-weight women, women with overweight or obesity had a significant, increased obesity-related cancer risk, with HRs of 1.09 (95% CI: 1.03-1.14) and 1.24 (95% CI: 1.14-1.34). In site-specific analyses, endometrial cancer displayed the strongest significant association with obesity, with an over two-fold increased risk (HR=2.18, 95% CI: 1.59-2.98). Furthermore, excess body weight significantly increased the risk of postmenopausal breast cancer (overweight HR=1.13, 95% CI: 1.00-1.27) and the association with obesity was of borderline significance (HR=1.20, 95% CI: 1.00-1.44; p=0.05). Excess body weight was also significantly associated with colorectal (overweight HR=1.12, 95% CI: 1.01-1.25), colon (overweight HR=1.21, 95% CI: 1.07-1.37), endometrial (overweight HR=1.61, 95% CI: 1.31-1.98), and

kidney cancer (obesity HR=1.95, 95% CI: 1.26-3.02). There was a significant linear trend between BMI and obesity-related cancer, postmenopausal breast, endometrial, and kidney cancer. There was no significant association between excess body weight and increased risk of rectal, ovarian, and pancreatic cancer (Table 2).

We found no significant interactions between HT use and BMI; however, menopausal status modified the effect of BMI in relation to endometrial cancer risk.

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by body mass index (BMI) category at enrolment. The Norwegian Women and Cancer study, 1991-2014 (n=135 708)

	Model 1 Age-adjusted				Model 2 Multivariable			
	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI
Overall obesity-related cancer*	135 708	9 328			117 913	7 963		
Underweight	3 022	173	0.95	0.82-1.10	2 626	149	0.92	0.78-1.08
Normal weight	87 595	5 689	1.00	Reference	77 064	4 961	1.00	Reference
Overweight	34 656	2 603	1.10	1.05-1.15	29 517	2 154	1.09	1.03-1.14
Obesity	10 435	863	1.26	1.17-1.35	8 706	699	1.24	1.14-1.34
P value for trend				<0.001				<0.001
Postmenopausal breast cancer†	59 331	1 918			43 493	1 386		
Underweight	899	27	0.96	0.66-1.41	650	19	0.98	0.62-1.55
Normal weight	32 831	1 047	1.00	Reference	24 224	730	1.00	Reference
Overweight	19 270	638	1.04	0.95-1.15	14 079	448	1.13	1.00-1.27
Obesity	6 331	206	1.07	0.92-1.24	4 540	139	1.20	1.00-1.44
P value for trend				0.285				0.017
Colorectal cancer*	135 708	1 927			128 568	1 805		
Underweight	3 022	39	1.11	0.80-1.52	2 902	38	1.10	0.80-1.52
Normal weight	87 595	1 146	1.00	Reference	83 411	1083	1.00	Reference
Overweight	34 656	585	1.12	1.02-1.24	32 511	544	1.12	1.01-1.25
Obesity	10 435	157	1.05	0.88-1.24	9 744	140	1.01	0.84-1.20

