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Weight change in middle adulthood and risk of cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; NW, normal weight; OB, obese; OW, overweight; SCC, squamous cell carcinoma.

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Abstract

Obesity is a risk factor for several major cancers. Associations of weight change in middle adulthood with cancer risk, however, are less clear. We examined the association of change in weight and body mass index (BMI) category during middle adulthood with 42 cancers, using multivariable Cox proportional hazards models in the European Prospective Investigation into Cancer and Nutrition cohort. Of 241 323 participants (31% men), 20% lost and 32% gained weight (>0.4 to 5.0 kg/year) during 6.9 years (average). During 8.0 years of follow-up after the second weight assessment, 20 960 incident cancers were ascertained. Independent of baseline BMI, weight gain (per one kg/year increment) was positively associated with cancer of the corpus uteri (hazard ratio [HR] = 1.14; 95% confidence interval: 1.05-1.23). Compared to stable weight (±0.4 kg/year), weight gain (>0.4 to 5.0 kg/year) was positively associated with cancers of the gallbladder and bile ducts (HR = 1.41; 1.01-1.96), postmenopausal breast (HR = 1.08; 1.00-1.16) and thyroid (HR = 1.40; 1.04-1.90). Compared to maintaining normal weight, maintaining overweight or obese BMI (World Health Organisation categories) was positively associated with most obesity-related cancers. Compared to maintaining the baseline BMI category, weight gain to a higher BMI category was positively associated with cancers of the postmenopausal breast (HR = 1.19; 1.06-1.33), ovary (HR = 1.40; 1.04-1.91), corpus uteri (HR = 1.42; 1.06-1.91), kidney (HR = 1.80; 1.20-2.68) and pancreas in men (HR = 1.81; 1.11-2.95). Losing weight to a lower BMI category, however, was inversely associated with cancers of the corpus uteri (HR = 0.40; 0.23-0.69) and colon (HR = 0.69; 0.52-0.92). Our findings support avoiding weight gain and encouraging weight loss in middle adulthood.

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KEYWORDS
BMI change, cancer, middle adulthood, weight gain, weight loss

1 | INTRODUCTION

Obesity is an acknowledged risk factor for the development of major cancers of the digestive system (oesophagus [adenocarcinoma], gastric cardia, colon and rectum, liver, gallbladder, pancreas), the female reproductive system (postmenopausal breast, corpus uteri, ovary), the thyroid, renal-cell carcinoma, meningioma and multiple myeloma.[1-3] Body mass index (BMI) at a single time point, usually at study recruitment, is the most commonly used measure of obesity.[1] Given that in a cancer-free middle-aged population, neither excess muscularity nor sarcopenia would be particularly prominent, BMI attained at cohort entry would primarily reflect the state of the adipose depots at this time point. Nevertheless, this could not distinguish between a lifelong fat excess and a more recent fat accumulation. Weight change over time, on the other hand, may reflect age-related metabolic changes and may also be more relevant from a public health perspective, as it may clarify whether lifestyle modifications in a particular period of life could influence the risk of cancer.

From a developmental point of view, middle adulthood represents a transitional period between early and later life, during which weight reaches peak levels and changes relatively slowly.[4] While genetic factors determining energy balance would likely present earlier in life, during adolescence or early adulthood, lifestyle and hormonal factors, especially peri-menopausal hormonal changes in women, would likely determine weight change during middle adulthood. Middle adulthood also precedes the loss of lean mass, a major contributor to weight loss in later life.[5] This raises the question whether weight loss during middle adulthood can mitigate the influence of fat accumulated during early adulthood and whether fat accumulated during middle adulthood can further increase the risk of cancer.

Studies examining the association of short-term weight change in middle adulthood with cancer risk, however, are limited and inconclusive. Published reports have addressed mainly colorectal cancer, postmenopausal breast cancer, or endometrial cancer, with only a limited number examining cancers at other locations or a wider range of cancers in a single study and several focusing only on men or women. A common constraint has been the limited number of cases, especially for less frequent cancer types, precluding some studies from reporting on individual cancer sites (see Supplementary Table S1 and Table S2 for summary of references).

Our aim in the current study was to examine in a large cohort, the European Prospective Investigation into Cancer and Nutrition (EPIC), the association of prospectively evaluated short-term changes in weight and BMI category during middle adulthood with the risk of cancer development in the most common tumour sites and the major morphological subtypes.

What's new

Obesity is well known as a risk factor for multiple cancers. What about gaining or losing weight mid-life? Here, the authors investigated the association between cancer and change in weight and BMI category during mid-life. Among 241,323 people, about a third gained weight and 20% lost weight during the study. Independent of starting weight, gaining weight was associated with several obesity-related cancers including cancers of the gallbladder, uterus, ovary, kidney, thyroid, breast after the menopause and in men pancreas. Losing weight was inversely associated with obesity-related cancers overall, and specifically colon and uterine cancer. The authors conclude that public health interventions to support weight loss in middle age could help reduce cancer incidence.

2 | MATERIALS AND METHODS

2.1 | Study population

EPIC is a well-established, prospective, multicentre cohort examining the association of nutrition and lifestyle with cancer and other chronic diseases.[6] Participants, mostly aged 40-70 years, from 10 European countries were recruited between 1991 and 1999. In our study, we excluded 280 001 participants due to missing information on weight or confounders, extreme anthropometry or a prevalent cancer at the second weight assessment (details shown in Figure 1), in accordance with previous reports.[7,8] We additionally restricted the analysis to participants in the age range 40 to 70 years between baseline and the second weight assessment, in order to focus on weight changes during middle adulthood as opposed to changes in early adulthood or in the elderly.

2.2 | Anthropometric assessments

Anthropometric characteristics were assessed twice: at baseline and after a mean follow-up for weight change of 6.9 years. Weight was mainly measured and adjusted for clothing at baseline and was self-reported at the second assessment (see details in Supplementary Methods).[7,8] Average annual weight change, that is, weight change rate (kg/year), was calculated by subtracting weight at baseline from weight at the second assessment and dividing by the years between

