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

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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 Cox proportional hazard models to calculate hazard ratios and restricted cubic splines to model potential non-linear dose–response relationships.

RESULTS: Excess body weight increased the risk of overall obesity-related cancer, postmenopausal breast, colorectal, colon, endometrial and kidney cancer, with endometrial cancer showing a threefold elevated risk. High weight gain (≥10 kg) increased the risk of overall obesity-related cancer, postmenopausal breast, endometrial and pancreatic cancer. The association between high weight gain and pancreatic cancer was strong, with 91% increased risk.

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

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%-point increase from the previous HUNT report covering the period 1984–1986. 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. Since 1998, the self-reported prevalence of obesity has increased in both women and men and reached 11% in women in 2015. Surely, there are differences in obesity prevalence according to age, 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) and the overall cancer incidence rate has increased.

In this study, we aimed to quantify separate risk estimates for body mass index (BMI) and short-term weight change in a nationally representative female cohort, for a large number of obesity-related cancers, including pancreatic and kidney cancer.
MATERIALS AND METHODS
Study design, participants and subsamples
The Norwegian Women and Cancer (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 response rate in the NOWAC study varied and were invited to complete a follow-up questionnaire (Q2) 5
agreed to participate completed an enrolment questionnaire (Q1)

Follow-up.9 The external validity in NOWAC is considered high as Norway allowed for linkages to national registers for complete unique personal identity number assigned to every resident of years after Q1. The response rate in the NOWAC study varied and were invited to complete a follow-up questionnaire (Q2) 5
agreed to participate completed an enrolment questionnaire (Q1)
differences.10 Details on the design, materials and procedures of the performed validation study showed that the distribution of
observed cumulative incidence of cancer vs expected national exposures was independent of the response rate and the
the performed validation study showed that the distribution of exposures was independent of the response rate and the observed cumulative incidence of cancer vs expected national figures from the Cancer Registry of Norway showed no substantial differences.10 Details on the design, materials and procedures of the NOWAC study have been described elsewhere.11

In the present study, 145,658 women who returned Q1 between 1991 and 2005 were considered eligible for inclusion (Fig. 1). 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 = 51 112), and women with missing weight in both Q1 and Q2 (n = 1678). 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 subsamples of the

Final analytical study sample. In the BMI analysis, we excluded women with < 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 = 1473). 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 with 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 = 2030), had < 2 years of follow-up after Q2 (n = 1174), or had missing information on weight in Q1 or Q2 were also excluded (n = 2967).

In site-specific analyses, we excluded premenopausal women from the postmenopausal breast cancer analysis (BMI analysis, n = 76,377; weight change analysis n = 34,222), women who reported hysterectomy from the endometrial cancer analysis (BMI analysis, n = 7394; weight change analysis, n = 5035) and women who reported bilateral oophorectomy from the ovarian cancer analysis (BMI analysis n = 2341, weight change analysis n = 1907).

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

Fig. 1 Flowchart of study participants
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 cutoff has been used previously to classify women as postmenopausal in the NOWAC study and represents ~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, owing to the small number of incident cases for each of these sites.

Assessment of BMI, weight change and covariates
BMI was calculated as self-reported weight in kg divided by the square of self-reported height in metres and categorised according to the World Health Organisation definition: underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5 ≤ 25 kg/m²), overweight (BMI 25 ≤ 30 kg/m²), or obesity (BMI ≥ 30 kg/m²). We used self-reported weight from Q1 and Q2 to calculate weight change, which was categorised into five groups: weight loss (≤ 2 kg), stable weight (2 – < 2 kg), low weight gain (2 – < 5 kg), moderate weight gain (5 – < 10 kg) or high weight gain (≥ 10 kg).

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 status and weight change category were assessed using χ² tests for categorical variables and one-way analysis of variance or Kruskal–Wallis test for continuous variables. We used Cox proportional hazard regression models with age as the underlying time metric to estimate hazard ratios 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. 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 >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. Participants with missing information on included covariates were excluded from the analyses. Tests based on Schoenfeld residuals showed no evidence of violation of the proportional hazard assumptions.