P value for trend				0.189				0.353
Colon cancer‡	135 708	1 290			135 231	1 283		
Underweight	3 022	26	1.14	0.77-1.69	3 017	26	1.13	0.76-1.67
Normal weight	87 595	746	1.00	Reference	87 355	743	1.00	Reference
Overweight	34 656	414	1.20	1.06-1.36	34 481	411	1.21	1.07-1.37
Obesity	10 435	104	1.05	0.85-1.29	10 378	103	1.06	0.86-1.30
P value for trend				0.123				0.093
Rectal cancer∫	135 708	637			122 607	562		
Underweight	3 022	13	1.05	0.60-1.82	2 805	11	0.99	0.54-1.81
Normal weight	87 595	400	1.00	Reference	79 948	354	1.00	Reference
Overweight	34 656	171	0.98	0.82-1.18	30 665	153	1.02	0.84-1.24
Obesity	10 435	53	1.05	0.78-1.40	9 189	44	1.03	0.75-1.42
P value for trend				0.935				0.791
Endometrial cancer‖	128 314	1 057			113 150	932		
Underweight	2 914	11	0.62	0.34-1.13	2 594	10	0.64	0.30-1.35
Normal weight	83 620	539	1.00	Reference	74 239	489	1.00	Reference
Overweight	32 163	321	1.50	1.30-1.72	27 991	277	1.61	1.31-1.98
Obesity	9 617	186	3.02	2.55-3.58	8 326	156	2.18	1.59-2.98
P value for trend				<0.001				<0.001
Ovarian cancer¶	133 367	642			125 148	605		
Underweight	2 991	11	0.75	0.41-1.36	2 851	10	0.71	0.38-1.33
Normal weight	86 442	429	1.00	Reference	81 300	404	1.00	Reference
Overweight	33 816	149	0.91	0.75-1.10	31 608	142	0.92	0.76-1.12
Obesity	10 118	53	1.13	0.85-1.51	9 425	49	1.09	0.81-1.48
P value for trend				0.676				0.746
Pancreatic cancer*	137 205	350			128 568	324		
Underweight	3 059	5	0.75	0.31-1.83	2 902	4	0.55	0.20-1.48
Normal weight	88 480	213	1.00	Reference	83 411	202	1.00	Reference
Overweight	35 092	104	1.11	0.87-1.41	32 511	97	1.18	0.92-1.51
Obesity	10 574	28	1.05	0.70-1.56	9 744	29	1.19	0.79-1.79
P value for trend				0.451				0.111
Kidney cancer**	137 205	292			104 666	211		

Underweight	3 059	2	0.40	0.10-1.60	2 295	2	0.50	0.12-2.04
Normal weight	88 480	158	1.00	Reference	68 745	120	1.00	Reference
Overweight	35 092	94	1.41	1.08-1.82	26 124	62	1.32	0.96-1.81
Obesity	10 574	38	1.97	1.38-2.83	7 502	27	1.95	1.26-3.02
P value for trend				<0.001				0.001

*Model 2 for overall obesity-related, colorectal, and pancreatic cancer was adjusted for age, smoking status, and education

†Only in women who were postmenopausal at enrolment, model 2 for postmenopausal breast cancer was adjusted for age, alcohol intake, education, parity/age at first full-term pregnancy, oral contraceptive use, hormone therapy use, and history of breast cancer in the mother

‡Model 2 for colon cancer was adjusted for age and smoking status

ʃModel 2 for rectal cancer was adjusted for age, alcohol intake, and education

‖Model 2 for endometrial cancer was adjusted for age, education, age at menarche, parity/age at first full-term pregnancy, oral contraceptive use, menopausal status, and the interaction between menopausal status and body mass index category

¶Model 2 for ovarian cancer was adjusted for age, parity/age at first full-term pregnancy, and oral contraceptive use

**Model 2 for kidney cancer was adjusted for age, smoking status, and diabetes

Weight change and obesity-related cancer risk

Weight gain was significantly associated with increased obesity-related cancer risk, with the strongest association observed among women with high weight gain (HR=1.16, 95% CI: 1.04-1.31) as compared to women with stable weight. The strongest significant association with high weight gain was detected for pancreatic cancer (HR=1.91, 95% CI: 1.11-3.30). Furthermore, weight gain significantly increased the risk

of postmenopausal breast cancer (moderate weight gain HR=1.20, 95% CI: 1.01-1.43; high weight gain HR=1.36, 95% CI: 1.08-1.71), as well as colorectal cancer (moderate weight gain HR=1.24, 95% CI: 1.05-1.48), rectal cancer (low weight gain HR=1.37, 95% CI: 1.00-1.86; moderate weight gain HR=1.38, 95% CI: 1.00-1.91; p=0.05), endometrial cancer (moderate weight gain HR=1.27, 95% CI: 1.01-1.61; high weight gain HR=1.40, 95% CI: 1.04-1.88), and pancreatic cancer (moderate weight gain HR=1.60, 95% CI: 1.03-2.47). There was a significant linear trend between weight change and risk of obesity-related, postmenopausal breast and endometrial cancer. Weight loss was significantly associated with an increased risk of colorectal cancer (HR=1.25, CI: 1.01-1.55) and displayed positive associations with all obesity-related cancers under study, although they did not reach statistical significance (Table 3).