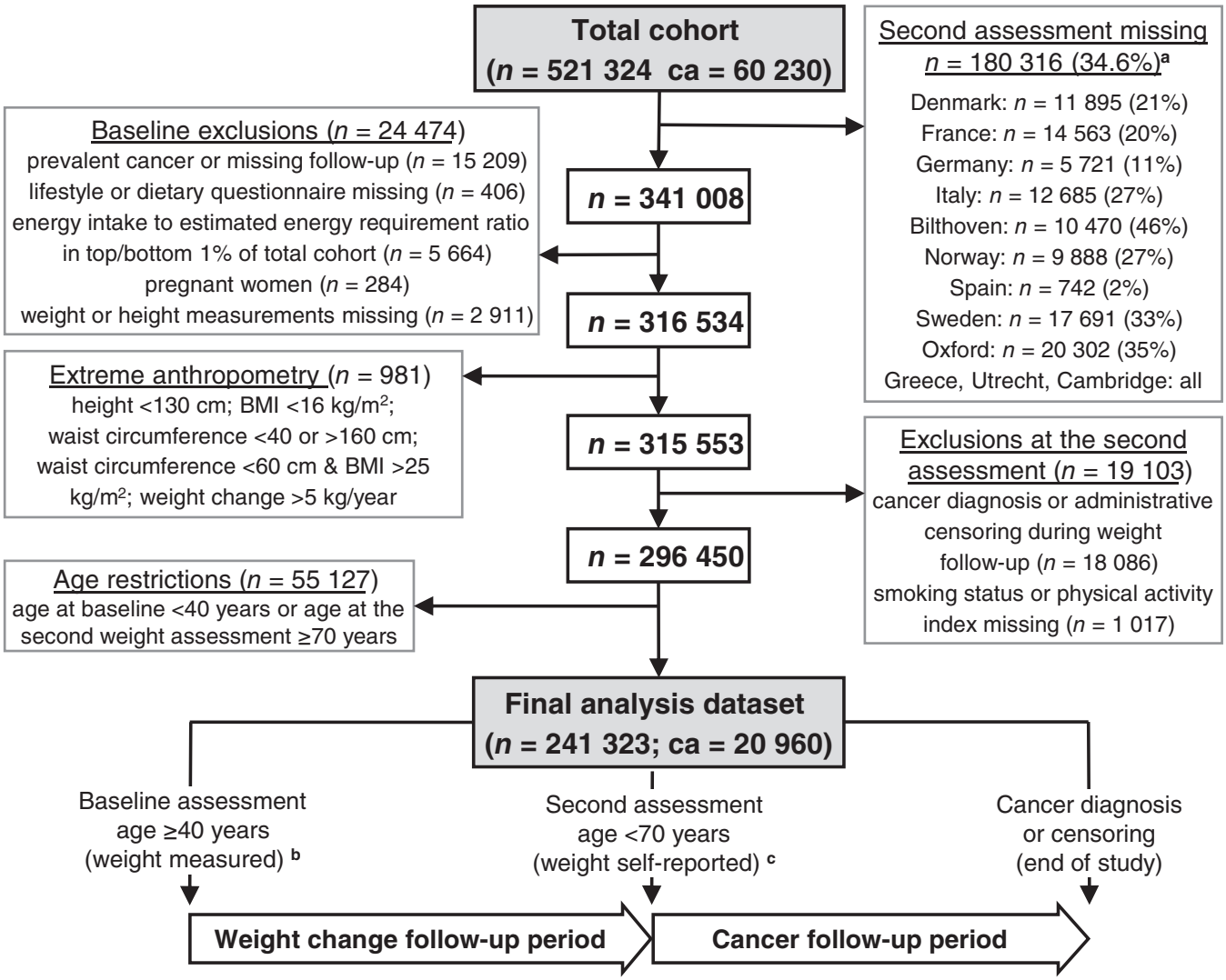

FIGURE 1 Flow diagram of participants included in the current study. Superscript "a" indicates the percentage from the number of participants per country or centre in the total cohort; "b" indicates that the weight at baseline was measured in 68.8% of participants, except in France and Norway, where weight and height were self-reported, and in Oxford (United Kingdom), where correcting equations were used for self-reported weight (see details in Supplementary Methods); "c" indicates that the weight at the second assessment was self-reported in most centres, except Umea (Sweden) and part of the cohort from Bilthoven (Netherlands), where weight was measured (4.6%) and Oxford, where correcting equations were used for self-reported weight (7.8%); "n" is the number of participants; "ca" is the number of cancer cases; the exclusion criteria were applied sequentially, that is, each excluded participant was counted only once, in a single exclusion step

the two assessments, to account for the difference in the time interval between the centres. BMI was calculated as weight/height^2 (kg/m^2).

2.3 | Cancer ascertainment

The outcome of interest was first primary cancer diagnosed after the second weight assessment. We defined cancer types, subtypes and morphologies according to the International Classification of Diseases for Oncology, as specified in Supplementary Table S3 and Reference 9. Participants diagnosed with a second (or third) cancer, as well as those with cancers with unconfirmed or behavioural codes other than 3 (malignant, primary site) were censored at the date of diagnosis of the first cancer. We defined breast cancer as premenopausal when the diagnosis was before 55 years of age in women premenopausal at the second weight assessment. We defined postmenopausal breast cancer as those diagnosed at age 55 years or later, irrespective of menopausal status at the second weight assessment, censoring women with breast cancer diagnosed before age 55 years. The group of obesity-related cancers included oesophageal adenocarcinoma, colorectal cancer (overall), cancers of the stomach (overall), liver (overall), pancreas, kidney, breast (postmenopausal), ovary, corpus uteri (overall), thyroid and multiple myeloma.

2.4 | Assessment of lifestyle and personal history

Participants completed detailed questionnaires on lifestyle, diet and, in women, menstrual and reproductive history and use of exogenous hormones at both weight assessments. Variables were harmonised to enable compatibility between EPIC centres.[6] Supplementary Figure S1 shows the dichotomisation rules for menopausal status. We used more recent updates for incident cancer cases and lifestyle factors compared to the earlier EPIC reports on short-term weight change and risk of colorectal and breast cancer.[7,8]

2.5 | Statistical analysis

We examined weight change as a continuous variable (interpreted as the risk associated with weight gain per one kg/year increment) and as a categorical variable, with categories defined as weight loss (−5.0 to <−0.4 kg/year), stable weight (−0.4 to 0.4 kg/year, reference) or weight gain (>0.4 to 5.0 kg/year), using similar cut-offs to previous reports.[7,8,10] A benefit of using fixed-value cut-offs is that they are independent of the anthropometric characteristics of the study population. Examining associations with weight loss and weight gain categories could highlight potential departures from linearity and enables a more intuitive interpretation. Examining weight change as a continuous variable, however, would provide more power to detect opposite effects of weight loss and weight gain when there is a continuum in the effect of weight change, which may suggest that the amount of adipose tissue and the related metabolic characteristics are mechanistically related to cancer.

We further examined change in BMI category, defined according to the World Health Organisation as normal weight (NW, 18.5 to <25 kg/m^2), overweight (OW, 25 to <30 kg/m^2) or obese (OB, ≥30 kg/m^2). We compared maintaining OW or OB BMI category at both assessments to maintaining NW BMI category as reference. We further compared changing the baseline BMI category to a higher or lower BMI category at the second weight assessment to maintaining the corresponding baseline BMI category as reference. We performed these comparisons by repeating the same model three times, using each of the maintaining BMI category groups as reference, and have shown only the comparisons of interest. Due to very small numbers, we excluded participants with BMI < 18.5 kg/m^2 (n = 4043) and those changing between NW and OB BMI categories (n = 559).

We estimated hazard ratios (HR) (95% confidence intervals [CIs]) using delayed-entry Cox proportional hazards models, that is, entry was conditional on surviving to the start of cancer follow-up. The underlying time scale for survival analysis was age in years. The origin of time was age zero, that is, participants were considered at risk from birth, even though they were not observed until entering the cohort. Entry time was age at the second weight assessment, which was the start of cancer follow-up. Exit time was age at diagnosis of the first incident cancer, or death, or last complete follow-up, whichever occurred first. Models with weight change as exposure were adjusted for baseline BMI (per 5 kg/m^2 increment), as this may influence associations with subsequent weight change. All models were adjusted for the time interval between the two weight assessments, to account for differences in total weight change.

We additionally stratified all models by study centre, sex (except for sex-specific cancers) and age at the second weight assessment in 5-year categories (one category below 50 years) and adjusted for major risk factors for cancer and weight change and potential confounders (see rational for selection in Supplementary Table S4): height, energy intake (log-transformed), fruit and vegetable consumption (log-transformed), attained education, smoking status and intensity, alcohol consumption, physical activity index and for women also the major determinants of oestrogen levels: menopausal status and indicators of ever use of exogenous oestrogens, that is, oral contraceptives and hormone replacement therapy (HRT) (categories are listed in Table 1). To enable comparability, we used the same set of adjustment variables for all cancer sites. Height, energy intake, fruit and vegetable consumption and education were assessed at baseline and the remaining covariates at the second weight assessment, complementing missing information with baseline assessments (Supplementary Table S5). To account for information missing at both time points, we performed multiple sequential imputations using chained equations (function *mi impute* in STATA-13) and created m = 5 imputed datasets (Supplementary Table S6). To account for variability within and between imputations, we derived the estimates of coefficients and standard errors using Rubin's combination rules (function *mi estimate* in Stata 13.0[11]). We considered as stronger evidence for association $P < .001$, which corresponds to Bonferroni correction for 50 comparisons (the approximate number of examined cancer types), and a weaker evidence for association a *P*-value between .05 and .001.

