# Excess Body Fatness during Early to Mid-Adulthood and Survival from Colorectal and Breast Cancer: A Pooled Analysis of Five International Cohort Studies

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## ABSTRACT

**Background:** Here, we explore the association between excess weight during early to mid-adulthood and survival in patients diagnosed with breast and colorectal cancer, using a pooled analysis of five cohort studies and study participants from 11 countries.

**Methods:** Participant-level body mass index (BMI) trajectories were estimated by fitting a growth curve model using over 2 million repeated BMI measurements from close to 600,000 cohort participants. Cumulative measures of excess weight were derived. Data from over 23,000 patients with breast and colorectal cancer were subsequently analyzed using time-to-event models for death with the date of diagnosis as start of follow-up. Study-specific results were combined through a random effect meta-analysis.

**Results:** We found a significant dose–response relationship ($P$ trend = 0.013) between the average BMI during early and mid-adulthood and death from breast cancer, with a pooled HR of 1.31 (1.07–1.60) and the time to death shortened by 16% for average BMI above 25 kg/m$^2$ compared with average BMI less than or equal to 22.5 kg/m$^2$, respectively. Similar results were found for categories of cumulative time spent with excess weight. There was no association between excess body fatness during early to mid-adulthood and death in patients with colorectal cancer.

**Conclusions:** Excess body fatness during early to mid-adulthood is associated not only with an increased risk of developing cancer, but also with a lower survival in patients with breast cancer.

**Impact:** Our results emphasize the importance of public health policies aimed at reducing overweight during adulthood and inform future studies on the relationship between excess weight and cancer outcomes.

## Introduction

Excess body fatness, herein referred to as excess weight, is an established risk factor for several cancer sites and other noncommunicable diseases and accounts for at least 4% of the global cancer burden (1). The prevalence of excess weight has continued to increase, and recent birth cohorts spend a greater proportion of their lives with overweight or obesity than any generation before (2). In 2015, approximately two billion adults globally were estimated to be overweight [defined as body mass index (BMI) ≥25 kg/m$^2$], with more than a quarter of them being obese (BMI ≥ 30 kg/m$^2$); trends show a continuing increase, especially in children and adolescents (3). These trends affect the obesity-related disease burden and may explain an increasing number of cancer cases in successively younger generations born since around 1950 (4) in high-income countries, such as the United States.

The effect of excess weight on the occurrence of health-related outcomes is usually investigated based on height and weight assessments at only one time point (e.g., at study entry or baseline). Although a single BMI assessment informs on the severity of an individual's overweight at some point in time, it fails to reflect the temporality of the exposure as well as its cumulative impact. Indeed, the impact of excess

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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weight on health outcomes might depend not only on its magnitude but also on its duration (5, 6), and the biological mechanisms mediating the effect of excess weight on health probably act through long-term processes such as chronic exposure to elevated insulin levels, chronic inflammation, and increased levels of estrogens in postmenopausal women (7).

Although the association between excess weight and cancer incidence is well established (8) and has been shown to be dose-dependent with increasing duration and intensity leading to higher risks (9, 10), its impact on the survival of patients with cancer is less clear. Previous studies demonstrated a detrimental effect of overweight and obesity on all-cause mortality and cancer-specific mortality in the general population (11–13); however, important questions remain concerning the impact of excess weight during adulthood on prognosis after a cancer diagnosis. In a recent study, we examined the association between excess weight during adulthood and survival in postmenopausal women with breast or colorectal cancer, two of the most commonly diagnosed cancers that have been causally related with body fatness. We found that the intensity and duration of excess weight were related to lower survival in breast cancer but not in patients with colorectal cancer (14). However, the size of the study population was limited so that our results needed to be confirmed.

In the present study, we conducted a pooled analysis of 5 prospective cohort studies with participants from 11 countries, enabling us to explore the association between excess weight during early to mid-adulthood, hereafter defined as the period between 20 and 50 years of age, and the survival of patients diagnosed with breast (women only) or colorectal cancer after the age of 50 years.

## Material and Methods

### Study design and participants

This study is part of the SurvPool project aiming to assess the cumulative impact of lifestyle-related risk factors, in particular overweight and obesity, on cancer incidence and mortality using data from international population-based prospective cohort studies (https://survival.iarc.fr/survpool/). Inclusion criteria were the availability of individual-level data on breast and colorectal cancer occurrence and mortality, demographic and lifestyle-related variables from the baseline questionnaire, as well as a minimum of two assessments of BMI (or separate assessments of height and weight) per study participant. The corresponding participant flow chart is shown in Supplementary Fig. S1.