There was no significant interaction between BMI and weight change category in relation to obesity-related cancer risk. In addition, we found no significant interactions between HT use or menopausal status and weight change category.

Table 3. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by weight change category between the enrolment (Q1) and follow-up questionnaire (Q2). The Norwegian Women and Cancer study, 1991-2014 (n=80 930)

	Model 1 Age-adjusted				Model 2 Multivariable			
	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI
Overall obesity-related cancer*	80 930	4 831			71 440	4 232		
Weight loss (<-2kg)	7 876	478	1.15	1.04-1.28	6 886	406	1.09	0.97-1.22
Stable weight (-2 to <2kg)	23 711	1 315	1.00	Reference	20 950	1 142	1.00	Reference
Low weight gain (2 to <5kg)	22 362	1 356	1.10	1.02-1.19	19 844	1 209	1.14	1.05-1.23
Moderate weight gain (5 to <10kg)	19 495	1 218	1.14	1.06-1.24	17 202	1 069	1.14	1.05-1.25
High weight gain (≥10kg)	7 486	464	1.19	1.06-1.32	6 558	406	1.16	1.04-1.31
P value for trend				0.031				0.016
Postmenopausal breast cancer†	46 708	1 332			36 452	1 023		
Weight loss (<-2kg)	5 456	128	1.00	0.82-1.22	4 040	97	1.16	0.92-1.47

Stable weight (-2 to <2kg)	14 997	388	1.00	Reference	11 605	277	1.00	Reference
Low weight gain (2 to <5kg)	12 462	383	1.11	0.97-1.28	9 858	293	1.16	0.98-1.36
Moderate weight gain (5 to <10kg)	10 103	312	1.08	0.93-1.25	8 025	254	1.20	1.01-1.43
High weight gain (≥10kg)	3 690	121	1.15	0.93-1.41	2 924	102	1.36	1.08-1.71
P value for trend				0.153				0.041
Colorectal cancer‡	80 930	1 007			80 918	1 006		
Weight loss (<-2kg)	7 876	120	1.28	1.03-1.58	7 874	120	1.25	1.01-1.55
Stable weight (-2 to <2kg)	23 711	286	1.00	Reference	23 705	286	1.00	Reference
Low weight gain (2 to <5kg)	22 362	273	1.11	0.94-1.31	22 361	273	1.11	0.94-1.32
Moderate weight gain (5 to <10kg)	19 495	253	1.24	1.05-1.48	19 492	252	1.24	1.05-1.48
High weight gain (≥10kg)	7 486	75	1.04	0.8-1.34	7 486	75	1.02	0.79-1.33
P value for trend				0.977				0.990
Colon cancer∫	80 930	710			80 892	707		
Weight loss (<-2kg)	7 876	91	1.30	1.01-1.66	7 872	91	1.26	0.98-1.61
Stable weight (-2 to <2kg)	23 711	212	1.00	Reference	23 695	210	1.00	Reference
Low weight gain (2 to <5kg)	22 362	181	1.01	0.83-1.24	22 355	181	1.03	0.84-1.26
Moderate weight gain (5 to <10kg)	19 495	174	1.19	0.97-1.47	19 487	173	1.19	0.97-1.46
High weight gain (≥10kg)	7 486	52	1.01	0.74-1.38	7 483	52	0.98	0.72-1.34
P value for trend				0.623				0.635
Rectal cancer‖	80 930	297			80 930	297		
Weight loss (<-2kg)	7 876	29	1.22	0.80-1.88	7 876	29	1.22	0.80-1.88
Stable weight (-2 to <2kg)	23 711	74	1.00	Reference	23 711	74	1.00	Reference
Low weight gain (2 to <5kg)	22 362	92	1.37	1.00-1.86	22 362	92	1.37	1.00-1.86
Moderate weight gain (5 to <10kg)	19 495	79	1.38	1.00-1.91	19 495	79	1.38	1.00-1.91
High weight gain (≥10kg)	7 486	23	1.11	0.69-1.78	7 486	23	1.11	0.69-1.78
P value for trend				0.484				0.484
Endometrial cancer¶	75 895	571			71 597	539		
Weight loss (<-2kg)	7 281	59	1.24	0.92-1.68	6 813	55	1.03	0.75-1.41
Stable weight (-2 to <2kg)	22 238	153	1.00	Reference	20 899	139	1.00	Reference
Low weight gain (2 to <5kg)	20 998	136	0.94	0.75-1.19	19 798	127	0.99	0.78-1.26
Moderate weight gain (5 to <10kg)	18 389	154	1.23	0.98-1.54	17 413	150	1.27	1.01-1.61
High weight gain (≥10kg)	6 989	69	1.51	1.13-2.01	6 674	68	1.40	1.04-1.88