For cancers observed in both sexes, we explored further heterogeneity by sex because some cancers have sex-specific incidence and some published studies include only men or women. We examined separately subgroups of men and women, additionally adjusting for menopausal status and use of oral contraceptives and HRT in women.

In sensitivity analyses, we excluded the first 2 years of follow-up, to mitigate possible reverse causality. To examine the influence of adjustment, we derived unadjusted HR estimates retaining only the stratification by study centre, sex (except for sex-specific cancers) and age.

We used R version 3.6.1[12] for management of data and results, and STATA-13 for statistical analyses.[11]

3 | RESULTS

3.1 | Characteristics of study participants

Our study comprised 241 323 participants (31.3% men), with a mean age at baseline of 51.5 years. During a mean weight follow-up of 6.9 years, 20.0% experienced weight loss and 32.2% weight gain >0.4 to 5.0 kg/year (Table 1). Fewer participants experienced weight change to higher (13.0%) or lower (6.8%) BMI category at the second assessment (Supplementary Table S7). Participants with weight gain

TABLE 1 Cohort characteristics by weight change subgroup

	Total	Weight loss (−5.0 to <−0.4 kg/year)	Stable weight (−0.4 to 0.4 kg/year)	Weight gain (>0.4 to 5.0 kg/year)
Demographics: n (%), mean (SD)				
Cohort size	241 323	48 261 (20.0)	115 429 (47.8)	77 633 (32.2)
Cancer cases	20 960	5322 (25.4)	8999 (42.9)	6639 (31.7)
Men	75 435 (31.3)	18 828 (39.0)	33 012 (28.6)	23 595 (30.4)
Age at baseline (years)	51.5 (6.3)	53.0 (6.6)	51.5 (6.1)	50.5 (6.2)
Weight follow-up period (years)	6.9 (3.2)	5.3 (2.2)	7.6 (3.3)	6.8 (3.0)
Cancer follow-up period (years)	8.0 (4.2)	9.5 (4.0)	7.2 (4.2)	8.1 (4.1)
Anthropometry: mean (SD)				
Weight change (kg/year)	0.11 (0.86)	−1.06 (0.70)	0.04 (0.21)	0.95 (0.58)
BMI at baseline (kg/m^2)	25.5 (4.2)	28.0 (4.5)	24.6 (3.8)	25.2 (3.9)
Height (cm)	166.3 (8.9)	166.7 (9.4)	165.8 (8.7)	166.7 (8.8)
Dietary factors: median (25th-75th centile)				
Energy intake (kcal/day)	2028 (1657-2472)	2023 (1648-2474)	2046 (1681-2480)	2002 (1626-2456)
Fruit and vegetables (g/day)	462 (330-636)	459 (327-643)	473 (339-644)	447 (319-621)
Alcohol consumption (g/day)	6.5 (1.2-16.7)	6.4 (0.8-17.6)	7.0 (1.5-17.0)	6.0 (1.2-15.7)
Smoking status and intensity: n (%)				
Never smoked	113 518 (47.0)	22 029 (45.6)	56 963 (49.3)	34 526 (44.5)
Former: quit time >20 years	37 849 (15.7)	6789 (14.1)	19 521 (16.9)	11 539 (14.9)
Former: quit time ≤20 years	41 327 (17.1)	7819 (16.2)	17 207 (14.9)	16 301 (21.0)
Former: quit time missing	3994 (1.7)	621 (1.3)	1841 (1.6)	1532 (2.0)
Current: ≤10 cigarettes/day	18 870 (7.8)	4158 (8.6)	9008 (7.8)	5704 (7.3)
Current: >10 cigarettes/day	20 893 (8.7)	5486 (11.4)	8822 (7.6)	6585 (8.5)
Current: cigarettes missing	4872 (2.0)	1359 (2.8)	2067 (1.8)	1446 (1.9)
Physical activity index: n (%)				
Inactive	51 195 (21.2)	13 015 (27.0)	21 457 (18.6)	16 723 (21.5)
Moderately inactive	79 840 (33.1)	14 899 (30.9)	38 784 (33.6)	26 157 (33.7)
Moderately active	67 856 (28.1)	11 181 (23.2)	34 186 (29.6)	22 489 (29.0)
Active	42 432 (17.6)	9166 (19.0)	21 002 (18.2)	12 264 (15.8)
Education: n (%)				
None/primary school	73 471 (30.4)	19 714 (40.8)	31 197 (27.0)	22 560 (29.1)
Secondary/technical school	102 066 (42.3)	17 436 (36.1)	50 387 (43.7)	34 243 (44.1)
University/longer education	59 582 (24.7)	10 139 (21.0)	30 973 (26.8)	18 470 (23.8)
Missing information	6204 (2.6)	972 (2.0)	2872 (2.5)	2360 (3.0)
Menopausal status: n (%)[a]				
Premenopausal	30 665 (18.5)	6234 (21.2)	12 473 (15.1)	11 958 (22.1)
Postmenopausal	135 223 (81.5)	23 199 (78.8)	69 944 (84.9)	42 080 (77.9)
Oral contraceptives: n (%)[a]				
Never used	58 549 (35.3)	12 286 (41.7)	28 806 (35.0)	17 457 (32.3)
Ever used	105 184 (63.4)	16 927 (57.5)	52 589 (63.8)	35 668 (66.0)
Missing information	2155 (1.3)	220 (0.7)	1022 (1.2)	913 (1.7)
Hormone replacement therapy: n (%)[a]				
Never used	77 135 (46.5)	16 217 (55.1)	35 706 (43.3)	25 212 (46.7)
Ever used	80 617 (48.6)	11 624 (39.5)	43 120 (52.3)	25 873 (47.9)
Missing information	8136 (4.9)	1592 (5.4)	3591 (4.4)	2953 (5.5)

Abbreviations: SD, standard deviation;

[a]Used as covariates in women; all covariates were derived from questionnaires at the second weight assessment, except from education, energy intake and fruit and vegetable consumption, which were derived from questionnaires at baseline; n (%), number of individuals (percentage from total number in category or from total cohort size and cancer cases).