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. We tested for plausible 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 status 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. In order to model potential non-linear dose–response relationships, we fitted restricted cubic spline transformations (four knots) of the exposure variables. We evaluated non-linearity by testing the null hypothesis of equal spline coefficients. The knots were placed at equally spaced percentiles as recommended by Harrell (2001). 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 (Fig. 1). In the BMI analysis, average follow-up time was 16.9 (standard deviation (SD) = 5.8) years, during which 9328 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 4831 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/m², respectively. The majority of women were of normal weight (64.6%), followed by overweight (25.5%), obesity (7.7%) and underweight (2.2%) (Table 1). Compared with 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 and more likely to report former use of HT.

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/m², 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 (Supplementary Information, Table S1). Population characteristics differed across these weight change...
Women with high weight gain were younger and reported lower physical activity at Q1 compared with 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.

**BMI and obesity-related cancer risk**

Compared with normal-weight women, women with overweight or obesity had an 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) (Table 2). In site-specific analyses, endometrial cancer displayed a significant association with obesity, with an almost threefold increased risk (HR = 2.78, 95% CI: 2.30–3.35), as well as a significant association with 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). In addition, excess body weight was significantly associated with colorectal (overweight HR = 1.12, 95% CI: 1.01–1.25), colon (overweight HR = 1.21, 95% CI:

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**Table 1.** Population characteristics by body mass index (BMI) category at enrolment

| BMI category (kg/m²) | Underweight | Normal weight | Overweight | Obesity |
|---------------------|-------------|---------------|------------|---------|
| Number of women, n (%) | 135,708     | 9328          | 34,656 (25.5) | 10,435 (7.7) |
| Obesity-related cancer, n | 9328        | 173           | 2603       | 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     | 24.0 | 21.7 | 29.8 | 34.3 |
| Physical activity level % | 123,531     | 22.1 | 23.5 | 24.6 | 24.4 |
| Smoking status % | 135,231     | 53.9 | 54.9 | 45.6 | 41.3 |

| 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     | 13.0 | 9.5 | 8.1 | 11.1 |
| Oral contraceptive use % | 131,415     | 56.8 | 55.7 | 50.1 | 46.3 |
| Menopausal status % | 135,708     | 61.8 | 59.4 | 50.2 | 45.6 |
| 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 |
| Hormone therapy use % | 126,669     | 46.7 (5.9) | 48.3 (4.8) | 48.8 (4.7) | 48.5 (5.2) |

| Never | 38.2 | 40.6 | 49.8 | 54.4 |
| Ever | 61.8 | 59.4 | 50.2 | 45.6 |

| Age at menopause (y), mean (SD) | 45,160     | 46.7 (5.9) | 48.3 (4.8) | 48.8 (4.7) | 48.5 (5.2) |
| Menopause status % | 135,708     | 85.7 | 79.6 | 72.7 | 73.7 |
| Never | 5.6 | 8.2 | 12.9 | 14.4 |
| Current | 8.7 | 12.2 | 14.4 | 11.9 |

The Norwegian Women and Cancer study 1991–2005 (n = 135,708)

N is the total amount of responses for the specific variable

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

y years, SD standard deviation
Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by body mass index (BMI) category at enrolment

