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Associations between cardiometabolic comorbidities and mortality in adults with cancer: multinational cohort study

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ABSTRACT

OBJECTIVE To examine separate and joint associations between pre-existing cardiometabolic comorbidities and all cause and cause specific mortality in adults with cancer.

DESIGN Multinational cohort study.

SETTING Seven European countries from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 1 January 1992 to 31 December 2013.

PARTICIPANTS 26 987 participants (54% women) who developed a first primary cancer. 2113 had a history of type 2 diabetes, 1529 had a history of cardiovascular disease, and 531 had a history of both, at the time of diagnosis of cancer.

MAIN OUTCOME MEASURES Hazard ratios (95% confidence intervals, CIs) for associations between pre-existing cardiometabolic comorbidities and all cause and cause specific mortality in adults with cancer, estimated with multivariable Cox regression models. Associations were also estimated by groups of five year relative survival of cancer (survival ≤40%, 40-80%, and ≥80%) according to Surveillance, Epidemiology, and End Results (SEER) statistics, and for the most common site specific cancers.

RESULTS At the time of diagnosis of cancer, 84.5% (n=22 814) of participants had no history of a cardiometabolic disease, 7.8% (n=2113) had a history of type 2 diabetes, 5.7% (n=1529) had a history of cardiovascular disease, and 2.0% (n=531) had a history of both cardiovascular disease and type 2 diabetes. 12 782 deaths (10 492 cancer deaths) occurred over a mean follow-up period of 7.2 years. After multivariable adjustments, pre-existing comorbidities were positively associated with all cause mortality, with hazard ratios 1.25 (95% CI 1.17 to 1.34), 1.30 (1.21 to 1.39), and 1.60 (1.42 to 1.80) for participants with type 2 diabetes, cardiovascular disease, or both, respectively, compared with participants with no cardiometabolic comorbidity. Corresponding hazard ratios for cancer specific mortality were 1.13 (95% CI 1.05 to 1.22), 1.13 (1.04 to 1.23), and 1.33 (1.16 to 1.53), respectively. Associations for all cause mortality were stronger among participants with cancers with a five year relative survival ≥80%. In a subsample, duration of type 2 diabetes ($P_{interaction}$=0.73) or cardiovascular disease ($P_{interaction}$=0.24), categorised as <5 years or ≥5 years, did not modify associations between these comorbidities and all cause mortality.

CONCLUSIONS In this study, cardiovascular disease or type 2 diabetes, or a combination of both, before a diagnosis of cancer, was associated with increased mortality (all cause mortality, and cancer and cardiovascular disease specific mortality). These findings support a direct role of cardiometabolic comorbidities on the prognosis of cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A history of comorbidity in adults with cancer has been consistently associated with reduced overall survival and, less consistently, with cancer specific survival

⇒ Comorbid conditions are often grouped into comorbidity indexes or counts, which conceal how specific conditions might affect cancer survival differently or whether comorbid conditions interact in their association with cancer survival

WHAT THIS STUDY ADDS

⇒ The findings suggest that adults with cancer who had a history of type 2 diabetes or cardiovascular diseases, or both, had a survival disadvantage compared with those with no history of these comorbidities

⇒ This survival disadvantage was also seen for less common cancers, such as brain, stomach, ovarian, and bladder cancers

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Clinicians treating people with cancer are encouraged to optimally manage cardiometabolic comorbidities

⇒ Further research on effectively converting the study's findings into practical benefits for patients with cancer with cardiometabolic comorbidities would be valuable

Introduction

The proportion of adults in the general population with multiple long term chronic conditions is rising rapidly,[1] and >50% of adults with cancer have at least one other chronic condition.[2–4] Coexistence of disorders in the presence of a primary disease, such as cancer, is defined as comorbidity.[5] Comorbidity at the time of a diagnosis of cancer is often associated with a compromised health status and reduced quality of life,[6 7] and has practical implications for

clinical care, such as complicating the choice of cancer treatment or increasing the risk of readmission to hospital.[5 8]

The most common comorbid conditions at the time of diagnosis of cancer are cardiovascular diseases and type 2 diabetes.[4] In an umbrella review of meta-analyses, type 2 diabetes was associated with an increased risk of death from cancer,[9] but heterogeneity between studies was high and the relation was unclear for most cancer types. A recommendation was that future studies should account for stage of cancer at diagnosis, investigate cause specific mortality, and consider type 2 diabetes (and cardiovascular disease) identified during follow-up in prospective designs to avoid misclassification of comorbidity status.[9–11] Similarly, a history of cardiovascular diseases, such as myocardial infarction or stroke, could affect survival in individuals with cancer, especially among older patients with cancer where mortality related to cardiovascular disease can be higher than cancer mortality.[12]

Previous studies focused on patients with cancer in hospital settings with a primary diagnosis of cardiovascular disease, or cancer as a risk factor for death from cardiovascular disease.[13–15] Other gaps in this area are links between a history of type 2 diabetes or cardiovascular disease and cancer survival that might depend on the type of cancer or the prognosis of cancer.[5] Another question relates to the effect of type 2 diabetes or cardiovascular disease on cancer specific mortality and other specific causes of death. In the Women's Health Initiative cohort,[15] a history of type 2 diabetes was positively associated with both cardiovascular disease specific and cancer specific deaths.[16] Furthermore, the time interval (duration) between the occurrence of a comorbidity and a diagnosis of cancer has rarely been investigated. This information could be important, as shown in a cohort study where new onset diabetes was associated with an increased risk of pancreatic cancer death, whereas diabetes of longer duration (≥2 years) was not.[17]

The objective of this study was to investigate separate and joint associations between a history of type 2 diabetes and cardiovascular disease at the time of diagnosis of cancer and all cause and cause specific mortality. We also aimed to examine effect modification of the associations with duration of cardiometabolic comorbidities, and investigated these relations by site specific cancers and by groups of cancers based on their five year relative survival.

Methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a population based, multinational prospective cohort study, carried out in 23 centres across 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK). More than 520 000 participants (70% women), mostly aged 35-70 years, were recruited between 1992 and 2000 and have been followed up for cancer events, type 2 diabetes, cardiovascular disease, and mortality status.[18–20] The study populations were samples of convenience and were recruited from the general population with a few exceptions. In France, Norway, Utrecht (the Netherlands), and Naples (Italy), only women were recruited. In France, state school employees were recruited. Centres in Utrecht and Florence (Italy) included women attending a local population based breast cancer screening programme. Some centres in Italy and Spain recruited members of local blood donor associations. In Oxford (UK), half of the cohort were participants following a lacto-ovo vegetarian or vegan diet.[18]

For our analysis, we excluded participants from France, Greece, and Norway, because incident events of type 2 diabetes or cardiovascular disease, or both, were not determined in these countries (n=140 284). We also excluded participants with a missing lifestyle questionnaire at baseline (n=6360), missing information on type 2 diabetes status (n=56 986), missing date of diagnosis of incident type 2 diabetes or cardiovascular disease, or both (n=101), missing end of follow-up date (n=1774), prevalent cancers at recruitment (n=13 042), and participants without a first primary cancer diagnosis (n=288 831). After all exclusions, 26 987 participants were available for analysis (online supplemental figure 1). Data for sex were taken from information in the EPIC study rather than from patient reported gender.

Identifying first primary cancers

The incident primary cancer was established based on ICD-10 (international classification of diseases, 10th revision) and ICD-O-3 (international classification of diseases for oncology, third revision) codes, excluding non-melanoma skin cancer and in situ tumour histology. Incident cancers were identified through linkage of the EPIC cohort with cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden, and the UK, and a combination of health insurance records, cancer pathology registries, and active follow-up in Germany.[18] Tumour stage at diagnosis was categorised as localised, advanced (regional or distant metastatic cancer combined because this distinction was unavailable for 30% of advanced cancers), or no staging (staging was missing for 100% of participants in the Netherlands and for 33% in all other countries).

Identifying type 2 diabetes and cardiovascular disease

Diagnoses of type 2 diabetes (ICD-10, E11) were identified from multiple sources across different centres, including self-report, linkage to primary care registers, secondary care registers, drug treatment use

(drug registers), hospital admission, and mortality data.[19] Incident cardiovascular disease events (non-fatal or fatal coronary heart disease or stroke) were defined by codes 410-414 and 430-438 of ICD-9 (international classification of diseases, ninth revision) and codes I20-I25 and I60-I69 of ICD-10, and were identified by active follow-up through questionnaires, medical records, hospital morbidity registers, contact with medical professionals, retrieving and assessing death certificates, or verbal autopsy, as detailed previously.[20] Type 2 diabetes and cardiovascular disease were independently determined by trained medical staff. Prevalent type 2 diabetes and cardiovascular disease events were identified with self-reported questionnaires at recruitment.[21] No information on the duration of disease was available for these patients with prevalent disease.

Mortality outcomes and follow-up

Death was the primary endpoint in this study. Information on the cause and date of death was established from record linkages with cancer registries, boards of health, and death indices in Denmark, Italy, the Netherlands, Spain, Sweden, and the UK, or from active follow-up (enquiries by mail or telephone to municipal registries or regional health departments or to physicians or hospitals) in Germany. The end of follow-up of participants was from December 2009 to December 2013 for countries with record linkage and to the last known contact with participants in Germany (December 2009). Loss to follow-up was low (1.5%).[21] ICD-10 codes were used to classify the underlying cause of death grouped into common causes: cancer (C00-D48), circulatory system or cardiovascular death (I00-I99), and other cause of death (non-C00-D48 or I00-I99).