TABLE 2 Weight change in relation to cancer risk

	Weight gain (cont.)[a] (per 1 kg/year increment)		Weight loss (cat.)[b] (−5.0 to <−0.4 kg/year)		Stable weight[b] (reference)	Weight gain (cat.)[b] (>0.4 to 5.0 kg/year)	
Cancer type/ ^subtype	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	Cases	HR (95% CI)
Any cancer (overall)	20 960	1.00 (0.99-1.02)	5322	1.00 (0.97-1.04)	8999	6639	1.02 (0.99-1.05)
Obesity-related cancers	9569	1.03 (1.00-1.05)*	2223	0.98 (0.93-1.03)	3977	3024	1.08 (1.03-1.13)*
Head and neck							
Head and neck (overall)	381	0.94 (0.85-1.06)	107	1.07 (0.83-1.38)	154	120	1.01 (0.79-1.29)
^Mouth and oropharynx	190	0.85 (0.73-1.00)*	55	1.15 (0.80-1.66)	76	59	0.98 (0.69-1.38)
^Larynx	126	1.03 (0.85-1.25)	34	0.98 (0.63-1.53)	52	40	1.05 (0.69-1.59)
Digestive system							
Oesophagus (overall)	157	1.02 (0.86-1.20)	42	0.78 (0.52-1.16)	72	43	0.73 (0.50-1.08)
^Oesophageal adenocarcinoma	57	1.16 (0.89-1.52)	17	0.98 (0.50-1.90)	22	18	0.99 (0.53-1.86)
^Oesophageal SCC	71	0.88 (0.68-1.14)	19	0.75 (0.42-1.36)	35	17	0.57 (0.32-1.04)
Stomach (overall)	354	0.95 (0.85-1.07)	99	0.92 (0.71-1.21)	153	102	0.91 (0.71-1.18)
^Gastric adenocarcinoma	165	0.90 (0.76-1.06)	52	1.32 (0.90-1.95)	63	50	1.10 (0.76-1.61)
Colorectal (overall)	2381	0.98 (0.94-1.03)	629	0.98 (0.88-1.09)	1007	745	1.03 (0.93-1.13)
^Colon	1503	0.99 (0.94-1.05)	396	0.96 (0.84-1.09)	624	483	1.07 (0.94-1.20)
^Rectum and rectosigmoid junction	878	0.97 (0.90-1.05)	233	1.02 (0.86-1.21)	383	262	0.96 (0.82-1.13)
Liver and bile ducts (overall)	323	1.11 (0.99-1.24)	96	1.20 (0.90-1.59)	111	116	1.43 (1.10-1.86)*
^Hepatocellular carcinoma	77	0.85 (0.67-1.08)	31	1.95 (1.11-3.43)*	24	22	1.24 (0.69-2.23)
^Gallbladder and bile ducts	194	1.20 (1.03-1.39)*	47	0.88 (0.60-1.29)	72	75	1.41 (1.01-1.96)*
Pancreas	549	0.95 (0.87-1.04)	156	1.05 (0.85-1.30)	228	165	1.03 (0.84-1.27)
Respiratory system							
Lung (overall)	1560	0.94 (0.88-0.99)*	453	1.23 (1.09-1.40)*	614	493	1.07 (0.94-1.20)
^Lung adenocarcinoma	603	0.98 (0.89-1.07)	157	1.12 (0.91-1.38)	251	195	1.07 (0.89-1.30)
^Lung SCC	296	0.85 (0.75-0.96)*	95	1.28 (0.97-1.69)	121	80	0.83 (0.62-1.10)
^Lung small-cell carcinoma	182	1.05 (0.90-1.24)	54	1.16 (0.80-1.68)	70	58	1.19 (0.83-1.69)
Urinary system							
Kidney	429	1.06 (0.96-1.17)	119	0.95 (0.74-1.22)	171	139	1.10 (0.88-1.38)
Renal pelvis and ureter	60	1.27 (0.97-1.68)	14	0.71 (0.36-1.38)	28	18	0.93 (0.51-1.70)
Bladder	643	0.98 (0.90-1.06)	185	1.07 (0.88-1.31)	253	205	1.03 (0.85-1.24)
Reproductive system							
Prostate	3751	1.02 (0.98-1.06)	960	0.93 (0.86-1.01)	1695	1096	0.95 (0.87-1.02)
Breast (female) (overall)	4179	1.03 (0.99-1.06)	886	0.98 (0.90-1.07)	1858	1435	1.06 (0.98-1.13)
^Breast (premenopausal)	377	0.98 (0.88-1.09)	82	0.98 (0.73-1.30)	159	136	0.86 (0.68-1.09)
^Breast (postmenopausal)	3802	1.03 (1.00-1.07)	804	0.98 (0.90-1.07)	1699	1299	1.08 (1.00-1.16)*
Ovary	500	1.01 (0.91-1.11)	111	0.93 (0.73-1.19)	221	168	1.00 (0.81-1.22)
Corpus uteri	688	1.14 (1.05-1.23)*	160	0.91 (0.74-1.12)	277	251	1.19 (1.00-1.41)
^Uterine adenocarcinoma	188	1.23 (1.06-1.43)*	39	0.87 (0.57-1.32)	74	75	1.23 (0.89-1.71)
^Endometrioid adenocarcinoma	401	1.12 (1.01-1.24)*	91	0.84 (0.64-1.10)	169	141	1.14 (0.91-1.43)
Cervix uteri	98	0.96 (0.78-1.17)	24	0.81 (0.47-1.37)	43	31	0.90 (0.56-1.44)
Anogenital	132	0.99 (0.82-1.21)	45	1.61 (1.04-2.49)*	47	40	1.18 (0.77-1.82)
Skin							
Skin SCC	727	0.87 (0.80-0.95)*	192	0.99 (0.82-1.19)	347	188	0.78 (0.65-0.93)*
Melanoma	858	0.97 (0.89-1.05)	201	1.07 (0.89-1.28)	375	282	1.01 (0.87-1.19)
Nervous and endocrine system							
Brain and CNS	309	0.94 (0.83-1.07)	80	0.90 (0.67-1.20)	143	86	0.80 (0.61-1.05)
Thyroid	232	1.11 (0.96-1.27)	56	1.23 (0.85-1.77)	89	87	1.40 (1.04-1.90)*
Haematopoietic system							
Leukaemia (overall)	695	1.00 (0.92-1.09)	169	0.94 (0.77-1.15)	297	229	1.02 (0.85-1.21)
^Multiple myeloma	254	1.05 (0.92-1.21)	58	0.86 (0.62-1.21)	111	85	1.01 (0.76-1.35)
Lymphoma (overall)	549	0.98 (0.89-1.08)	139	1.00 (0.81-1.25)	241	169	0.92 (0.75-1.12)
^Non-Hodgkin lymphoma	466	0.98 (0.88-1.09)	121	1.05 (0.83-1.33)	201	144	0.96 (0.77-1.19)

Abbreviations: CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; premenopausal, breast cancer diagnosed at age < 55 years in women premenopausal at the second weight assessment; postmenopausal, breast cancer diagnosed at age ≥ 55 years, irrespective of menopausal status at the second weight assessment; obesity-related cancers, oesophageal adenocarcinoma, cancers of the stomach (overall), colorectum (overall), liver (overall), pancreas, kidney, postmenopausal breast, ovary, corpus uteri (overall), thyroid and multiple myeloma.

[a]HR estimates were obtained from Cox proportional hazards models including weight change as a continuous variable (interpreted as the risk associated with weight gain per one kg/year increment), stratified by study centre, sex (except for sex-specific cancers) and age at the second weight assessment and adjusted for baseline body mass index (per 5 kg/m^2 increment), height, education, energy intake, fruit and vegetable consumption (assessed at baseline), as well as for smoking status and intensity, physical activity, alcohol consumption and for female cancers also menopausal status (except premenopausal cancer), ever using oral contraceptive and hormone replacement therapy (at the second assessment) and time interval between the two weight assessments.

[b]The models included weight change as a categorical variable and compared weight loss or weight gain categories to stable weight (−0.4 to 0.4 kg/year) as reference, with stratification and adjustments as in footnote a.

*P < .05. **P < .001.

were more likely younger (Table 1). Participants with stable weight had the lowest BMI at baseline (mean = 24.6 kg/m^2). Participants with weight loss had considerably higher BMI at baseline (mean = 28.0 kg/m^2) and were more likely men, current smokers or inactive. Energy, fruit, vegetable and alcohol consumption were comparable between the groups with weight loss, weight gain or stable weight. Women who lost weight were less likely to have ever used HRT. Compared to women, men were more likely smokers (either former or current), with higher baseline BMI, higher energy intake and alcohol consumption, but lower fruit and vegetable consumption (Supplementary Table S8).

In total, 20 960 incident cancers were diagnosed during a mean follow-up of 8.0 years (Supplementary Table S9). Participants diagnosed with cancer had a higher baseline BMI (mean = 26.2 kg/m^2) than the cohort overall and a larger proportion experienced weight loss (25.4%). Participants with hepatocellular carcinoma (HCC) had the highest baseline BMI (mean = 28.3 kg/m^2) and the largest proportion with weight loss (40.3%). Participants from Denmark, Spain and Sweden contributed 65.7% of all cancer cases.