|                  | Model 1 age-adjusted |                  | Model 2 multivariable |                  |
|------------------|----------------------|------------------|-----------------------|------------------|
|                  | N Cancer cases | HR 95% CI     | N Cancer cases | HR 95% CI     |
| Overall obesity-related cancer<sup>a</sup> |                      |                  |                      |                  |
| Underweight      | 3022 | 173 | 0.95 | 0.82–1.10 | 2626 | 149 | 0.92 | 0.78–1.08 |
| Normal weight    | 87,595 | 5689 | 1.00 | Reference | 77,064 | 4961 | 1.00 | Reference |
| Overweight       | 34,656 | 2603 | 1.10 | 1.05–1.15 | 29,517 | 2154 | 1.09 | 1.03–1.14 |
| Obesity          | 10,435 | 863 | 1.26 | 1.17–1.35 | 8706 | 699 | 1.24 | 1.14–1.34 |
| 5 BMI unit increment | 135,708 | 9328 | 1.11 | 1.08–1.14 | 117,913 | 7963 | 1.10 | 1.07–1.13 |
| Postmenopausal breast cancer<sup>b</sup> |                      |                  |                      |                  |
| Underweight      | 899 | 27 | 0.96 | 0.66–1.41 | 650 | 19 | 0.98 | 0.62–1.55 |
| Normal weight    | 32,831 | 1047 | 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          | 633 | 206 | 1.07 | 0.92–1.24 | 4540 | 139 | 1.20 | 1.00–1.44 |
| 5 BMI unit increment | 59,331 | 1918 | 1.03 | 0.97–1.08 | 43,493 | 1336 | 1.07 | 1.00–1.15 |
| Colorectal cancer<sup>c</sup> |                      |                  |                      |                  |
| Underweight      | 3022 | 39 | 1.11 | 0.80–1.52 | 2902 | 38 | 1.10 | 0.80–1.52 |
| Normal weight    | 87,595 | 1146 | 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          | 633 | 157 | 1.05 | 0.88–1.24 | 9744 | 140 | 1.01 | 0.84–1.20 |
| 5 BMI unit increment | 135,708 | 1290 | 1.05 | 0.99–1.11 | 128,568 | 1805 | 1.04 | 0.98–1.11 |
| Colon cancer<sup>d</sup> |                      |                  |                      |                  |
| Underweight      | 3022 | 26 | 1.14 | 0.77–1.69 | 3017 | 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 |
| 5 BMI unit increment | 135,708 | 1290 | 1.06 | 0.99–1.11 | 135,231 | 1283 | 1.07 | 0.99–1.14 |
| Rectal cancer<sup>e</sup> |                      |                  |                      |                  |
| Underweight      | 3022 | 13 | 1.05 | 0.60–1.82 | 2805 | 11 | 0.99 | 0.54–1.81 |
| Normal weight    | 87,595 | 400 | 1.00 | Reference | 87,355 | 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 | 9189 | 44 | 1.03 | 0.75–1.42 |
| 5 BMI unit increment | 135,708 | 637 | 1.03 | 0.93–1.14 | 122,607 | 562 | 1.04 | 0.93–1.16 |
| Endometrial cancer<sup>f</sup> |                      |                  |                      |                  |
| Underweight      | 2914 | 11 | 0.62 | 0.34–1.13 | 2594 | 10 | 0.63 | 0.34–1.18 |
| 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 | 1.45 | 1.24–1.68 |
| Obesity          | 9617 | 186 | 3.02 | 2.55–3.58 | 8326 | 156 | 2.78 | 2.30–3.35 |
| 5 BMI unit increment | 128,314 | 1057 | 1.53 | 1.45–1.62 | 113,150 | 932 | 1.51 | 1.42–1.60 |
| Ovarian cancer<sup>g</sup> |                      |                  |                      |                  |
| Underweight      | 2991 | 11 | 0.75 | 0.41–1.36 | 2851 | 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 | 9425 | 49 | 1.09 | 0.81–1.48 |
| 5 BMI unit increment | 133,367 | 642 | 1.01 | 0.91–1.12 | 125,148 | 605 | 1.00 | 0.90–1.12 |
| Pancreatic cancer<sup>h</sup> |                      |                  |                      |                  |
| Underweight      | 3059 | 5 | 0.75 | 0.31–1.38 | 2902 | 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 | 9744 | 29 | 1.19 | 0.79–1.79 |
| 5 BMI unit increment | 135,708 | 350 | 1.02 | 0.89–1.17 | 128,568 | 324 | 1.11 | 0.96–1.27 |
| Kidney cancer<sup>i</sup> |                      |                  |                      |                  |
| Underweight      | 3059 | 2 | 0.40 | 0.10–1.60 | 2295 | 2 | 0.50 | 0.12–2.04 |
| Normal weight    | 88,480 | 158 | 1.00 | Reference | 68,745 | 120 | 1.00 | Reference |
1.07–1.37) and kidney cancer (obesity HR = 1.95, 95% CI: 1.26–3.02). An increment of five BMI units was significantly associated with increased risk of overall obesity-related cancer, postmenopausal breast cancer, endometrial and kidney cancer. There was no significant association between excess body weight and increased risk of rectal, ovarian and pancreatic cancer.