Covariates

Data on sociodemographic characteristics, lifestyle behaviours, and reproductive and medical history were collected at recruitment with questionnaires.[21] Information on habitual diet was collected by validated country or centre specific dietary questionnaires at recruitment[21] and used to estimate total energy intake (kcal/day), alcohol intake (g/day), and the components of the Mediterranean diet score (range 0-18 units).[22] Height and weight were measured at recruitment with a standardised protocol; in the Oxford centre, height and weight were self-reported. Body mass index was calculated and categorised as <25, 25-<30, and ≥30. Self-reported menopausal status was categorised as premenopausal, perimenopausal, or postmenopausal. If data were incomplete, women aged ≥55 years at recruitment were classified as postmenopausal. History of hypertension at recruitment (no, yes, or unknown) was determined based on a combination of medical history, measurements by trained health professionals at recruitment (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both), or self-reported information of receiving antihypertensive treatment.[23]

Statistical analysis

Cardiometabolic disease status was modelled with a four level categorical variable as no cardiometabolic comorbidity (reference), type 2 diabetes, cardiovascular disease, and type 2 diabetes with cardiovascular disease. Kaplan-Meier curves for overall survival according to pre-existing cardiometabolic comorbidities were estimated. The survival time scale was from the date of a diagnosis of cancer until the date of death or censoring. Kaplan-Meier curves were also grouped by age at cancer diagnosis, stage at cancer diagnosis, smoking status at baseline, and five year relative survival of the diagnosed cancer (survival <40%, 40-80%, and ≥80%) according to the Surveillance, Epidemiology, and End Results (SEER) statistics (online supplemental table 1).[24] Because the sample size for specific analyses of cancer type was limited for many cancers, we grouped cancers by five year relative survival to account for survival differences.

Cox proportional hazard regression was used to estimate hazard ratios and 95% confidence intervals (CIs) for overall mortality and cause specific mortality associated with pre-existing cardiometabolic comorbidities. Because we were interested in answering an aetiological question, we implemented cause specific hazard models rather than a subdistribution hazard model, which is more appropriate for clinical prediction.[25] Follow-up time was from the date of diagnosis of the first incident cancer until death or censoring date.

The multivariable models were grouped by age at recruitment (five year categories), country, smoking status (never, former, current smoking, and unknown), stage at cancer diagnosis, and categories of five year relative survival of the diagnosed cancer according to SEER, and adjusted for sex (men, women), educational level (none, primary school, technical or professional school, secondary school, university, or unknown), alcohol intake (continuous, g/day), total energy intake (continuous, kcal/day), Mediterranean diet score (continuous, units), physical activity (inactive, moderately inactive, moderately active, active, or unknown),[26] body mass index (continuous), hypertension (yes, no, or unknown), menopausal status (premenopause, perimenopause, postmenopause, or men), and hormone treatment (no, yes, unknown, or men).

We assumed linearity in associations between continuous covariates and outcomes. Missing values in any of the categorical covariates were treated as a separate category. Confounder adjustment was based on previous knowledge, as depicted in a directed acyclic graph (online supplemental figure 2). For analyses on cause specific mortality, participants who died from a cause other than the one

under study were censored at the date they died. The proportional hazards assumption was tested with Schoenfeld residuals and was met.

To test for multiplicative interaction between type 2 diabetes and cardiovascular disease associated with mortality outcomes, we modelled both type 2 diabetes and cardiovascular disease as binary indicators (no/yes) with a multiplicative term (type 2 diabetes×cardiovascular disease) and mutual adjustment. Effect modification by duration of type 2 diabetes or cardiovascular disease on associations with all cause mortality was investigated by comparing a model with, in turn, type 2 diabetes (no/yes) and cardiovascular disease (no/yes), with a model where the time difference between the date of diagnosis of incident type 2 diabetes or cardiovascular disease and the cancer diagnosis was categorised as no type 2 diabetes or cardiovascular disease, <5 years, and ≥5 years. Participants with prevalent cardiovascular disease or type 2 diabetes (at recruitment) were excluded from this analysis because information on duration of disease was not available.

Predefined subgroup analyses were carried out by sex, age at cancer diagnosis, educational level, smoking status, categories of body mass index, five year relative survival of cancer, and stage of cancer at diagnosis. All multiplicative interaction models were evaluated with a likelihood ratio test comparing the log difference of the models with and without multiplicative interaction terms between comorbidity status and the potential effect modifier to a χ^2 distribution with df equal to the number of terms.

In sensitivity analyses: we only included incident type 2 diabetes or cardiovascular disease events to evaluate bias caused by misclassification of self-reported type 2 diabetes or cardiovascular disease at recruitment and caused by covariates being affected by cardiovascular disease or type 2 diabetes; we excluded participants with missing covariate information (complete case analysis) to evaluate the validity of using a missing value indicator (cancer stage at diagnosis was not missing at random, which is why we did not consider multiple imputation); we computed E values, which are defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the variable and the outcome to fully explain the observed associations[27]; we adjusted for type of cancer at diagnosis instead of five year relative survival of cancer to evaluate residual confounding by type of cancer; and we adjusted for waist circumference (four categories of sex specific values), which reflects central adiposity, instead of body mass index. All tests were two sided, and P values were considered significant if <0.05. Statistical analyses were performed with Stata/MP 15.1 software (College Station, TX).

Patient and public involvement

This study used pseudo-anonymised data, and hence we had no means of contacting the study participants. Participants of this study were therefore not involved in this research. We intend to engage the public to disseminate the results of our study through the cohort's website (https://epic.iarc.fr/) and the media center of the International Agency for Research on Cancer (https://www.iarc.who.int/).