3.2 | Associations between weight change and cancer risk independent of baseline BMI

The main analyses are presented in Table 2 and the subgroup analyses by sex in Supplementary Table S10.

Obesity-related cancers showed positive associations with weight gain, independent from baseline BMI. Compared to the stable weight category (−0.4 to 0.4 kg/year), weight gain (>0.4 to 5.0 kg/year) was positively associated with obesity-related cancers overall (HR: 1.08; 95% CI: 1.03, 1.13) and specifically with cancers of the gallbladder and bile ducts (HR: 1.41; 95% CI: 1.01, 1.96), postmenopausal breast (HR: 1.08; 95% CI: 1.00, 1.16) and thyroid (HR: 1.40; 95% CI: 1.04, 1.90). Weight gain as a continuous variable (per one kg/year increment) was also positively associated with obesity-related cancers overall (HR: 1.03; 95% CI: 1.00, 1.05) and specifically with cancers of the gall bladder and bile ducts (HR: 1.20; 95% CI: 1.03, 1.39), corpus uteri (HR: 1.14; 95% CI: 1.05, 1.23) and thyroid in men (HR: 1.55; 95% CI: 1.08, 2.23). The only exception among obesity-related cancers was HCC, which was positively associated with weight loss (−5.0 to <−0.4 kg/year) compared to the stable weight category (HR: 1.95; 95% CI: 1.11, 3.43) and in women was inversely associated with weight gain as a continuous variable (per one kg/year increment) (HR: 0.59; 95% CI: 0.38, 0.93).

Squamous cell carcinomas (SCC), on the contrary, showed inverse associations. Weight gain as a continuous variable (per one kg/year increment) was inversely associated with cancers of the mouth and oropharynx (HR: 0.85; 95% CI: 0.73, 1.00), lung SCC (HR: 0.85; 95% CI: 0.75, 0.96), skin SCC (HR: 0.87; 95% CI: 0.80, 0.95) and oesophageal SCC in women (HR: 0.62; 95% CI: 0.39, 0.99). Further, compared to the stable weight category, weight gain (>0.4 to 5.0 kg/year) was inversely associated with skin SCC (HR: 0.78; 95% CI: 0.65, 0.93), while weight loss (−5.0 to <−0.4 kg/year) was positively associated with anogenital cancers (HR: 1.61; 95% CI: 1.04, 2.49).

Lung adenocarcinoma showed complex sex-specific associations. In women, the association was inverse for weight gain as a continuous variable (per one kg/year increment) (HR: 0.84; 95% CI: 0.74, 0.96) and was positive for weight loss (−5.0 to <−0.4 kg/year) compared to the stable weight category (HR: 1.33; 95% CI: 1.02, 1.73), while in men the association was positive both for weight gain as a continuous variable (per one kg/year increment) (HR: 1.15; 95% CI: 1.00, 1.33) and for weight gain (>0.4 to 5.0 kg/year) compared to the stable weight category (HR: 1.34; 95% CI: 1.01, 1.77). Weight gain as a continuous variable (per one kg/year increment) showed an additional positive association with cancers of the renal pelvis and ureter in women (HR: 1.64; 95% CI: 1.08, 2.50), while in men weight gain (>0.4 to 5.0 kg/year) compared to the stable weight category showed inverse associations with cancers of the brain and central nervous system (CNS) (HR: 0.58; 95% CI: 0.38, 0.88) and non-Hodgkin lymphoma (HR: 0.71; 95% CI: 0.50, 1.00).

3.3 | Associations between change in BMI category and cancer risk

The main analyses are presented in Table 3 and the subgroup analyses by sex in Supplementary Table S11.

Compared to maintaining NW BMI (18.5 to <25 kg/m^2), maintaining OW (25 to <30 kg/m^2) or OB BMI category (≥30 kg/m^2) at both assessments was positively associated with obesity-related cancers overall and individually with oesophageal adenocarcinoma, HCC, cancers of the colon, gallbladder and bile ducts, pancreas, kidney, postmenopausal breast, ovary, corpus uteri and thyroid, but not

TABLE 3 Change in body mass index category in relation to cancer risk

BMI category change	Weight loss to a lower BMI category				Stable weight—maintaining the same BMI category					Weight gain to a higher BMI category			
	OB→OW vs OB-OB		OW→NW vs OW-OW		NW-NW	OW-OW vs NW-NW		OB-OB vs NW-NW		NW→OW vs NW-NW		OW→OB vs OW-OW	
Cancer type/ˆsubtype	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Any cancer (overall)	663	0.92 (0.85-1.00)	1000	0.97 (0.91-1.04)	7179	6829	1.04 (1.00-1.08)*	2720	1.13 (1.08-1.18)**	1499	1.04 (0.98-1.10)	821	1.06 (0.99-1.14)
ˆObesity-related cancers	302	0.87 (0.77-0.98)*	427	0.93 (0.84-1.03)	3392	2772	1.15 (1.09-1.22)**	1406	1.42 (1.33-1.52)**	734	1.12 (1.04-1.22)*	424	1.18 (1.06-1.31)*
Head and neck (overall)	17	1.38 (0.79-2.42)	15	0.74 (0.43-1.27)	122	143	0.92 (0.71-1.19)	45	0.75 (0.52-1.08)	28	1.06 (0.70-1.61)	7	–
Digestive system													
Oesophagus (overall)	5	–	6	–	46	52	1.00 (0.66-1.52)	29	1.61 (0.98-2.66)	8	–	8	–
ˆOesophageal AC	4	–	3	–	8	21	2.22 (0.97-5.10)	14	4.76 (1.93-11.7)**	3	–	4	–
ˆOesophageal SCC	1	–	1	–	32	19	0.51 (0.28-0.94)*	10	0.59 (0.26-1.34)	4	–	1	–
Stomach	13	0.87 (0.48-1.59)	16	0.89 (0.53-1.50)	96	134	1.06 (0.80-1.40)	59	1.06 (0.74-1.50)	12	0.56 (0.31-1.02)	20	1.37 (0.85-2.19)
ˆGastric AC	9	–	7	–	42	61	1.23 (0.81-1.85)	26	1.38 (0.82-2.33)	9	–	8	–
Colorectal (overall)	87	0.91 (0.72-1.16)	100	0.84 (0.68-1.03)	737	826	1.08 (0.97-1.20)	365	1.26 (1.10-1.45)**	134	0.86 (0.72-1.04)	111	1.22 (1.00-1.49)
ˆColon	51	0.77 (0.57-1.04)	53	0.69 (0.52-0.92)*	456	527	1.13 (0.99-1.29)	254	1.42 (1.20-1.68)**	75	0.80 (0.62-1.02)	71	1.22 (0.95-1.57)
ˆRectum and rectosigmoid junction	36	1.25 (0.85-1.82)	47	1.10 (0.81-1.49)	281	299	1.00 (0.84-1.18)	111	1.01 (0.80-1.28)	59	0.97 (0.73-1.28)	40	1.21 (0.87-1.69)
Liver and bile ducts (overall)	19	0.99 (0.60-1.65)	10	0.63 (0.33-1.21)	73	108	1.36 (1.00-1.86)*	74	2.35 (1.66-3.33)**	21	1.33 (0.81-2.16)	12	0.99 (0.54-1.80)
ˆHepatocellular CA	7	–	2	–	16	23	1.14 (0.59-2.19)	19	2.58 (1.27-5.24)*	5	–	3	–
ˆGallbladder and bile ducts	9	–	7	–	45	70	1.58 (1.07-2.34)*	38	2.02 (1.27-3.21)*	13	1.40 (0.75-2.60)	8	–
Pancreas	21	0.97 (0.60-1.57)	26	0.85 (0.56-1.28)	157	196	1.27 (1.02-1.59)*	82	1.42 (1.07-1.88)*	43	1.39 (0.99-1.95)	22	1.02 (0.66-1.59)
Respiratory system													
Lung (overall)	38	0.94 (0.66-1.35)	99	1.39 (1.12-1.74)*	641	436	0.68 (0.60-0.77)**	142	0.60 (0.49-0.72)**	102	0.80 (0.65-0.99)*	65	1.30 (1.00-1.68)
ˆLung AC	11	0.85 (0.44-1.64)	38	1.37 (0.96-1.95)	255	162	0.71 (0.58-0.87)*	46	0.56 (0.40-0.78)**	41	0.84 (0.60-1.17)	29	1.52 (1.02-2.26)*
ˆLung SCC	9	–	21	1.63 (1.01-2.63)*	119	91	0.62 (0.46-0.82)**	29	0.48 (0.31-0.75)**	17	0.65 (0.39-1.09)	6	–
ˆLung small-cell CA	6	–	15	1.47 (0.82-2.61)	62	55	0.99 (0.68-1.44)	20	1.02 (0.60-1.73)	12	1.02 (0.55-1.90)	9	–
Urinary system													
Kidney	18	0.76 (0.46-1.26)	25	1.18 (0.77-1.81)	95	149	1.48 (1.13-1.94)*	86	2.38 (1.74-3.25)**	26	1.28 (0.83-1.98)	29	1.80 (1.20-2.68)*
Bladder	25	1.04 (0.67-1.63)	37	1.19 (0.84-1.68)	173	240	1.04 (0.85-1.28)	85	1.04 (0.79-1.36)	47	1.20 (0.87-1.66)	32	1.29 (0.89-1.87)
Reproductive system													
Prostate	115	0.91 (0.74-1.12)	179	0.88 (0.75-1.02)	1010	1648	1.02 (0.94-1.11)	421	0.92 (0.82-1.03)	236	0.99 (0.86-1.14)	124	0.89 (0.74-1.07)
Breast (female) (overall)	111	1.05 (0.85-1.29)	198	1.06 (0.91-1.23)	1834	973	1.09 (1.01-1.19)*	453	1.16 (1.04-1.30)*	379	1.15 (1.03-1.29)*	164	1.08 (0.91-1.27)
ˆBreast (premenopausal)	10	1.43 (0.70-2.92)	18	1.23 (0.74-2.06)	184	79	1.00 (0.76-1.32)	31	0.85 (0.57-1.27)	30	0.88 (0.60-1.30)	17	1.18 (0.70-2.01)
ˆBreast (postmenopausal)	101	1.02 (0.82-1.26)	180	1.04 (0.89-1.22)	1650	894	1.11 (1.02-1.20)*	422	1.20 (1.07-1.35)*	349	1.19 (1.06-1.33)*	147	1.07 (0.90-1.28)
Ovary	8	–	26	1.46 (0.94-2.25)	205	95	0.86 (0.67-1.10)	81	1.61 (1.22-2.13)**	53	1.40 (1.04-1.91)*	22	1.55 (0.97-2.47)