Five cohorts that met these criteria were included: the Cancer Prevention Study II (CPS-II, data access was granted to the authors for breast cancer only; ref. 15); the European Prospective Investigation into Cancer and Nutrition (EPIC) study (16); the Japan Public Health Center-based Prospective Study, Cohort I (JPHC-I; ref. 17); the Japan Public Health Center-based Prospective Study, Cohort II (JPHC-II; ref. 17); and the Women's Lifestyle and Health (WLHS) study (18). A summary table of the characteristics of the included cohorts with 783,338 participants is presented in **Table 1**. The Institutional Review Board of each cohort as well as the International Agency for Research on Cancer Ethics Committee approved the study, which was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before participating in the respective cohort study.

### Identification and follow-up of cancer cases

Incident cases of invasive breast and colorectal cancer (respectively, codes C50 and C18-C20 of the International Classification of Diseases for Oncology, 3rd edition) and deaths were identified by active patient notification from major local hospitals and data linkage with population-based cancer registries or national death registries. In EPIC, for France, Germany, and Naples, Italy, a combination of methods was used to identify cases and vital status, including health insurance records, cancer and pathology registries, and an active follow-up of study participants. In CPS-II, deaths were identified based on linkages with the U.S. National Death Index.

### Statistical analyses

For each participating cohort, the impact of BMI on all-cause mortality in patients with cancer was assessed through a two-step approach: (14, 19) first, we used repeated BMI assessments to create individual-specific BMI trajectories among all cohort participants. Then, these trajectories were used to construct BMI-related variables reflecting cumulative exposure, which were subsequently used as predictors of death in individuals diagnosed with breast or colorectal cancer in survival models adjusted for potential confounding factors.

#### Cohort-specific BMI-related variables construction

For the first step, we used BMI values (computed from height and weight measurements or self-reports) taken at or after the age of 18 years and, subject to data availability, verifying the following criteria: height greater than 130 cm, BMI greater than 16 kg/m$^2$, and waist circumference between 40 and 160 cm. Individuals were included if they contributed at least two valid BMI assessments before the end of the study follow-up, death, or at most 1 year before a diagnosis of cancer, whichever came first.

We used a growth curve model to describe the trajectory of BMI as a function of age. More precisely, the BMI for individual $i$ assessed on occasion $j$, $\mathrm{BMI}_{ij}$, was modeled using the following equation:

$$\mathrm{BMI}_{ij} = (\alpha_0 + u_{0i}) + (\alpha_1 + u_{1i}) \cdot \mathrm{Age}_{ij} + \alpha_2 \cdot \mathrm{Age}_{ij}^2 + \varepsilon_{ij}$$

This model describes BMI as a quadratic polynomial function of age with random intercepts and slopes ($u_{0i}$ and $u_{1i}$, respectively) assumed to be multivariate normally distributed. In the EPIC study, the intercept as well as the linear and quadratic effects of age were allowed to vary between countries.

Using the estimates from the growth curve model, it was thus possible to construct for each individual a model-based BMI trajectory corresponding to a quadratic polynomial of age with individual-specific intercept and slope. These model-based BMI trajectories were then used to compute the average BMI during early and mid-adulthood (this cumulative measure corresponds to the area under the BMI trajectory from age 20 to 50 years divided by the length of the period, i.e., 30 years) and the time spent with overweight or obesity during early and mid-adulthood (defined as the interval of time between age 20 and 50 years during which the model-based BMI was equal to or greater than 25 kg/m$^2$). It should be noted that the average BMI between age 20 and 50, as a cumulative measure of excess weight, cannot be interpreted as a single BMI assessment, and consequently, as such this should not be directly interpreted or associated with the standard definitions of "overweight" and "obesity," based on BMI measured at a given point in time. Nonetheless, to allow comparison with studies using single point-in-time BMI, sensitivity analyses using the most recent prediagnostic BMI assessments obtained at least 1 year preceding cancer diagnosis were also performed. For analysis and presentation purposes, average BMI across this 30-year time span was then categorized into less or equal than 22.5 kg/m$^2$, greater than 22.5 kg/m$^2$and less or equal than 25 kg/m$^2$, and more than 25 kg/m$^2$,

**Table 1.** Characteristics of the cohorts included in the cohort consortium assessing the relationship between BMI and mortality in patients with breast and colorectal cancers.