P value for trend				0.045				0.013
Ovarian cancer**	79 023	310			70 022	278		
Weight loss (<-2kg)	7 614	37	1.62	1.09-2.41	6 650	30	1.52	0.99-2.34
Stable weight (-2 to <2kg)	23 041	74	1.00	Reference	20 409	66	1.00	Reference
Low weight gain (2 to <5kg)	21 890	90	1.25	0.92-1.71	19 497	84	1.29	0.93-1.79
Moderate weight gain (5 to <10kg)	19 133	84	1.32	0.96-1.81	16 955	75	1.30	0.93-1.82
High weight gain (≥10kg)	7 345	25	1.05	0.66-1.66	6 511	23	1.08	0.67-1.74
P value for trend				0.566				0.794
Pancreatic cancer††	80 930	186			74 609	170		
Weight loss (<-2kg)	7 876	25	1.84	1.12-3.02	7 176	21	1.58	0.93-2.69
Stable weight (-2 to <2kg)	23 711	42	1.00	Reference	21 697	39	1.00	Reference
Low weight gain (2 to <5kg)	22 362	50	1.37	0.91-2.07	20 641	43	1.28	0.83-1.98
Moderate weight gain (5 to <10kg)	19 495	48	1.59	1.04-2.43	18 124	46	1.60	1.03-2.47
High weight gain (≥10kg)	7 486	21	1.95	1.14-3.32	6 971	21	1.91	1.11-3.30
P value for trend				0.234				0.114
Kidney cancer‡‡	80 930	148			62 654	94		
Weight loss (<-2kg)	7 876	17	1.29	0.73-2.28	5 750	10	1.08	0.52-2.27
Stable weight (-2 to <2kg)	23 711	41	1.00	Reference	18 350	26	1.00	Reference
Low weight gain (2 to <5kg)	22 362	40	1.07	0.69-1.66	17 697	27	1.14	0.66-1.96
Moderate weight gain (5 to <10kg)	19 495	35	1.10	0.70-1.74	15 223	23	1.14	0.64-2.01
High weight gain (≥10kg)	7 486	15	1.31	0.72-2.38	5 634	8	1.10	0.49-2.45
P value for trend				0.803				0.806

*Model 2 for obesity-related cancer was adjusted for age, BMI (Q1), physical activity (Q1), smoking status, and smoking transition

†Only in women who were postmenopausal at Q2, model 2 for postmenopausal breast cancer was adjusted for age, education, parity/age at first full-term pregnancy, history of breast cancer in the mother, and hormone therapy use

‡Model 2 for colorectal cancer was adjusted for age and smoking status

ʃModel 2 for colon cancer was adjusted for age, BMI (Q1), and smoking status

‖Model 2 for rectal cancer did not significantly differ from model 1 and is only adjusted for age