(Continues)

TABLE 3 (Continued)

BMI category change Cancer type/ˆsubtype	Weight loss to a lower BMI category				Stable weight—maintaining the same BMI category					Weight gain to a higher BMI category			
	OB→OW vs OB-OB		OW→NW vs OW-OW		NW-NW	OW-OW vs NW-NW		OB-OB vs NW-NW		NW→OW vs NW-NW		OW→OB vs OW-OW	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Corpus uteri (overall)	14	0.40 (0.23-0.69)*	22	0.64 (0.41-1.00)	207	193	1.69 (1.38-2.07)**	154	2.85 (2.27-3.58)**	56	1.42 (1.06-1.91)*	35	1.15 (0.80-1.66)
ˆUterine AC	5	—	1	—	60	44	1.28 (0.85-1.91)	48	3.05 (2.01-4.62)**	16	1.22 (0.70-2.13)	10	1.33 (0.67-2.65)
ˆEndometrioid AC	7	—	14	0.64 (0.37-1.11)	119	118	1.85 (1.42-2.41)**	85	2.78 (2.04-3.77)**	35	1.63 (1.12-2.39)*	20	1.10 (0.68-1.77)
Skin													
Skin SCC	24	1.13 (0.72-1.80)	35	1.07 (0.75-1.54)	298	213	0.73 (0.61-0.88)**	76	0.79 (0.61-1.04)	52	0.92 (0.69-1.24)	20	0.98 (0.62-1.55)
Melanoma	22	0.97 (0.61-1.55)	46	1.12 (0.82-1.53)	346	266	1.04 (0.88-1.23)	88	1.05 (0.82-1.34)	60	0.87 (0.66-1.15)	21	0.66 (0.42-1.02)
Nervous/endocrine system													
Brain and CNS (overall)	10	1.00 (0.50-2.00)	13	0.75 (0.42-1.34)	102	118	1.14 (0.86-1.51)	38	0.91 (0.61-1.36)	11	0.53 (0.28-0.99)*	9	—
Thyroid	7	—	9	—	80	74	1.58 (1.12-2.22)*	31	1.41 (0.90-2.21)	18	1.15 (0.69-1.93)	12	1.07 (0.58-1.98)
Haematopoietic system													
Leukaemia (overall)	29	1.09 (0.72-1.65)	28	0.91 (0.61-1.34)	230	220	0.94 (0.77-1.14)	104	1.16 (0.90-1.49)	48	0.97 (0.71-1.32)	28	1.12 (0.75-1.66)
ˆMultiple myeloma	10	1.08 (0.54-2.17)	10	0.85 (0.44-1.65)	84	82	1.02 (0.74-1.41)	38	1.21 (0.80-1.82)	19	1.06 (0.64-1.75)	10	1.06 (0.55-2.05)
Lymphoma (overall)	20	1.21 (0.73-2.01)	22	0.76 (0.49-1.18)	188	187	1.18 (0.96-1.46)	62	1.12 (0.83-1.51)	45	1.19 (0.86-1.66)	18	0.83 (0.51-1.34)
ˆNon-Hodgkin lymphoma	20	1.45 (0.87-2.43)	20	0.82 (0.52-1.32)	160	154	1.15 (0.91-1.45)	52	1.09 (0.78-1.51)	40	1.26 (0.89-1.79)	15	0.83 (0.49-1.41)

Abbreviations: AC, adenocarcinoma; BMI, body mass index; CA, carcinoma; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NW, normal weight (BMI ≥18.5 to <25 kg/m^2); OB, obese (BMI ≥30 kg/m^2); OW, overweight (BMI ≥25 to <30 kg/m^2); SCC, squamous cell carcinoma; premenopausal, breast cancer diagnosed at age < 55 years in women premenopausal at the second weight assessment; postmenopausal, breast cancer diagnosed at age ≥ 55 years, irrespective of menupausal status at the second weight assessment; obesity-related cancers, oesophageal adenocarcinoma, cancers of the stomach, colorectum, liver, pancreas, kidney, postmenopausal breast, ovary, corpus uteri, thyroid and multiple myeloma; HR estimates were obtained from Cox proportional hazards models with change in BMI category between the two assessments (categorical) as exposure, stratification by study centre, sex (except for sex-specific cancers) and age at the second weight assessment and adjustment for height, education, energy intake, fruit and vegetable consumption (assessed at baseline), smoking status and intensity, physical activity, alcohol consumption and for women menopausal status, ever using oral contraceptive and hormone replacement therapy (at the second assessment) and time interval between the two assessments; participants with BMI <18.5 kg/m^2 and those changing between normal weight and obese (n = 4602, 1.9%) were excluded from the analysis; HR estimates for categories with less than 10 cases are not shown; Groups maintaining stable overweight (OW-OW) or stable obese (OB-OB) at both assessments were compared to the group maintaining stable normal weight (NW-NW), while the groups with weight change to a higher or lower BMI category were compared to the group maintaining the corresponding baseline BMI category as follows: weight gain from normal weight to overweight (NW→OW) was compared to stable normal weight (NW-NW); weight gain from overweight to obese (OW→OB) and weight loss from overweight to normal weight (OW→NW) were compared to stable overweight (OW-OW); weight loss from obese to overweight (OB→OW) was compared to stable obese (OB-OB).
*P < .05.**P < .001.