| Study cohort | CPS-II Nutrition Survey | EPIC PANACEA | JPHC-I | JPHC-II | WLHS |
|---|---|---|---|---|---|
| **Country** | United States | Denmark, France, Germany, Italy, Norway, Spain, Sweden, the Netherlands, United Kingdom | Japan | Japan | Sweden |
| **Years of recruitment** | 1992–1993 | 1992–1999 | 1990 | 1993–1994 | 1991–1992 |
| **Age at recruitment, years** | 40–80 | 35–70 | 40–59 | 40–69 | 30–49 |
| **Original population size** | 184,194 | 450,112 | 43,140 | 56,634 | 49,258 |
| **Anthropometric assessments** | Height at baseline<br>Weight at baseline, in 1992, and every 2 years from 1997 to 2013 | Height at baseline<br>Weight at age 20 (18 for Norway), baseline, and at 5 years of follow-up | Height and weight at baseline, 5-year, and 10-year follow-up | Height at baseline, 5-year, and 10-year follow-up<br>Weight at age 20, baseline, 5 years, and 10 years of follow-up | Height at baseline<br>Weight at age 18, baseline, and 10 years of follow-up |
| **Population included for BMI trajectory estimation** | 78,936 | 389,123 | 38,611 | 52,478 | 33,031 |
| **Total number of BMI assessments (mean number per participant)** | 711,352 (9.01) | 920,241 (2.36) | 107,491 (2.78) | 174,694 (3.33) | 95,670 (2.90) |
| **Censoring date** | December 31, 2014 | December 12, 2013 | December 31, 2016 | December 31, 2016 | December 31, 2012 |
| **Cancer ascertainment** | Cancer and national death registries | Cancer registries (Denmark, Italy, Norway, Spain, Sweden, the Netherlands, United Kingdom), combination of methods in France; Germany; and Naples, Italy | Cancer registries and death certificates | Cancer registries and death certificates | Cancer and national death registries |

and time spent with overweight was categorized into never, less than or equal to 15 years, and more than 15 years.

### Cohort-specific time-to-event analyses

The second step was restricted to individuals diagnosed with breast (women only) or colorectal cancer after the age of 50 years and with information on vital status at the end of follow-up. The analysis was restricted to patients diagnosed after the age of 50 years so that the cumulative BMI-related variables for each participant could be defined on the same exposure window of 30 years. Follow-up time for each participant was defined from the date of cancer diagnosis to the date of death or end of follow-up (ranging between December 31, 2012, and December 31, 2016, depending on the cohort, see **Table 1**), whichever came first. We used Cox proportional regression models with time since diagnosis as the time scale. We adjusted for the following potential confounders of the association between excess weight and cancer survival assessed at study entry: smoking status, alcohol consumption, vigorous physical activity, education, and history of diabetes. All models were stratified on cancer stage at diagnosis (localized, regional, and distant tumor) and age at diagnosis (using 5-year age categories), and for the EPIC study, a further stratification on the country was made. Although each study was analyzed separately, we harmonized the definition of the adjusting and stratifying variables between cohorts in order to facilitate the analysis: The correspondence between the original and harmonized definitions can be found in Supplementary Table S1. The proportionality of hazards assumption for the other variables included in the model was tested using the Grambsch–Therneau test. When there was evidence of nonproportionality for some of the adjusting factors, these were introduced in the model as strata. The proportion of missing values in the adjusting factors considered in the model ranged from 12.4% (JPHC-I cohort) to 62.9% (EPIC cohort) for breast cancer and from 14.1% (JPHC-I cohort) to 72.3% (EPIC cohort) for colorectal cancer. High proportions of missing values in the EPIC study were largely due to missing information on stage at diagnosis. The distribution of the confounding factors, including missing values, in each cohort is shown in Supplementary Tables S2 to S6. Multiple imputation was used to account for missing values: For each combination of cancer- and BMI-related variable, 50 datasets were imputed using the multiple imputation by chained equations method (20), and results combined using Rubin's rule (21).

We also conducted survival analyses using the same procedure as above, but replacing the Cox proportional hazard model by a Weibull accelerated failure time model to provide time ratios that quantify how much faster individuals in a higher-risk group die compared with the unexposed group (22, 23). For example, if a given proportion of deaths is reached after time $t$ in the unexposed group, the same proportion of deaths will be reached after time $\alpha t$ in the group exposed to the risk factor, where $\alpha$ is the time ratio. This means that if the time ratio is smaller than 1, exposure to the risk factor will accelerate the occurrence of deaths, while a time ratio greater than 1 corresponds to a slowing down of death occurrence.

Finally, to allow comparison with previous studies, we also performed the above-mentioned analyses using a single BMI assessment (namely, the most recent BMI assessed at least 1 year before cancer diagnosis).

**Table 2.** Characteristics of patients with breast and colorectal cancer in the international cohort consortium according to cohort study and cancer types.