¶Model 2 for endometrial cancer was adjusted for age, BMI (Q1), age at menarche, parity/age at first full-term pregnancy, oral contraceptive use, and menopausal status

**Model 2 for ovarian cancer was adjusted for age, physical activity (Q1), and parity/age at first full-term pregnancy

††Model 2 for pancreatic cancer was adjusted for age, education, and smoking status

‡‡Model 2 for kidney cancer was adjusted for age, alcohol intake, and diabetes

Discussion

In this study, we assessed the relationship between BMI, weight change and obesity-related cancer risk in a large and representative cohort of women in Norway. We found that overweight and obesity significantly increased overall obesity-related cancer risk by 9 and 24%. Furthermore, weight gain less than 10 kg over 6 years, significantly increased obesity-related cancer risk by 14%, whilst gaining 10 kg or more was associated with a significant increased risk of 16%, independent of BMI category at baseline. These findings highlight the health risks of excess body weight and continuous increase in body weight among middle-aged women in Norway. As in other studies, we found clear evidence of a significant association between excess body weight and postmenopausal breast, colorectal, colon, endometrial, and kidney cancer[9], but no significant association with rectal, ovarian, or pancreatic cancer. In addition, we found significant associations between weight gain and postmenopausal breast, colorectal, rectal, endometrial, and pancreatic cancer but not between weight gain and ovarian or kidney cancer. These results suggest a similar effect of excess body weight and weight gain on hormone-related cancers (postmenopausal breast, endometrial, and ovarian cancer), but a differential effect on kidney, colon, rectal, and pancreatic cancer. Excess body weight and weight gain may affect organs differently,

depending on the mechanism of cancer development.[10] For instance, pancreatic cancer was not significantly associated with excess body weight, but there was a significant positive association with moderate and high weight gain. Pancreatic cancer development could be related to increased insulin levels and higher bioavailability of insulin-like growth factor,[21] in which weight gain, rather than BMI, may play a more essential role. To our knowledge, there has only been one previous study that included a separate analysis of pancreatic cancer and weight change in women, and it showed a non-significant negative association.[22] Another study including both women and men, demonstrated a non-significant, positive association.[23] These two studies were included in a recent meta-analysis of weight gain and several cancers, wherein the authors hypothesised that in the presence of strong risk factors such as smoking, weight gain is not able to establish itself as an individual risk factor for pancreatic cancer.[6] Our study sample included 170 pancreatic cancer cases, and we showed a significant association of moderate and high weight gain with pancreatic cancer risk, which remained after including smoking and smoking transition as potential confounders. Thus, our results suggest a possible role of weight development in the aetiology of pancreatic cancer, which must be confirmed by future studies, particularly among women. Diabetes has been reported to increase the risk of several cancers [24]; however, in our study it was a confounder only in analyses of kidney cancer. Undiagnosed diabetes could have played a role in the weight change and pancreatic cancer analyses, but we were unable to assess this factor.

Obesity, moderate and high weight gain were significantly associated with increased risk of postmenopausal breast cancer with positive linear trends across both BMI and weight change categories, which is in accordance with previous studies.[5, 6] The risk of postmenopausal breast cancer was higher in women experiencing moderate and high weight gain than among women with obesity, suggesting that weight gain may have an influence on postmenopausal breast cancer development beyond that of body composition.

In our study, overweight, but not obesity, was associated with a significant increased risk of colorectal/colon cancer. This result may have been influenced by reverse causality, namely that weight loss was an early, pre-clinical symptom of colorectal cancer. There is inconsistency across studies on the association between weight change and colorectal cancer in women, with different results for colon and rectal cancers, but an overall indication of no association.[6, 25] We found a significant association between weight loss and moderate weight gain and colorectal cancer, but there was no significant association between high weight gain and colorectal cancer. For rectal cancer we found a significant association for low and moderate weight gain but not high weight gain. Although we excluded all women with follow-up less than 2 years, we can still not entirely rule out reverse causality, as we cannot differentiate between intentional and unintentional weight loss. Supporting this suggestion are studies of cancer incidence in women with obesity who have undergone bariatric surgery, showing a decrease in overall and female-specific (breast and gynaecological) cancer risk compared to controls.[26] Thus, large population-based prospective cohort studies that can differentiate intentional and unintentional weight loss are warranted to improve our understanding of the effect of weight loss on cancer risk.