Further, a clear dose–response relationship with increasing BMI was found for overall obesity-related cancer, endometrial and kidney cancer (Fig. 2). These dose–response relationships were statistically significant at different BMI; kidney cancer was statistically significant only after BMI 30, whereas overall obesity-related cancer and endometrial cancer were statistically significant at BMI 24 (Supplementary Information, Table S3–5). We found no statistically significant interactions between HT use and BMI; however, menopausal status modified the effect of BMI in relation to endometrial cancer risk with a statistically significant interaction between perimenopausal status and obesity. We performed stratified analysis by menopausal status (Supplementary Information, Table S2) but the subgroup analysis result should be interpreted with caution due to the low number of cases (58) in the perimenopausal status group.

Table 2 continued

| N | Cancer cases | HR 95% CI | N | Cancer cases | HR 95% CI |
|---|-------------|-----------|---|-------------|-----------|
| 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 | 7502 | 27 | 1.95 | 1.26–3.02 |
| $5$ BMI unit increment | 135,708 | 292 | 1.34 | 1.18–1.51 | 104,666 | 211 | 1.33 | 1.15–1.54 |

*Model 2 for overall obesity-related cancer was adjusted for age, education, physical activity and smoking status
*Only in women who were postmenopausal at enrolment, model 2 for postmenopausal breast cancer was adjusted for age, education, alcohol intake, parity/age at first full-term pregnancy, oral contraceptive use, hormone therapy use and history of breast cancer in the mother
*Model 2 for colorectal and pancreatic cancer was adjusted for age, education and smoking status
*Model 2 for colon cancer was adjusted for age and smoking status
*Model 2 for rectal cancer was adjusted for age, education and alcohol intake
*Model 2 for endometrial cancer was adjusted for age, education, 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, parity/age at first full-term pregnancy and oral contraceptive use
*Model 2 for kidney cancer was adjusted for age, smoking status and diabetes

The Norwegian Women and Cancer study, 1991–2014 (n = 135,708)

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**DISCUSSION**

In this study, we assessed the relationship between BMI, weight change and obesity-related cancer risk in a large and nationally representative cohort of women in Norway. We found that overweight and obesity increased overall obesity-related cancer risk by 9 and 24%. Furthermore, weight gain < 10 kg over 6 years, increased obesity-related cancer risk by 14%, whereas gaining 10 kg or more increased the risk by 16%, independent of BMI status at baseline. These findings highlight the health risks of excess body weight and increase in body weight among middle-aged women in Norway. Thus, maintaining stable weight is of utmost importance for the prevention of overall obesity-related cancer, especially as the increase in risk started at low levels of weight gain and most women gained weight. 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, 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 and 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.

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,\textsuperscript{20} in which weight gain, rather than BMI, may play a more essential role. Our findings on weight gain and pancreatic cancer is novel. To the best of 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.\textsuperscript{21} Another study including both women and men, demonstrated a non-significant, positive association.\textsuperscript{22} 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.\textsuperscript{4} 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. Kidney cancer is also an obesity-related cancer less-commonly diagnosed and we found only one previous study on weight change and kidney cancer in women.\textsuperscript{23} This aforementioned study showed no association with weight gain, consistent with our findings. On the contrary, obesity is reported as a strong predictor of kidney cancer,\textsuperscript{6} which is in line with our results of a 95% increased risk of kidney cancer among women with obesity.