| Study (cohort) | Cases | Deaths | Person-years | Estimated average BMI during early and mid-adulthood[a] | Missing stage information, *N* (%) | Stage at diagnosis, *N* (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Localized | Regional | Distant |
| Breast cancer (women) | | | | | | | | |
| CPS-II | 5,292 | 1,802 | 56,135 | 22.8 (21.5–24.6) | 63 (1.2) | 3,963 (75.8) | 1,170 (22.4) | 96 (1.8) |
| EPIC | 9,171 | 1,414 | 69,767 | 22.5 (20.8–24.3) | 3,921 (42.8) | 3,651 (69.6) | 1,414 (26.9) | 185 (3.5) |
| JPHC-I | 363 | 89 | 3,263 | 22.5 (20.8–24.2) | 25 (6.9) | 215 (63.6) | 102 (30.2) | 21 (6.2) |
| JPHC-II | 383 | 115 | 2,948 | 22.9 (21.6–24.2) | 48 (12.5) | 203 (60.6) | 112 (33.4) | 20 (6.0) |
| WLHS | 863 | 65 | 5,342 | 22.1 (20.9–23.5) | 275 (31.9) | 342 (58.2) | 234 (39.8) | 12 (2.0) |
| Colorectal cancer (women) | | | | | | | | |
| EPIC | 2,635 | 1,025 | 14,580 | 23.0 (21.5–25.0) | 1,371 (52.0) | 555 (43.9) | 271 (21.4) | 438 (34.7) |
| JPHC-I | 402 | 146 | 2,714 | 22.4 (20.7–24.2) | 48 (11.9) | 154 (43.5) | 143 (40.4) | 57 (16.1) |
| JPHC-II | 494 | 234 | 3,155 | 22.9 (21.9–24.1) | 81 (16.4) | 203 (49.1) | 135 (32.7) | 75 (18.2) |
| WLHS | 177 | 40 | 688 | 22.3 (21.3–23.8) | 63 (35.6) | 24 (21.0) | 62 (54.4) | 28 (24.6) |
| Colorectal cancer (men) | | | | | | | | |
| EPIC | 2,029 | 943 | 10,617 | 25.1 (23.6–26.9) | 1,185 (58.4) | 436 (51.7) | 135 (16.0) | 273 (32.3) |
| JPHC-I | 567 | 302 | 3,634 | 22.8 (21.3–24.7) | 60 (10.6) | 248 (48.9) | 149 (29.4) | 110 (21.7) |
| JPHC-II | 754 | 416 | 4,718 | 23.2 (22.1–24.4) | 99 (13.1) | 355 (54.2) | 205 (31.3) | 95 (14.5) |

[a]Median (25th–75th percentiles).

### Pooled analysis

The cohort-specific results were pooled through a random effect model (24, 25). As described above, multiple imputation for covariates was performed at the study level, before aggregating the results, as suggested by Burgess and colleagues (26).

All analyses were performed using R statistical software (version 3.6.0; R Development Core Team, 2019).

## Results

A total of 592,179 cohort participants contributing 2,009,448 BMI assessments were included in the estimation of cohort-specific BMI trajectories across time. The pooled analysis included data on 16,072 women diagnosed with breast cancer, as well as 3,350 men and 3,708 women diagnosed with colorectal cancer at the age of 50 years or above. In patients with breast cancer, 3,485 deaths were observed during 137,455 person-years, and in patients with colorectal cancer, 3,106 deaths were observed during 40,106 person-years (**Table 2**). The median value of average BMI between ages 20 and 50 years among women diagnosed with breast cancer ranged from 22.1 kg/m$^2$ in the WLHS cohort to 22.9 kg/m$^2$ in the JPHC-II cohort. Among patients diagnosed with colorectal cancer, the median value of average BMI between ages 20 and 50 years ranged from 22.3 kg/m$^2$ in the WLHS cohort to 23.0 kg/m$^2$ in the EPIC cohort for women, and from 22.8 kg/m$^2$ in the JPHC-I cohort to 25.1 kg/m$^2$ in the EPIC cohort for men (see **Table 2**). A large proportion of patients with breast cancer was diagnosed with localized breast cancer (between 58.2% and 75.8%), while for colorectal cancer, these proportions varied from 21.0% to 49.1% for women and between 48.9% and 54.2% for men.

The pooled HRs by BMI groups and stratified by stage at diagnosis and age group are presented in **Figs. 1** to **3**. Among women diagnosed with breast cancer after the age of 50 years, the pooled HR increased in a dose-response manner ($P$ trend = 0.01) in patients who experienced a higher average BMI during early and mid-adulthood: 1.13 [95% confidence interval (CI), 0.99–1.29) in the category of average BMI between 22.5 and 25 kg/m$^2$; and 1.32 (95% CI, 1.08–1.60) in the category of average BMI greater than 25 kg/m$^2$ (**Fig. 1A**). A significant dose–response relationship ($P$ trend = 0.011) was also found when we investigated the time spent with excess weight during early or mid-adulthood and its impact on death among patients with breast cancer. Compared with women who were never in excess weight, women with less than 15 years with excess weight had an HR of 1.10 (95% CI, 0.96–1.26) of dying and reached 1.26 (95% CI, 1.04–1.51) for women who spent more than 15 years with excess weight (**Fig. 1B**).

Among women diagnosed with colorectal cancer after the age of 50 years, there was no significant dose–response association between mean BMI during early and mid-adulthood and mortality (**Fig. 2A**). Likewise, no significant association was found for time spent with excess weight during early and mid-adulthood (**Fig. 2B**). For men diagnosed with colorectal cancer after the age of 50 years, there was also no significant dose–response association between average BMI during early and mid-adulthood and time spent with excess weight and mortality (**Fig. 3**).