Results

Characteristics of study population

We included in our study 26 987 participants (54% women) with a first primary incident cancer. Mean age at recruitment and the proportion of men were higher in this cancer subsample than in the overall EPIC cohort: 56.9 years verus 51.4 years and 46% versus 40%, respectively. The distribution for educational level was more similar (eg, 18% *v* 21% had a university degree). The prevalence of cancer in the EPIC cancer subsample (online supplemental table 1) was similar to cancer occurrence in Europe, and cancers of the breast, colon and rectum, lung, and prostate showed the highest age standardised incidence in 2012.[28]

At the time of diagnosis of cancer, mean age of participants was 63.5 (standard diviation 8.4) years. We found that 84.5% (n=22 814) of participants had no history of a cardiometabolic disease, 7.8% (n=2113) had a history of type 2 diabetes, but no cardiovascular disease, 5.7% (n=1529) had a history of cardiovascular disease, but no type 2 diabetes, and 2.0% (n=531) had a history of both cardiovascular disease and type 2 diabetes. Table 1 shows the characteristics of participants at cancer diagnosis according to pre-existing cardiometabolic comorbidities.

Cardiometabolic comorbidities and all cause mortality

We estimated all cause mortality and found that 12 782 deaths occurred after a median follow-up of 7.2 years (interdecile range 0.4-14.5). In unadjusted analyses (figure 1), survival was highest among those with no pre-existing cardiometabolic comorbidities; survival was gradually reduced for those with type 2 diabetes, cardiovascular disease, and both type 2 diabetes and cardiovascular disease (P<0.001, log rank test for overall comparison between the four groups). This trend was replicated in all analyses by subgroups of stage of cancer at diagnosis, five year relative survival of the cancer, age, and smoking status (online supplemental figure 3).

In multivariable adjusted Cox models (figure 2), pre-existing comorbidities were positively associated with all cause mortality, with hazard ratios 1.25 (95% CI 1.17 to 1.34), 1.30 (1.21 to 1.39), and 1.60 (1.42 to 1.80) in individuals with type 2 diabetes, cardiovascular disease, and both type 2 diabetes

Table 1 | Characteristics of study participants by cardiometabolic comorbidity at the time of diagnosis of cancer

Characteristics	No comorbidity (n=22 814)	Type 2 diabetes (n=2113)	Cardiovascular disease (n=1529)	Type 2 diabetes and cardiovascular disease (n=531)
Sex:				
Men	9672 (42.4)	1228 (58.1)	1020 (66.7)	397 (74.8)
Women	13 142 (57.6)	885 (41.9)	509 (33.3)	134 (25.2)
Mean±SD age at recruitment (years)	56.4±7.9	58.3±6.5	61.0±6.6	60.5±6.4
Age at recruitment (years):				
<50	4160 (18.2)	199 (9.4)	72 (4.7)	25 (4.7)
50-65	16 104 (70.6)	1677 (79.4)	1091 (71.4)	402 (75.7)
≥65	2550 (11.2)	237 (11.2)	366 (23.9)	104 (19.6)
Mean±SD age at cancer diagnosis (years)	62.7±8.3	67.0±6.9	68.1±6.9	71.0±7.1
Cause of exit from study:				
Endpoint of study	12 374 (54.2)	987 (46.7)	528 (34.5)	200 (37.7)
Died	10 334 (45.3)	1123 (53.2)	995 (65.1)	330 (62.2)
Withdrew from study	21 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)
Emigrated	85 (0.4)	2 (0.1)	5 (0.3)	0 (0.0)
Mean±SD follow-up survival (years)	7.6±5.3	5.2±4.4	5.5±4.7	3.5±3.4
Educational level:				
None	977 (4.3)	191 (9.0)	50 (3.3)	26 (4.9)
Primary school completed	8037 (35.2)	879 (41.6)	640 (41.9)	251 (47.3)
Technical or professional school	6186 (27.1)	540 (25.6)	388 (25.4)	114 (21.5)
Secondary school	2878 (12.6)	175 (8.3)	156 (10.2)	44 (8.3)
University degree	4185 (18.3)	288 (13.6)	234 (15.3)	78 (14.7)
Not specified	551 (2.4)	40 (1.9)	61 (4.0)	18 (3.4)
Lifestyle at recruitment				
Smoking status:				
Never	9061 (39.7)	739 (35.0)	392 (25.6)	124 (23.4)
Former	6888 (30.2)	704 (33.3)	576 (37.7)	222 (41.8)
Smoker	6673 (29.3)	654 (31.0)	551 (36.0)	180 (33.9)
Unknown	192 (0.8)	16 (0.8)	10 (0.7)	5 (0.9)
Mean±SD alcohol intake (g/day)	14.8±20.7	17.0±23.9	16.7±22.3	18.4±26.2
Mean±SD total energy intake (kcal/day)	2032.3±641.8	2040.2±681.0	2062.2±714.6	2017.3±654.6
Mean±SD Mediterranean diet score	2.6±1.0	2.6±1.1	2.4±1.0	2.4±1.0
Physical activity:				
Inactive	5143 (22.5)	629 (29.8)	458 (30.0)	186 (35.0)
Moderately inactive	7648 (33.5)	698 (33.0)	475 (31.1)	171 (32.2)
Moderately active	5040 (22.1)	396 (18.7)	290 (19.0)	78 (14.7)
Active	4647 (20.4)	375 (17.8)	278 (18.2)	88 (16.6)
Unknown	336 (1.5)	15 (0.7)	28 (1.8)	8 (1.5)
Body mass index:				
<25	9976 (43.7)	371 (17.6)	502 (32.8)	76 (14.3)
25-30	9432 (41.3)	938 (44.4)	737 (48.2)	261 (49.2)
≥30	3406 (14.9)	804 (38.1)	290 (19.0)	194 (36.5)
Clinical characteristics				
Hypertension:				
No	11 579 (50.8)	913 (43.2)	471 (30.8)	159 (29.9)
Yes	4717 (20.7)	834 (39.5)	589 (38.5)	250 (47.1)
Unknown	6518 (28.6)	366 (17.3)	469 (30.7)	122 (23.0)
Status menopause:				
Premenopause	2417 (10.6)	78 (3.7)	36 (2.4)	0 (0.0)
Postmenopause	8677 (38.0)	702 (33.2)	417 (27.3)	122 (23.0)
Perimenopause or not known	2048 (9.0)	105 (5.0)	56 (3.7)	12 (2.3)
Hormone replacement therapy:				
Never used	9891 (43.4)	724 (34.3)	414 (27.1)	109 (20.5)
Yes	2601 (11.4)	132 (6.3)	72 (4.7)	19 (3.6)
Unknown	650 (2.9)	29 (1.4)	23 (1.5)	6 (1.1)
Clinical cancer				
Stage of cancer:				