Obesity, moderate and high weight gain were significantly associated with increased risk of postmenopausal breast cancer, which is in accordance with previous studies.\textsuperscript{1,24} 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 an 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.\textsuperscript{4,25} We found a positive 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 < 2 years, we can still not entirely rule out reverse causality, as we cannot differentiate between intentional and unintentional weight loss. In fact, studies of cancer incidence in women who have undergone bariatric surgery, show a decrease in overall and female-specific (breast and gynaecological) cancer risk compared with controls, suggesting that intentional weight loss may decrease cancer risk.\textsuperscript{26} However, large observational prospective cohort studies that can
| Model 1 age-adjusted | Model 2 Multivariable |
|----------------------|-----------------------|
| **Overall obesity-related cancer**<sup>a</sup> | **Overall obesity-related cancer**<sup>a</sup> |
| Weight loss (<−2kg) | 7876 478 1.15 1.04−1.28 | 6886 406 1.09 0.97−1.22 |
| Stable weight (−2−< 2 kg) | 23,711 1315 1.00 Reference | 20,950 1 142 1.00 Reference |
| Low weight gain (2−< 5 kg) | 22,362 1356 1.10 1.02−1.19 | 19,844 1 209 1.14 1.05−1.23 |
| Moderate weight gain (5−< 10 kg) | 19,495 1218 1.14 1.06−1.24 | 17,202 1 069 1.14 1.05−1.25 |
| High weight gain (≥ 10 kg) | 7486 464 1.19 1.06−1.32 | 6558 406 1.16 1.04−1.31 |
| 5 kg increment | 80,930 4831 1.02 1.00−1.05 | 71,440 4 232 1.03 1.00−1.07 |

**Postmenopausal breast cancer**<sup>b</sup>

| Weight loss (<−2kg) | 5456 128 1.00 0.82−1.22 | 4040 97 1.16 0.92−1.47 |
| Stable weight (−2−< 2 kg) | 14,997 388 1.00 Reference | 11,605 277 1.00 Reference |
| Low weight gain (2−< 5 kg) | 12,462 383 1.11 0.97−1.28 | 9858 293 1.16 0.98−1.36 |
| Moderate weight gain (5−< 10 kg) | 10,103 312 1.08 0.93−1.25 | 8025 254 1.20 1.01−1.43 |
| High weight gain (≥ 10 kg) | 3690 121 1.15 0.93−1.41 | 2924 102 1.36 1.08−1.71 |
| 5 kg increment | 46,708 1 332 1.04 0.98−1.09 | 36,452 1023 1.08 1.02−1.14 |

**Colorectal cancer**<sup>c</sup>

| Weight loss (<−2kg) | 7876 120 1.28 1.03−1.58 | 7874 120 1.25 1.01−1.55 |
| Stable weight (−2−< 2 kg) | 23,711 286 1.00 Reference | 23,705 286 1.00 Reference |
| Low weight gain (2−< 5 kg) | 22,362 273 1.11 0.94−1.31 | 22,361 273 1.11 0.94−1.32 |
| Moderate weight gain (5−< 10 kg) | 19,495 253 1.24 1.05−1.48 | 19,492 252 1.24 1.05−1.48 |
| High weight gain (≥ 10 kg) | 7486 75 1.04 0.8−1.34 | 7486 75 1.02 0.79−1.33 |
| 5 kg increment | 80,930 1007 0.99 0.94−1.06 | 80,918 1006 1.00 0.94−1.06 |