Similar results were obtained when we used accelerated failure time models (see Supplementary Figs. S2–S4). The pooled time ratios for women diagnosed with breast cancer after the age of 50 years showed a significant dose–response effect for average BMI during early and mid-adulthood ($P$ trend = 0.032), as well as for time spent with excess weight ($P$ trend < 0.001). The time ratio for women in the category of average BMI in early and mid-adulthood greater than 25 kg/m$^2$ compared with the reference category was 0.84 (95% CI, 0.73–0.96), and the time ratio for women who spent more than 15 years with excess weight during early and mid-adulthood was 0.85 (95% CI, 0.78–0.93), indicating that time to death was shortened by up to 15% in these groups when compared with their reference. For colorectal cancer, we found no significant association between the BMI-related variables and mortality among men or women.

Results obtained when using a single BMI assessment were qualitatively similar (Supplementary Figs. S5–S7). In particular, BMI was found to have a significant detrimental effect on survival in women diagnosed with breast cancer ($P$ trend = 0.001), although HRs were of lower magnitude than those based on the average BMI during early and mid-adulthood: 0.97 (95% CI, 0.89–1.06) in the category of BMI between 22.5 and 25 kg/m$^2$; and 1.18 (95% CI, 1.07–1.30) in the category of average BMI greater than 25 kg/m$^2$ (Supplementary Fig. S5A).

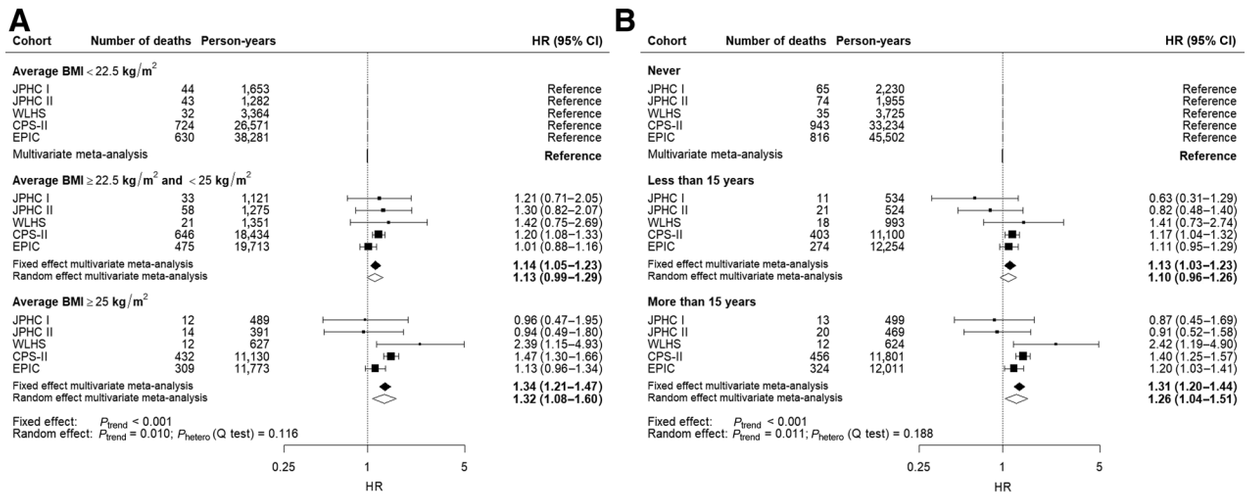


**Figure 1.**

Cohort-specific and pooled effect (measured in terms of HRs) of mortality among women diagnosed with breast cancer after the age of 50 years (**A**) by categories of average BMI and (**B**) by categories of cumulative time spent with overweight (BMI ≥ 25 kg/m$^2$) during early and mid-adulthood. The model was adjusted for smoking status, alcohol consumption, vigorous physical activity, education, and history of diabetes at study entry, and stratified on cancer stage at diagnosis, age at diagnosis, and country (for the EPIC study only).

## Discussion

In this study, we provide novel evidence on the impact of prediagnostic excess weight duration during early and mid-adulthood on mortality in patients diagnosed with breast and colorectal cancer after the age of 50, based on a pooled analysis from an international cohort consortium. We found that an average BMI greater than 25 kg/m$^2$ during early and mid-adulthood and more than 15 years spent with excess weight between age 20 and 50 years were positively associated with mortality in women diagnosed with breast cancer. The time to death after a breast cancer diagnosis was shortened by up to 15% in a dose–response manner for women with an average BMI greater than 25 kg/m$^2$ compared with women with an average BMI lower than 22.5 kg/m$^2$ during early and mid-adulthood. For colorectal cancer, we found no statistically significant evidence for a positive association between cumulative measures of excess weight duration and mortality. These findings reinforce public health recommendations for preventing overweight and obesity at any age.