Of all site-specific analyses, the strongest association with obesity was found for endometrial cancer, with a significant linear association with increased body weight. Moderate and high weight gain also significantly increased the risk of endometrial cancer, with a positive linear trend across the weight change categories. However, the association for weight gain was not as strong as that for excess body weight. The evidence for a positive association between obesity, weight change, and endometrial cancer risk is consistent with other studies.[5, 27, 28] Many studies on weight gain and endometrial cancer risk reported an increased risk for substantially higher weight gain categories than those included in our study[29-31], whilst we report a significant increased risk starting at moderate weight gain (between 5 to 10 kg). We found only one previous study on weight change and kidney cancer in women, which showed no significant association with weight gain, consistent with our findings.[32] Moreover, obesity is a strong

predictor of kidney cancer,[9] which is in line with our results of a 95% significant increased risk of kidney cancer among women with obesity.

The main strength of our study is its large, representative, population-based sample of women in Norway with long follow-up time. The comprehensive questionnaires enabled us to control for important confounders such as anthropometric, sociodemographic, lifestyle, reproductive, and menopausal factors, and the linkage with the Norwegian Cancer Registry provided us with virtually complete cancer case ascertainment. Because of the sample size and the extensiveness of the Norwegian Cancer Registry, we had the possibility to assess overall obesity-related cancer, and both common and less common site-specific obesity-related cancers. There have been very few published articles on weight change and incidence of pancreatic and kidney cancer in women, and here we have added evidence to the current literature. Nevertheless, this study has several limitations. Height and weight were self-reported, and there is a well-established tendency to overestimate height as well as underestimate weight that increases with age and BMI.[33] A validation study of BMI has been conducted in the NOWAC study and showed substantial agreement between self-reports and objective measurements.[34] Furthermore, the covariate physical activity was also self-reported and displayed a moderate significant correlation with heart rate and movement in a previous validation study.[35] Total energy intake was omitted from the analyses because the food-frequency questionnaire was not provided to all participants in this study, leading to a large amount of missing data (61%), and because of known biases with respect to obesity.[36] Finally, as mentioned above, the lack of information on intentionality of weight loss to avoid reverse causality hampered the weight loss analysis.

In summary, maintaining stable weight in middle adulthood, as well as avoiding excess body weight, are both of importance for the prevention of several obesity-related cancers. We found the strongest associations between obesity and endometrial cancer risk, and high weight gain and pancreatic cancer risk. Our findings on weight gain and pancreatic cancer risk are particularly interesting given the

increasing incidence of pancreatic cancer in women in Norway, and the very poor prognosis of the disease.[13] If our findings are confirmed, avoidance of weight gain could be considered a potential preventive measure for pancreatic cancer.

Additional Information

Ethics approval and consent to participate

The NOWAC study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate (P REK NORD 141/2008), and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Availability of data and material

For the data supporting the presented results, please contact the person responsible for the NOWAC study - https://site.uit.no/nowac/contact-information/.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

MdS performed the statistical analysis and drafted the manuscript. MdS, EW, IL, and CR developed the research plan. EW, IL, LL, and CR critically revised the manuscript. All authors approved the final version of the manuscript.

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Supplementary Information

Supplementary information Table 1 presents population characteristics by weight change category in PDF file format.