**Colon cancer**<sup>d</sup>

| Weight loss (<−2kg) | 7876 91 1.30 1.01−1.66 | 7872 91 1.26 0.98−1.61 |
| Stable weight (−2−< 2 kg) | 23,711 212 1.00 Reference | 23,695 210 1.00 Reference |
| Low weight gain (2−< 5 kg) | 22,362 181 1.01 0.83−1.24 | 22,355 181 1.03 0.84−1.26 |
| Moderate weight gain (5−< 10 kg) | 19,495 174 1.19 0.97−1.47 | 19,487 173 1.19 0.97−1.46 |
| High weight gain (≥ 10 kg) | 7486 52 1.01 0.74−1.38 | 7483 52 0.98 0.72−1.34 |
| 5 kg increment | 80,930 710 0.98 0.91−1.05 | 80,892 707 0.98 0.91−1.05 |

**Rectal cancer**<sup>e</sup>

| Weight loss (<−2kg) | 7876 29 1.22 0.8−1.88 | 7876 29 1.22 0.80−1.88 |
| Stable weight (−2 to < 2 kg) | 23,711 74 1.00 Reference | 23,711 74 1.00 Reference |
| Low weight gain (2 to < 5 kg) | 22,362 92 1.37 1.00−1.86 | 22,362 92 1.37 1.00−1.86 |
| Moderate weight gain (5 to < 10 kg) | 19,495 79 1.38 1.00−1.91 | 19,495 79 1.38 1.00−1.91 |
| High weight gain (≥ 10 kg) | 7486 23 1.11 0.69−1.78 | 7486 23 1.11 0.69−1.78 |
| 5 kg increment | 80,930 297 1.03 0.92−1.15 | 80,930 297 1.03 0.92−1.15 |

**Endometrial cancer**<sup>f</sup>

| Weight loss (<−2kg) | 7281 59 1.24 0.92−1.68 | 6813 55 1.03 0.75−1.41 |
| Stable weight (−2−< 2 kg) | 22,238 153 1.00 Reference | 20,899 139 1.00 Reference |
| Low weight gain (2−< 5 kg) | 20,998 136 0.94 0.75−1.19 | 19,798 127 0.99 0.78−1.26 |
| Moderate weight gain (5−< 10 kg) | 18,389 154 1.23 0.98−1.54 | 17,413 150 1.27 1.01−1.61 |
| High weight gain (≥ 10 kg) | 6989 69 1.51 1.13−2.01 | 6674 68 1.40 1.04−1.88 |
| 5 kg increment | 75,895 571 1.10 1.02−1.19 | 71,597 539 1.12 1.04−1.20 |

**Ovarian cancer**<sup>g</sup>

| Weight loss (<−2kg) | 7614 37 1.62 1.09−2.41 | 6650 30 1.52 0.99−2.34 |
| Stable weight (−2−< 2 kg) | 23,041 74 1.00 Reference | 20,409 66 1.00 Reference |
| Low weight gain (2−< 5 kg) | 21,890 90 1.25 0.92−1.71 | 19,497 84 1.29 0.93−1.79 |
| Moderate weight gain (5−< 10 kg) | 19,133 84 1.32 0.96−1.81 | 16,955 75 1.30 0.93−1.82 |
| High weight gain (≥ 10 kg) | 7345 25 1.05 0.66−1.66 | 6511 23 1.08 0.67−1.74 |
| 5 kg increment | 79,023 310 0.96 0.86−1.06 | 70,022 278 0.98 0.87−1.10 |

**Pancreatic cancer**<sup>h</sup>

| Weight loss (<−2kg) | 7876 25 1.84 1.12−3.02 | 7176 21 1.58 0.93−2.69 |
Endometrial cancer was strongly associated with obesity with a threefold elevated risk compared with women in normal weight. Moderate and high weight gain also increased the risk of endometrial cancer but 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.24,27–28 However, many studies on weight gain and endometrial cancer risk reported an increased risk only for substantially higher weight gain categories than those included in our study,29 whereas we report an increased risk starting at moderate weight gain.