Continued

Table 1 Continued

Characteristics	No comorbidity (n=22 814)	Type 2 diabetes (n=2113)	Cardiovascular disease (n=1529)	Type 2 diabetes and cardiovascular disease (n=531)
Localised	6740 (29.5)	522 (24.7)	368 (24.1)	104 (19.6)
Metastatic	7297 (2.0)	650 (30.8)	439 (28.7)	138 (26.0)
Unknown	8777 (38.5)	941 (44.5)	722 (47.2)	289 (54.4)
5 year relative survival of cancer (%):				
<40	4899 (21.5)	588 (27.8)	452 (29.6)	147 (27.7)
40-80	6597 (28.9)	639 (30.2)	450 (29.4)	179 (33.7)
≥80	11 318 (49.6)	886 (41.9)	627 (41.0)	205 (38.6)

Data are number (%) unless indicated otherwise.

Covariates, except stage of cancer at diagnosis, were assessed at recruitment into the cohort, and median time difference between the date of recruitment and cancer diagnosis was 6.7 years (interquartile range 3.8-9.3).

SD, standard deviation.

and cardiovascular disease, respectively, compared with those with no pre-existing comorbidities. Adjustment for waist circumference, instead of body mass index, gave similar risk estimates: hazard ratios 1.23 (95% CI 1.15 to 1.32), 1.30 (1.21 to 1.39), and 1.58 (1.40 to 1.78), respectively. The hazard ratio for type 2 diabetes with cardiovascular disease was, as expected, on the multiplicative scale ($P_{interaction}$=0.83).

Hazard ratios in unadjusted Cox models had larger effect sizes than the multivariable adjusted Cox models (online supplemental table 2). In contrast, in models that adjusted for type of cancer instead of groups of cancer according to their five year relative survival, we found similar estimates (online supplemental table 2). Results of the multivariable adjusted models were robust across subgroups, as defined by sex, age at cancer diagnosis, educational level, smoking status, categories of body mass index, and cancer stage at diagnosis (online supplemental table 3).

Results were also robust to a sensitivity analysis where only incident comorbidities, identified during follow-up, were considered (after excluding 1998 participants with prevalent type 2 diabetes or cardiovascular disease at recruitment; online supplemental table 4). Similarly, risk estimates were not different when excluding participants with missing information for any covariate (online supplemental table 5).

Duration of type 2 diabetes ($P_{interaction}$=0.73) or cardiovascular disease ($P_{interaction}$=0.24), categorised as <5 years or ≥5 years, did not modify associations between these comorbidities and all cause mortality (table 2). A secondary analysis with alternative categorisations (<3 years and ≥3 years, and <1 year, 1-5 years, and >5 years) showed similar results (online supplemental table 6).

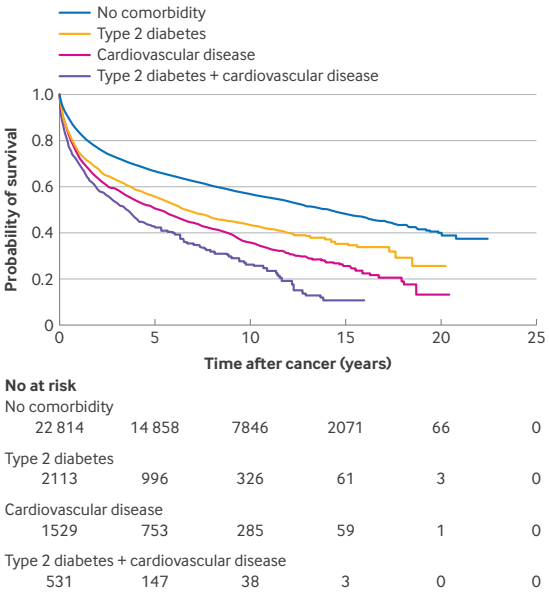

Figure 1 | Kaplan-Meier curves for overall survival after a diagnosis of cancer by pre-existing cardiometabolic comorbidities, in participants with no pre-existing cardiometabolic comorbidities, and in those with type 2 diabetes, cardiovascular disease, and both type 2 diabetes and cardiovascular disease