Table 1. Population characteristics by weight change category between enrolment questionnaire (Q1) and the follow-up questionnaire (Q2). The Norwegian Women and Cancer study, 1991-2011 (n=80 930)

		Weight change category (kg)				
	N†	Weight loss (<-2kg)	Stable weight (-2 to <2kg)	Low weight gain (2 to <5kg)	Moderate weight gain (5 to <10kg)	High weight gain (≥10kg)
Number of women. n (%)	80 930	7 876 (9.7)	23 711 (29.3)	22 362 (27.6)	19 495 (24.1)	7 486 (9.3)
Obesity-related cancer. n	80 930	478	1 315	1 356	1 218	464
Characteristics*						
Age (y). mean (SD)	80 930	55.3 (9.3)	53.9 (9.0)	52.0 (8.1)	50.8 (7.5)	49.8 (7.0)
Body mass index (kg/m). mean (SD) (Q1)	80 904	26.2 (4.8)	23.5 (3.5)	23.0 (3.1)	23.6 (3.4)	24.5 (4.0)
Education (y). %	77 415					
<10		31.1	25.4	22.6	23.3	25.7
10-12		23.7	22.9	23.3	25.0	25.3
>12		45.1	51.7	54.1	51.7	49.0
Physical activity level. % (Q1)	74 097					
Low		32.8	23.8	22.9	26.8	31.7
Moderate		39.5	42.6	43.0	42.5	38.9
High		27.7	33.6	34.0	30.7	29.4
Smoking status. %	80 918					
Never smoker		33.5	39.1	39.9	37.6	31.9
Former smoker		31.4	32.4	34.9	36.9	42.3
Current smoker		35.1	28.5	25.3	25.6	25.9
Alcohol intake (g/day). median	79 349	1.4	1.6	1.9	1.8	1.5
Age at menarche (y). mean (SD) (Q1)	79 788	13.2 (1.4)	13.4 (1.4)	13.3 (1.4)	13.3 (1.4)	13.1 (1.4)
Age at first full-term pregnancy (y). mean (SD)	74 062	23.7 (4.5)	24.2 (4.4)	24.1 (4.3)	24.0 (4.4)	23.7 (4.5)
Parity. %	80 930					
Nulliparous		8.3	8.3	7.9	7.6	9.1
1-2 children		49.0	51.3	53.2	54.6	53.0
≥ 3 children		42.8	40.4	38.9	37.8	37.8
Oral contraceptive use. %	80 004					
Never		48.7	45.7	42.4	39.4	38.1
Ever		51.3	54.3	57.6	60.6	61.9
Menopausal status. %	80 930					
Premenopausal		44.2	53.1	62.5	67.8	70.3
Perimenopausal		5.0	4.3	4.0	4.0	3.9
Postmenopausal		43.5	36.0	26.5	21.4	18.3
Unknown		7.3	6.7	6.9	6.8	7.6

		Weight change category (kg)				
	N†	Weight loss (<-2kg)	Stable weight (-2 to <2kg)	Low weight gain (2 to <5kg)	Moderate weight gain (5 to <10kg)	High weight gain (≥10kg)
Age at menopause (y). mean (SD)	45 881	48.7 (5)	49.0 (4.7)	48.9 (4.8)	48.6 (4.9)	47.9 (5.2)
Hormone therapy use. %	80 930					
Never		61.1	63.4	65.4	66.0	66.1
Former		18.2	14.1	12.3	12.0	13.2
Current		20.7	22.5	22.3	22.0	20.7
Characteristics transition Q1 → Q2						
Physical activity level. %	67 737					
Increase		29.6	24.3	21.9	20.6	16.6
Decrease		20.1	22.9	26.0	28.7	35.6
No change		50.3	52.9	52.0	50.7	47.8
Smoking status. %	78 008					
Cessation		5.4	5.7	7.8	11.8	19.3
Restart		7.0	4.6	4.2	4.1	4.1
No change		87.6	89.7	88.0	84.1	76.6
Menopausal status. %	80 930					
No transition to menopause		51.7	43.2	34.1	29.0	26.8
Transition to menopause		48.3	56.8	65.9	71.0	73.2

*Overall differences between weight change categories were significant for all variables ($p<0.001$)

†N is the total amount of responses for the specific variable

Abbreviations: y: years, SD: standard deviation