The relationship between excess weight and the survival of patients with cancer has already been the subject of several studies (27–29). A meta-analysis on the effect of obesity on survival of women diagnosed with breast cancer (27) showed a poorer overall and disease-specific

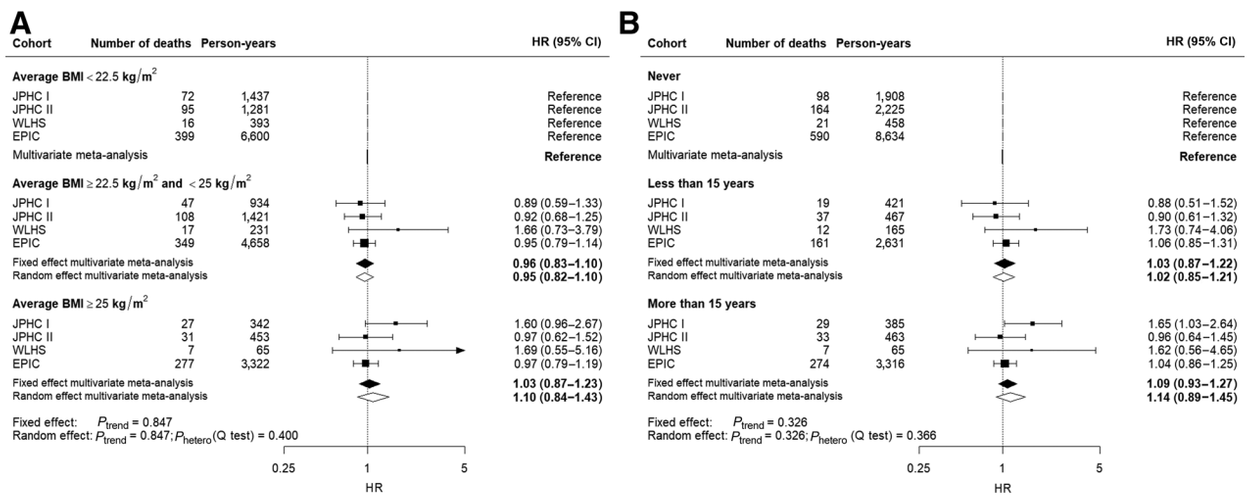


**Figure 2.**

Cohort-specific and pooled effect (measured in terms of HRs) of mortality among women diagnosed with colorectal cancer after the age of 50 years (**A**) by categories of average BMI and (**B**) by categories of cumulative time spent with overweight (BMI ≥ 25 kg/m$^2$) during early and mid-adulthood. The model was adjusted for smoking status, alcohol consumption, vigorous physical activity, education, and history of diabetes at study entry, and stratified on cancer stage at diagnosis, age at diagnosis, and country (for the EPIC study only).

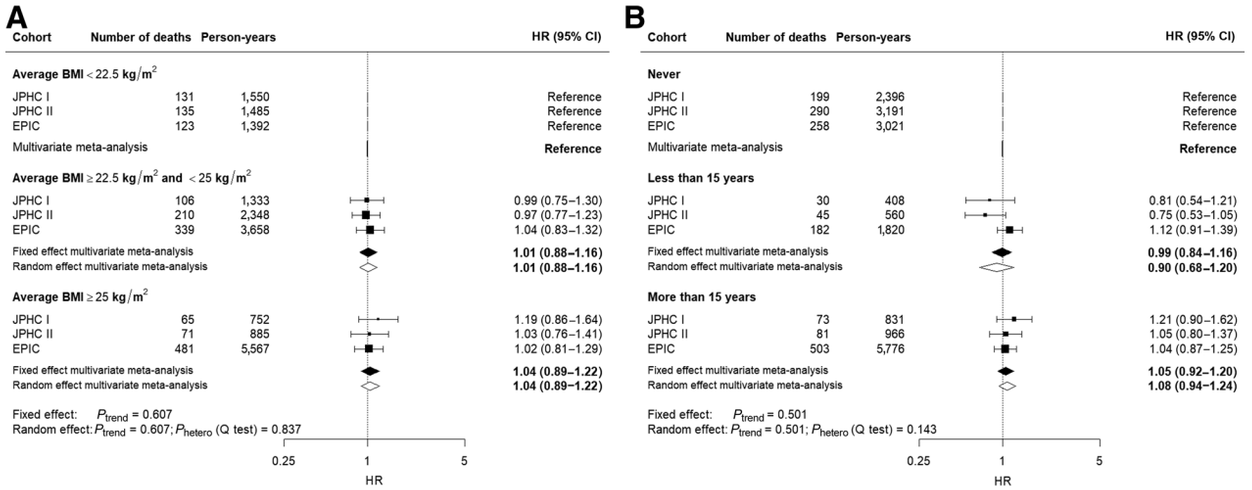


**Figure 3.**

Cohort-specific and pooled effect (measured in terms of HRs) of mortality among men diagnosed with colorectal cancer after the age of 50 years (**A**) by categories of average BMI and (**B**) by categories of cumulative time spent with overweight (BMI ≥ 25 kg/m$^2$) during early and mid-adulthood. The model was adjusted for smoking status, alcohol consumption, vigorous physical activity, education, and history of diabetes at study entry, and stratified on cancer stage at diagnosis, age at diagnosis, and country (for the EPIC study only).