Cardiometabolic comorbidities and cause specific mortality

For cause specific mortality, we identified 10 492 deaths from cancer, 891 deaths from cardiocirculatory events, and 1399 other causes of death. For cancer specific mortality (figure 2), pre-existing comorbidities were positively associated with cancer deaths, with hazard ratios 1.13 (95% CI 1.05 to 1.22), 1.13 (1.04 to 1.23), and 1.33 (1.16 to 1.53) for participants with type 2 diabetes, cardiovascular disease, and both type 2 diabetes and cardiovascular disease, respectively. We found an increase in cardiovascular disease specific mortality of about threefold in cancer survivors with pre-existing cardiovascular disease (or cardiovascular disease and type 2 diabetes) compared with cancer survivors with no pre-existing cardiometabolic comorbidity (figure 2). For other causes of death (eg, digestive diseases), we saw strong positive associations in cancer survivors with pre-existing type 2 diabetes and in those with type 2 diabetes and cardiovascular disease, compared with cancer survivors with no comorbidity (figure 2).

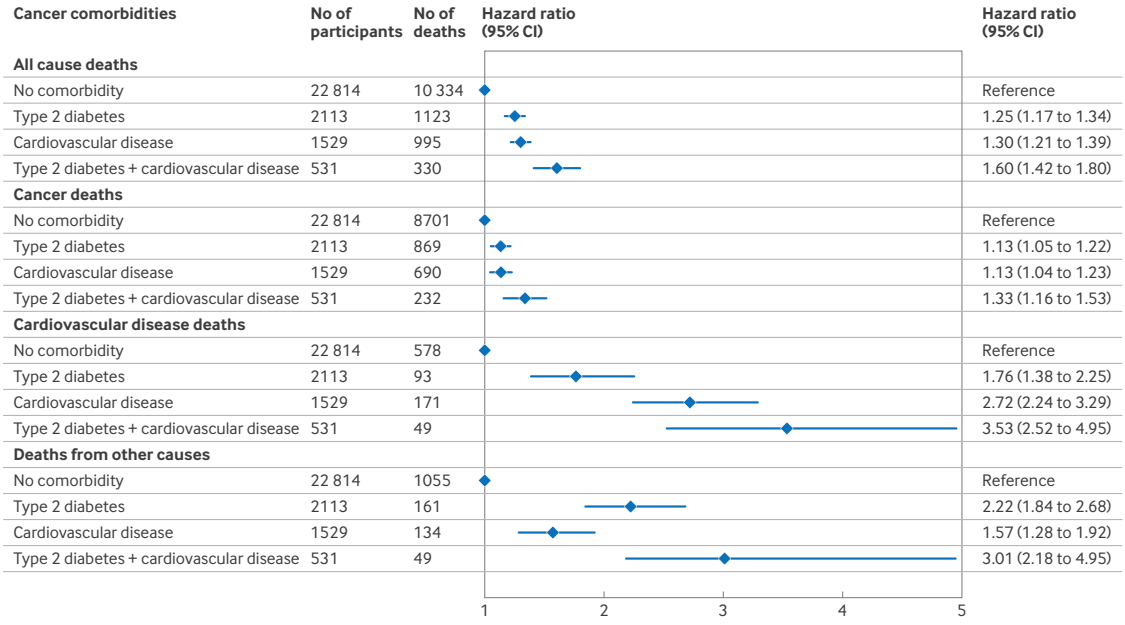

Figure 2 | Hazard ratios (95% confidence intervals, CIs) for associations between pre-existing cardiometabolic comorbidities and all cause and cause specific mortality in adults with cancer. Participants were grouped by age at recruitment, country, smoking status, stage of cancer, and five year relative survival of cancer, and adjusted for sex, educational level, alcohol intake, total energy intake, Mediterranean diet score, physical activity, body mass index, and hypertension, and menopausal status and hormone treatment (in women)

All cause mortality by cancer groups

Among all diagnosed cancers, 6086 (23%) had a five year relative survival of <40%, 7865 (29%) a five year relative survival of 40-80%, and 13 036 (48%) a five year relative survival of ≥80%. We saw marginally stronger associations between cardiometabolic comorbidities and all cause mortality for cancers with a five year relative survival of ≥80% (figure 3). In contrast, for cause specific deaths, we saw some definite associations (table 3). For example, compared with participants without pre-existing comorbidity, a history of type 2 diabetes was associated with death from cancer only in the group of cancers with the worst prognosis (five year relative survival <40%).