The main strength of our study is its large, nationally 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. Thanks to the sample size and the extensiveness of the Norwegian Cancer Registry, we had the possibility to assess the majority of all endometrial cancers but 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.24,27–28

Table 3 continued

| Model 1 age-adjusted | Model 2 Multivariable |
|----------------------|-----------------------|
|                      | N  | Cancer cases | HR  | 95% CI       | N  | Cancer cases | HR  | 95% CI       |
| Stable weight (−2<2 kg) | 23,711 | 42 | 1.00 Reference | 21,697 | 39 | 1.00 Reference |
| Low weight gain (2<5 kg) | 22,362 | 50 | 1.37 0.91–2.07 | 20,641 | 43 | 1.28 0.83–1.98 |
| Moderate weight gain (5<10 kg) | 19,495 | 48 | 1.59 1.04–2.43 | 18,124 | 46 | 1.60 1.03–2.47 |
| High weight gain (≥10 kg) | 7486 | 21 | 1.95 1.14–3.32 | 6971 | 21 | 1.91 1.11–3.30 |
| 5 kg increment | 80,930 | 186 | 1.09 0.95–1.26 | 74,609 | 170 | 1.12 0.97–1.29 |

Differentiate intentional and unintentional weight loss are warranted to improve our understanding of the effect of weight loss on cancer risk.

The main strengths of our study is its large, nationally 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 case ascertainment. Thanks to 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.30 In our study, we assume that the potential misclassification due to this information bias was non-differential between cases and non-cases. Therefore, our risk estimates may have been underestimated. Furthermore, a validation study of BMI has been conducted in the female general population and showed substantial agreement between self-reports and objective measurements.31 In addition, the covariate physical activity was also self-reported and displayed a moderate significant correlation with heart rate and movement in a previous validation study.32 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.33 Finally, as mentioned above, the lack of information on intentionality of weight loss to avoid reverse causality hampered the weight loss analysis.

The mean BMI in our study sample was 24.1. Thus, our study sample is slimmer than in many other high-income countries.34 The generalisability of our study is restricted to women in Norway but it is unlikely that the association between excess body weight/weight gain and obesity-related cancer substantially differs across regions. However, the impact of our findings, i.e., the number of cancer cases attributable to excess body weight and weight gain (given a causal relationship) may potentially be larger in regions with higher prevalence of excess body weight or higher weight gain. In summary, maintaining stable weight in middle adulthood, regardless BMI status, and avoiding excess body weight are important for the prevention of several obesity-related cancers. We found strong 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.35 If our findings are confirmed, avoidance of weight gain could be considered a potential preventive measure for pancreatic cancer.
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AUTHOR CONTRIBUTIONS
Md.S. performed the statistical analysis and drafted the manuscript. Md.S., E.W., I.L. and C.R. developed the research plan. E.W., I.L., L.L. and C.R. critically revised the manuscript. All authors approved the final version of the manuscript.

ADDITIONAL INFORMATION
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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/.

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REFERENCES
1. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 390, 2627–2642 (2017).
2. Lauby-Secretan, B. et al. Body fatness and cancer—viewpoint of the IARC Working Group. N. Engl. J. Med 375, 794–798 (2016).
3. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 3, 524–548 (2017).
4. Keum N., et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J. Natl. Cancer Inst. 107, pii: djv088 (2015).
5. World Cancer Research Fund/American Institute for Cancer Research. Body Fatness and Weight Gain and the Risk of Cancer (World Cancer Research Fund International, London, 2018).
6. Midhjell, K. et al. Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study, Norway. Clin. Obes. 3, 12–20 (2013).
7. Health, care and social relations, survey on living conditions. Statistics Norway: 2016. https://www.ssb.no/en/helse/statistikk/helselivforhold. Accessed 20 March 2018.
8. Cancer Registry of Norway. Cancer in Norway 2015—Cancer Incidence, Mortality, Survival and Prevalence in Norway. (Cancer Registry of Norway, Oslo, 2016).

Fig. 3 Non-linear effects of 6 years weight change and risk of specific and overall obesity-related cancers, with 95% CI. Restricted cubic splines were fitted with knots at −5, 1, 4 and 11 kg. \( p \) values are for non-linearity.