survival of obese women with HRs of 1.33 (95% CI, 1.21–1.47) and 1.33 (95% CI, 1.19–1.50), respectively. In another meta-analysis by Chan and colleagues (28), women diagnosed with breast cancer who were overweight or obese before cancer diagnosis had a relative risk of 1.07 (95% CI, 1.02–1.12) and 1.41 (95% CI, 1.29–1.53), respectively, for dying compared with the reference group of normal weight women. When looking at breast cancer–specific mortality, the relative risk estimates for overweight and obese women were 1.11 (95% CI, 1.06–1.17) and 1.35 (95% CI, 1.24–1.47), respectively. For colorectal cancer, a meta-analysis showed poorer overall and cancer-specific survival of obese patients with HRs of 1.14 (95% CI, 1.07–1.21) and 1.14 (95% CI, 1.05–1.24), respectively, but no association with overweight (29). These results were based on single BMI assessments before diagnosis; hence, they are not completely comparable with those of the present study. However, they support our finding of a negative impact of excess weight on breast cancer prognosis.

A number of mechanisms have been postulated to be responsible for the association between excess weight and cancer development (30–34). However, the association between excess weight and survival of patients with cancer is less well understood. From a general point of view, there are three broad classes of hypotheses that might explain the role of excess weight on the survival of patients with cancer.

First, excess weight has been associated with an increased tumor size, higher tumor grades, and an increased risk of metastasis (35). Consequently, the poor survival of overweight patients with cancer might be partly explained by tumor characteristics at diagnosis, and these might be caused by biological mechanisms similar to those associated with cancer incidence. Indeed, it has been shown that excess body fatness affects several signaling pathways associated with dysregulated cell growth and inhibition of apoptosis, resulting in more aggressive tumors (36). In particular, overweight is associated with insulin resistance, and subsequent increase in levels of insulin and free (unbound) insulin-like growth factor-1 (IGF-1) is associated with tumor growth and inhibition of apoptosis of micrometastases, resulting in poorer survival, particularly for breast and colorectal cancers (37, 38). Adipose tissue also stimulates the production of inflammatory factors such as IL6, IL1$\beta$, and TNF$\alpha$, and inhibits apoptosis (39). Increased levels of estrogens due to excess weight in postmenopausal women may also play a role (7). Yet, in the present study, we found an effect of excess weight on survival even after stratifying the analyses on stage at diagnosis, suggesting that tumor characteristics are not the only mediator of poor survival of patients with cancer with excess weight.

Second, excess weight is also known to be associated with several comorbidities such as diabetes or cardiovascular diseases which might further increase the risk of dying among patients with cancer. It has indeed recently been shown that specific adverse lifestyle factors, including excess weight, are associated with an increased risk of multimorbidity of cancer and cardiovascular diseases (40), suggesting that the effect of excess weight on survival of patients with cancer is indirectly mediated by these. With the exception of past history of diabetes mellitus, information on comorbidities such as cardiovascular diseases was not available from all included cohorts and therefore could not be accounted for in the analyses. Similarly, cause of death information was not consistently available across cohorts, meaning that it was not possible to analyze cause-specific mortality.

Third, another mechanism that might explain our results is the fact that excess weight might influence the choice of treatment, and consequently, there might be an increased risk of adverse consequences of cancer treatment in patients with excess weight (41). For example, severe obesity might contraindicate surgery and complicate the adjustment of chemotherapeutic treatment doses in overweight patients, potentially leading to suboptimal therapeutic concentrations and increased dose-related adverse effects such as cardiotoxicity (42, 43). Moreover, obese patients with reduced mobility might experience a higher risk of thrombosis and pulmonary complications such as pulmonary embolism and pneumonia after surgery (44, 45).

Although the above-mentioned mechanisms point to general explanations of the association between excess weight and survival in patients with cancer, it should be noted that in our study, we found no significant association between excess weight and survival for patients with colorectal cancer. A subgroup analysis restricted to patients with colon cancer only equally showed a lack of association

between excess weight and survival. It is possible that the association between excess weight and survival in patients with colorectal cancer is weaker than that for breast cancer. Indeed, in the meta-analysis by Doleman and colleagues (29), the association was limited to obese patients, with no significant effect for overweight patients, contrary to results for breast cancer (27, 28).

Our study has several strengths. First, by using data from five cohorts spanning three continents, we were able to assess the association between lifetime BMI and death in patients with cancer using a large-scale database, including exposure information from close to 600,000 study participants at over 2 million occasions and follow-up for all-cause death from over 23,000 breast and colorectal cancer survivors. Second, as opposed to previous studies with only baseline BMI, we assessed lifetime overweight using multiple assessments of body weight across adulthood and modeled BMI trajectories, which were then translated into indicators summarizing cumulative exposure such as time spent overweight and average BMI during early and mid-adulthood. Moreover, by defining average BMI between ages 20 and 50 years and looking at cancer cases that occurred after the age of 50 years, we ensured that the exposure was defined in a uniform way across subjects and was not conditional on the age at cancer diagnosis.