All cause mortality by cancer site

Online supplemental table 7 shows the associations between cardiometabolic comorbidities and all cause

Table 2 | Hazard ratios and 95% confidence intervals (CIs) for associations between pre-existing cardiometabolic comorbidities and all cause mortality in adults with cancer, by duration of type 2 diabetes or cardiovascular disease

	No of patients*	Hazard ratio (95% CI)
Type 2 diabetes:†		
No	23 608	Reference
Yes	1381	1.22 (1.13 to 1.33)
Duration of type 2 diabetes:†		
None	23 608	Reference
<5 years	863	1.21 (1.10 to 1.34)
≥5 years	518	1.25 (1.09 to 1.42)
Cardiovascular diseases:‡		
No	23 996	Reference
Yes	993	1.30 (1.19 to 1.42)
Duration of cardiovascular disease:‡		
None	23 996	Reference
<5 years	682	1.26 (1.14 to 1.40)
≥5 years	311	1.41 (1.21 to 1.65)

Participants were grouped by age at recruitment, country, smoking status, stage of cancer, and five year relative survival of cancer, and adjusted for sex, educational level, alcohol intake, total energy intake, Mediterranean diet score, physical activity, body mass index, and hypertension, and menopausal status and hormone treatment (in women).

*In this analysis, 1998 participants with prevalent type 2 diabetes or cardiovascular disease at recruitment were excluded.

†P=0.73 from log likelihood ratio test for a comparison of the case event binary model versus the category time duration model.

‡P=0.24 from log likelihood ratio test for a comparison of the case event binary model versus the category time duration model.

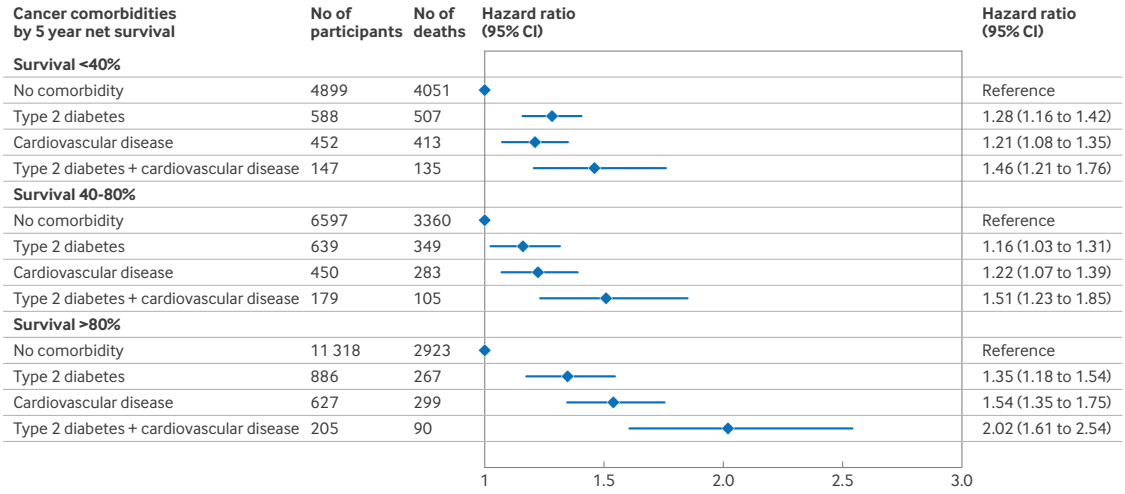

Figure 3 | Hazard ratios (95% confidence intervals, CIs) for associations between pre-existing cardiometabolic comorbidities and all cause mortality in adults with cancer, by five year relative survival of the diagnosed cancer. Participants were grouped by age at recruitment, country, smoking status, and stage of cancer, and adjusted for sex, educational level, alcohol intake, total energy intake, Mediterranean diet score, physical activity, body mass index, and hypertension, and menopausal status and hormone treatment (in women). Five year relative survival according to the Surveillance, Epidemiology, and End Results (SEER) project (online supplemental table 1)[24]

mortality for the 11 most common site specific cancers. Compared with cancer survivors with no cardiometabolic comorbidity, cancer survivors with pre-existing type 2 diabetes, cardiovascular disease, or both type 2 diabetes and cardiovascular disease generally had excess mortality. Exceptions were seen in individuals who received a diagnosis of stomach cancer (largely null association) or endometrial cancer, where an inverse association was observed among women with pre-existing type 2 diabetes compared with women with no comorbidity (hazard ratio 0.42, 95% CI 0.20 to 0.91). For some site specific cancers, the observed multiplicative interaction of type 2 diabetes and cardiovascular disease with all cause mortality was greater than expected, such as for ovarian cancer (hazard ratio 3.68, 95% CI 0.95 to 14.21).

Discussion

Principal findings

In this multinational prospective cohort study in almost 27 000 men and women with a first primary cancer diagnosis, 15.5% had a history of cardiometabolic comorbidity (cardiovascular disease or type 2 diabetes, or both) before cancer. These pre-existing cardiometabolic comorbidities were associated with early death from all causes, from cancer, from

Table 3 | Hazard ratios and 95% confidence intervals (CIs) for associations between pre-existing cardiometabolic comorbidities and cause specific mortality in adults with cancer, by five year relative survival of the diagnosed cancer