with cancers of the stomach, rectum and rectosigmoid junction or multiple myeloma. Compared to maintaining the baseline BMI category, weight gain from NW to OW BMI category was positively associated with obesity-related cancers overall (HR: 1.12; 95% CI: 1.04, 1.22) and specifically with cancers of the postmenopausal breast (HR: 1.19; 95% CI: 1.06, 1.33), ovary (HR: 1.40; 95% CI: 1.04, 1.91), corpus uteri (HR: 1.42; 95% CI: 1.06, 1.91) and pancreas in men (HR: 1.81; 95% CI: 1.11, 2.95), while weight gain from OW to the OB BMI category was similarly positively associated with obesity-related cancers overall (HR: 1.18; 95% CI: 1.06, 1.31) and specifically with kidney cancer (HR: 1.80; 95% CI: 1.20, 2.68). In accordance, weight loss from OB to OW BMI category was inversely associated with obesity-related cancers overall (HR: 0.87; 95% CI: 0.77, 0.98) and specifically with cancer of the corpus uteri (HR: 0.40; 95% CI: 0.23, 0.69), while weight loss from OW to NW BMI category was inversely associated with colon cancer (HR: 0.69; 95% CI: 0.52, 0.92).

At the same time, compared to maintaining NW BMI, maintaining OW or OB BMI category at both assessments was inversely associated with SCC of the oesophagus, lung and skin, while there was a positive association with lung SCC when losing weight from OW to NW, compared to maintaining OW BMI category (HR: 1.63; 95% CI: 1.01, 2.63). Associations with lung adenocarcinoma were in opposite directions for women and men. In women, compared to maintaining NW BMI category, there was an inverse association when gaining weight to OW BMI category (HR: 0.62; 95% CI: 0.39, 1.00), as well as when maintaining OW (HR: 0.69; 95% CI: 0.52, 0.92) or OB BMI category (HR: 0.47; 95% CI: 0.29, 0.76), while in men, there was a positive association when gaining weight from OW to OB, compared to maintaining OW BMI category (HR: 1.79; 95% CI: 1.05, 3.05). In women, compared to maintaining NW, maintaining OW BMI category was additionally positively associated with cancers of the brain and CNS (HR: 1.51; 95% CI: 1.03, 2.21) and lymphoma overall (HR: 1.34; 95% CI: 1.00, 1.79).

The evidence for all observed associations with change in weight or BMI category was considered weak, with *P*-values between .05 and .001.

3.4 | Sensitivity analyses

Removing individuals with less than 2 years of follow-up attenuated the positive association of weight loss (−5.0 to <−0.4 kg/year) with HCC (HR: 1.35; 95% CI: 0.70, 2.61) and indicated an inverse association of weight gain (>0.4 to 5.0 kg/year) with prostate cancer (HR: 0.92; 95% CI: 0.85, 1.00), compared to the stable weight category, but did not materially alter other associations. Compared to the unadjusted models, adjustment for smoking status and intensity and other confounders did not attenuate the inverse associations with cancers with SCC morphology (Supplementary Tables S12 and S13).

4 | DISCUSSION

We report positive associations of weight gain in middle adulthood with obesity-related cancers overall and individually with cancers of the gallbladder and bile ducts, postmenopausal breast, corpus uteri and thyroid, which were independent of associations with baseline BMI. Compared to maintaining NW, maintaining OW or OB BMI category was positively associated with most obesity-related cancers. Gaining weight to a higher BMI category was also positively associated with obesity-related cancers overall and specifically with cancers of the kidney, postmenopausal breast, ovary and corpus uteri, while losing weight to a lower BMI category was inversely associated with obesity-related cancers overall and specifically with cancers of the colon and corpus uteri. Cancers with SCC morphology of the upper aerodigestive tract, lung and skin showed inverse associations with weight gain and with maintaining OW or OB BMI category. Half of our study participants maintained stable weight, with comparable proportions gaining or losing >0.4 to 5 kg/year and only one in five changing their baseline BMI category. Our findings are thus compatible with reports of weight change trajectories, indicating that in middle adulthood weight reaches a plateau and the direction of weight change switches gradually from weight gain in early adulthood to weight loss in late adulthood.[4]

The major mechanisms linking obesity to cancer are excess oestrogens, which are generated via aromatase in adipocytes; high levels of leptin, which promotes the migration and invasion of cancer cells; low levels of adiponectin, which has anti-inflammatory, antiproliferative and pro-apoptotic properties; chronic low-grade inflammation accompanied by insulin resistance and hyperinsulinemia, which facilitate tumour growth and progression.[13] Although obesity-related mechanisms are often examined with respect to attained weight, they can also be influenced by short-term weight changes. Thus, short-term weight gain can be associated with increased leptin, pro-inflammatory markers and insulin resistance,[14,15] while weight loss can be associated with lower leptin, lower circulating oestrogens and improved insulin sensitivity.[15-17] Nevertheless, the overall effect of short-term weight change is not always predictable and can differ according to baseline weight. For example, in normal-weight individuals, high leptin resulting from moderate short-term weight gain induces adiponectin expression, while in individuals with established obesity, leptin signalling is impaired and hinders a concomitant adiponectin increase.[18] Adipose-derived factors, especially oestrogens, can also act and interact differentially in individual tissues. Thus in breast adipose tissue, leptin stimulates aromatase activity, which contributes to higher oestrogen levels and both promote breast cancer development,[19] while in HCC cell lines, oestradiol induces apoptosis and opposes the oncogenic actions of leptin.[20] Furthermore, obesity is not only accompanied by higher oestrogen levels but also by gonadal dysfunction, with higher testosterone levels in OB women and lower in OB men and changes in opposite directions with weight loss.[21] An additional constraint is the lack of studies specifically examining the dynamics of adipose-derived factors after weight changes in middle adulthood.

A notable pattern in our findings was the positive association of weight change in middle adulthood specifically with cancers promoted by oestrogens, either female specific or with higher incidence in women, despite the fact that maintaining OW or OB BMI category was positively associated with most obesity-related cancers. In

agreement with our findings, observational studies have consistently reported positive associations of weight gain in middle adulthood with cancers of the postmenopausal breast[7,10,22,23] and corpus uteri[10,22,24] and inverse associations with weight loss, especially when intentional,[25] sustained,[26] or after bariatric surgery.[27] No associations, however, have previously been reported with ovarian cancer.[10,25] An involvement of weight change in oestrogen-driven cancers of the female reproductive system is not surprising, given that adipose-derived oestrogens gain prominence in postmenopausal women, when gonadal oestrogen production decreases.[13] Nevertheless, although ERα activation promotes cancer development in the breast, ovary and corpus uteri, differences exist in the local regulation of ER expression,[28] oestrogen signalling[29] and aromatase transcription.[30] Leptin signalling pathways also differ.[31] This may partly explain the differences in the association patterns that we observed. While there was a consistent dose-response relationship between weight gain as a continuous variable and the risk of cancer of the corpus uteri, with both higher risk for weight gain and lower risk for weight loss compared to maintaining the baseline BMI category, only weight gain was associated with cancers of the ovary and postmenopausal breast, with no clear indication for lower risk with weight loss. Further, the hitherto unreported positive associations of weight gain with cancers of the gallbladder and bile ducts and the thyroid, which have higher incidence in women, are also compatible with a cancer promoting role of oestrogens. Oestrogens can stimulate the growth and migration of thyroid cancer stem cells,[32] while ERβ expression is higher in gallbladder cancers compared to normal tissues and is associated with worse prognosis.[33] Furthermore, although the incidence of renal cell carcinoma is higher in men, oestradiol can promote the progression of renal cancer cells via activation of ERβ[34] and a positive association with weight gain has previously been reported in women.[22]