Also, we presented two different measures to express the impact of lifetime overweight on survival in patients with cancer. Although they represent the most standard way of assessing the impact of risk factors in time-to-event analyses, HRs quantify how exposure to the risk factor modifies the mortality hazard rate, an instantaneous conditional probability. As such, they cannot be easily interpreted on the absolute risk scale, i.e., in terms of probabilities of survival at a given time. They consequently have a limited interest in clinical practice (46). Time ratios derived from accelerated failure time models provide an altogether different measure of impact of the risk factor: They quantify by how much the time until occurrence of the event is shortened (time ratio below 1) or prolonged (time ratio above 1) compared with the reference group (22). In this study, both approaches provided consistent and complementary results.

However, we also note some limitations. First, as frequent and regular BMI assessments during follow-up and for all years of age of all cohort participants are generally unavailable, we needed to use modeling procedures to estimate cumulative BMI-related variables. We mitigated the uncertainty by limiting our study to participants with information on BMI (or body height and weight) on at least two occasions before cancer diagnosis. Previous studies on the impact of lifetime excess weight on cancer risk showed that this is a robust methodology that allows for important insights into this relationship (9, 10). The self-reported (prospective and retrospective) assessments may have led to an underestimation of true BMI in overweight individuals contributing to some exposure misclassification, resulting in potential bias in our risk estimates. Second, as corresponding data were unavailable, we were unable to investigate associations across cancer-specific subgroups, for example by hormone receptor status for breast cancer or by tumor microsatellite instability status. Third, a large degree of heterogeneity existed between studies, particularly when comparing the Japanese cohorts with their U.S. and European counterparts. Although this may partly be driven by differences in sample size, it needs to be taken into account when interpretating the results. Although different cutoff points to define overweight have been suggested for Asian populations, for the purpose of international comparisons, we retained the traditional definitions of overweight and obesity (47). For the same reason, the impact of social determinants of health, such as socioeconomic status, could not be explored in this study. Last, the evidence of an association between excess weight, used as a proxy for body fatness, and survival in patients with cancer presented in this study is based only on BMI assessments. These are subjects to measurement error, especially as in most cohort, some of the BMI assessments were based on retrospectively self-reported measures. Moreover, BMI is an imperfect indicator of body fatness. In particular, the relationship between the percentage of body fat and BMI varies with age, sex, and ethnicity (48), and it might not appropriately reflect metabolic functions (41). This emphasizes the need to develop combined indicators taking account of various aspects of body fatness (BMI, waist and hip circumference, or quantification of the volume of adipose compartments based on imaging; ref. 41) in order to better understand the complex biological mechanisms between adiposity and survival of patients with cancer.

To our knowledge, this is the first large-scale study on the effects of excess weight in early and mid-adulthood on the survival of patients with breast and colorectal cancers. It highlights the negative impact of excess weight and time spent with excess weight before the age of 50 on the risk of dying among women diagnosed with breast cancer after the age of 50 years. These results emphasize the importance of public health policies aimed at preventing excess weight early in life. Future work should aim to understand in more detail how overweight and obesity are related to the prognosis of cancer, including the impact of postdiagnostic weight change and disentangling its complex relationships with treatment, comorbidities, and across cancer subtypes.

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## Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

## Authors' Contributions

**H. Charvat:** Formal analysis, validation, visualization, methodology, writing–original draft, writing–review and editing. **H. Freisling:** Conceptualization, formal analysis, supervision, methodology, writing–original draft. **H. Noh:** Methodology, writing–original draft. **M.M. Gaudet:** Data curation, writing–review and editing. **M.J. Gunter:** Writing–review and editing. **A.J. Cross:** Writing–review and editing. **K.K. Tsilidis:** Writing–review and editing. **A. Tjønneland:** Data curation, writing–review and editing. **V. Katzke:** Writing–review and editing. **M. Bergmann:** Writing–review and editing. **C. Agnoli:** Writing–review and editing. **C. Rylander:** Writing–review and editing. **G. Skeie:** Writing–review and editing. **P. Jakszyn:** Writing–review and editing. **A.H. Rosendahl:** Writing–review and editing. **M. Sund:** Writing–review and editing. **G. Severi:** Writing–review and editing. **S. Tsugane:** Writing–review and editing. **N. Sawada:** Writing–review and editing. **H. Brenner:** Writing–review and editing. **H.-O. Adami:** Writing–review and editing. **E. Weiderpass:** Writing–review and editing. **I. Soerjomataram:** Conceptualization, resources, supervision, investigation, methodology, writing–original draft, writing–review and editing. **M. Arnold:** Conceptualization, resources, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing.

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