On the other hand, cancers of the digestive system (colon, pancreas and liver), for which oestrogens can have protective effects, did not show prominent positive associations with weight gain in middle adulthood, despite clear positive associations with maintaining OW or OB BMI category. In agreement with our findings, published epidemiological studies have provided little evidence for positive associations of short-term weight gain with colorectal cancer,[8,10,22,35] but an inverse association has been reported with intentional weight loss,[25] which we have observed for weight loss from OW to NW BMI category. Although mechanistic studies have shown that colonocyte proliferation increases with weight gain and decreases with weight loss,[36] it has also been suggested that weight gain in middle adulthood is less hazardous for colorectal cancer compared to weight gain during early adulthood.[8,37] This might be related to different causes of weight gain or a different balance between the pro-carcinogenic and anti-proliferative properties of adipose-derive factors during different periods of adulthood. Thus, while leptin enhances the adhesion and invasion of colorectal cancer cells,[38] activation of ERβ by oestrogens is largely considered protective, as ERβ is lost from colon cancer cells during tumour progression[39] and HRT use is inversely associated with colorectal cancer risk.[40] Oestrogens can similarly show discordant effects with other adipose-derived factors for the development of pancreatic cancer. Thus, a positive association between prediagnostic levels of leptin and pancreatic cancer has been reported in men,[41] while exogenous oestrogens have shown a protective effect against pancreatic cancer in women.[42] This may explain the inconclusive findings of observational studies for pancreatic cancer, either providing little evidence for association in women,[25] or showing positive associations with recent weight gain,[10] which we have observed with a limited number of cases in men. Further in agreement with our findings, a positive association of recent unintentional weight loss with the risk of liver cancer in women has been reported.[25] Although activation of both ERα and ERβ has shown protective effects in HCC cells[20] and oestrogen levels decrease with weight loss,[17] unintentional weight loss is a major clinical feature of cancer and reverse causality would more likely explain the positive association of short-term weight loss with HCC observed in our study.

A further notable pattern in our findings was the inverse association between weight gain and cancers with SCC morphology. Cancers of the upper aero-digestive tract and lung with SCC morphology are all associated with smoking and have shown inverse association with BMI, considered controversial in the literature, but studies examining associations with weight change are limited. While a recent umbrella meta-analysis reported "highly suggestive" evidence for inverse associations of BMI with oesophageal SCC and lung cancer overall,[1] the International Agency for Research on Cancer considers the evidence insufficient[2] and the World Cancer Research Fund has acknowledged a positive association of OW and obesity with cancers of the mouth, pharynx and larynx.[3] Furthermore, a recent Mendelian randomisation study has provided evidence for positive associations of BMI with lung SCC and small-cell carcinoma, but not with lung adenocarcinoma.[43] Residual confounding from smoking, despite a detailed adjustment for smoking status and intensity, and reverse causality are possible explanations for inverse associations, but removing the first 2 years of follow-up had no material influence, making a reverse causality from cancer cachexia less likely. In addition, we found little evidence for inverse associations with lung small cell carcinoma, which is also strongly associated with smoking, but observed a hitherto unreported inverse association of weight gain with skin SCC. Intriguingly, recent mechanistic studies suggest a protective effect of oestrogens for cancers with SCC morphology. Thus, ERα is overexpressed in human papilloma virus positive (HPV+) oropharyngeal cancers and oestrogens suppress viral gene expression and growth of HPV+ cells.[44] Further, oestradiol suppresses in a dose-dependent manner the proliferation of oesophageal SCC cells[45] and, in women, HRT is inversely associated while menopause is positively associated with oesophageal SCC.[46] Furthermore, female mice have shown higher skin tumour resistance compared to male mice, with ovariectomy resulting in overexpression of ERα, suppression of ERβ and increased susceptibility to skin SCC, comparable to male mice.[47] In vitro, increased ERβ expression or stimulation with oestrogen agonists inhibits proliferation of SCC cells and promotes squamous cell differentiation.[48] It is thus possible that

adipose-derived oestrogens mitigate the risk of tumours with SCC morphology.

Supplementary Discussion includes comments on cancers with sex-specific or limited evidence for association with weight change and a comparison of the current with previous EPIC studies on weight change and cancer risk.

A major strength of our study is the prospective assessment of weight. EPIC is also a large multicentre cohort, including both men and women from several European countries, with a variety of lifestyles and dietary patterns and a sizeable number of incident cancer cases. This provided large statistical power for analyses of the most common cancer sites, although statistical power was limited for the less common cancer sites, especially for change in BMI category and for the sex-specific analyses.

A major limitation of our study is that the second weight assessment was mostly self-reported, which can result in underestimating weight, especially in heavier individuals.[49] Therefore, weight gain may have been underestimated and weight loss overestimated, with no obvious way to anticipate in which direction associations were biased.[50] Although for most centres we had no centre-specific equations to predict measured from self-reported weight, examining the application of correcting equations has shown that they improve the distribution of BMI but do not remove the bias in the estimates for associations between self-reported BMI and different disease outcomes.[51] Nevertheless, BMI categories based on measured and self-reported weight were in good agreement in EPIC-Norway (Cohen's kappa = 0.73).[52] A further limitation was that there were only two weight assessments and we could not explore fluctuations in weight and weight cycling, that is, alternating gain and loss, which have been associated with a higher risk of cancer.[27] Furthermore, we focused on change in weight and BMI category, whereas other anthropometric parameters, for example, central rather than overall adiposity, could be relevant for cancer aetiology.[1] The large proportion of missing values at the second assessment of waist circumference limited this evaluation in EPIC. Finally, we could not distinguish between intentional and unintentional weight loss, which can have different effects,[25] but we examined the possibility of reverse causality by excluding participants with less than 2 years follow-up after the second weight assessment. The caveats of this approach are that removing individuals could potentially introduce selection bias, while removing cancer cases would reduce statistical power and subclinical cancer development may take longer than 2 years.

5 | CONCLUSIONS

Our findings confirm a positive association between maintaining OW or OB BMI in middle adulthood and most obesity-related cancers. In addition, independent of baseline BMI, weight gain in middle adulthood was positively associated with obesity-related cancers overall and specifically with cancers of the gallbladder and bile ducts, postmenopausal breast, corpus uteri and thyroid. Weight gain to a higher BMI category was also positively associated with obesity-related cancers overall and specifically with cancers of the kidney, postmenopausal breast, ovary, corpus uteri and in men pacreas, while weight loss to a lower BMI category was inversely associated with obesity-related cancers overall and specifically with cancers of the colon and corpus uteri. Our observations support public health interventions in middle adulthood advocating maintenance of BMI in the NW category, avoidance of weight gain, and weight loss when BMI is high, in order to reduce the risk of some obesity related cancers.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in this article and they do not

necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organisation.

DATA AVAILABILITY STATEMENT

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

ETHICS STATEMENT

This research was conducted according to the principles expressed in the Declaration of Helsinki. Approval for the study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all participating EPIC centres. All EPIC participants provided written informed consent at baseline for use of their blood samples and data in future research. The EPIC Steering Committee approved this study in accordance with EPIC rules https://epic.iarc.fr/access/access_appl_assessed.php.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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