	5 year relative survival (hazard ratio (95% CI))		
Cause of death	Survival <40%	Survival 40-80%	Survival ≥80%
Cancer deaths:			
No cardiometabolic comorbidity	Reference	Reference	Reference
Type 2 diabetes	1.26 (1.14 to 1.41)	1.03 (0.90 to 1.18)	1.02 (0.86 to 1.21)
Cardiovascular disease	1.12 (1.00 to 1.26)	1.06 (0.91 to 1.23)	1.26 (1.06 to 1.50)
Type 2 diabetes and cardiovascular disease	1.38 (1.13 to 1.68)	1.27 (0.99 to 1.62)	1.35 (0.97 to 1.87)
Cardiovascular disease deaths:			
No cardiometabolic comorbidity	Reference	Reference	Reference
Type 2 diabetes	0.80 (0.39 to 1.64)	2.62 (1.77 to 3.89)	1.66 (1.16 to 2.36)
Cardiovascular disease	4.07 (2.56 to 6.47)	2.71 (1.90 to 3.87)	2.40 (1.83 to 3.14)
Type 2 diabetes and cardiovascular disease	3.01 (1.29 to 6.99)	4.36 (2.50 to 7.62)	3.44 (2.09 to 5.65)
Other causes:			
No cardiometabolic comorbidity	Reference	Reference	Reference
Type 2 diabetes	2.03 (1.33 to 3.11)	1.65 (1.16 to 2.35)	2.75 (2.11 to 3.56)
Cardiovascular disease	1.33 (0.82 to 2.17)	1.38 (0.95 to 2.00)	1.73 (1.31 to 2.29)
Type 2 diabetes and cardiovascular disease	2.41 (1.16 to 4.98)	2.19 (1.19 to 4.03)	4.02 (2.57 to 6.30)

Participants were grouped by age at recruitment, country, smoking status, and stage of cancer, and adjusted for sex, educational level, alcohol intake, total energy intake, Mediterranean diet score, physical activity, body mass index, and hypertension, and menopausal status and hormone treatment (in women).

Five year relative survival of cancer according to the Surveillance, Epidemiology, and End Results (SEER) programme 1975-2017 of the National Cancer Institute, US Mortality Files.[24]

cardiovascular disease, and from other causes. As expected, the hazard of dying from cardiovascular disease and from other causes (including digestive diseases) was substantially increased among cancer survivors with a history of cardiovascular disease and type 2 diabetes, respectively, compared with those with no such history. Cancer specific deaths, however, were also increased in cancer survivors with these cardiometabolic comorbidities compared with those with no comorbidities. The observed joint association between cardiovascular disease and type 2 diabetes and all cause and cause specific mortality was, as expected, on a multiplicative scale. For adults with some cancers, however, an interaction between cardiovascular disease and type 2 diabetes was suggested in their association with mortality (eg, ovarian cancer), which warrants investigation in future studies. We also found that the duration of cardiometabolic comorbidities before cancer did not seem to have a major effect on overall survival among adults with cancer.

Comparison with other studies

Comorbidity in adults with cancer has been consistently associated with reduced overall survival and, less consistently, with cancer specific survival.[5] Previous studies often grouped comorbid conditions into comorbidity indexes or counts,[6] which conceal how specific conditions might affect cancer survival differently.[29–31] Given the heterogeneity in defining cancer comorbidities, we focused on cardiometabolic diseases, which are among the most common comorbidities in adults with cancer,[32] but also originate from shared risk factors (eg, obesity).

Associations between comorbidities (in general) and survival tend to be larger for cancers with a better prognosis and for early stage cancer compared with advanced cancer, because patients with diagnoses of cancers with a high mortality rate are more likely to die from cancer, regardless of their comorbidity.[5] An exception in our analysis was the finding that a history of type 2 diabetes was associated with an increased cancer specific mortality only in adults who had a diagnosis of a cancer with a poor prognosis (ie, five year relative survival ≤40%). Type 2 diabetes is perhaps associated with faster growing or more aggressive cancers, such as pancreatic cancer. This hypothesis was supported in our cancer site specific analysis, where a history of type 2 diabetes was associated with all cause mortality in adults with pancreatic cancer compared with those who did not have type 2 diabetes (online supplemental table 7).

Pre-existing diabetes in adults with cancer increased all cause mortality compared with adults who did not have diabetes.[11] Respective evidence for site specific cancers suggested increased all cause mortality for cancers of the endometrium, breast, and colorectum, but evidence for other types of cancer is less consistent.[9 11 33 34] Our findings are consistent with these site specific cancers and add to the evidence suggesting positive associations between a history of type 2 diabetes and all cause mortality in adults with cancers of the pancreas and prostate (online supplemental table 7). We also found that cancer specific and cardiovascular disease specific mortality was higher in cancer survivors with type 2 diabetes than in those who did not have type 2 diabetes. Effect sizes were much larger for cardiovascular disease specific mortality than for cancer specific mortality. These findings are similar to a study from the Women's Health Initiative,[16] which based their findings on a self-reported history of type 2 diabetes at baseline and was restricted to postmenopausal women.

Compared with diabetes, fewer studies reported that pre-existing cardiovascular diseases in adults with cancer were associated with higher all cause mortality,[13 35–37] cancer specific mortality,[35 38] and cardiovascular disease specific mortality[35] compared with adults with cancer and no pre-existing cardiovascular disease. Our findings are in agreement with other studies and add to the data for less frequently studied cancers, such as brain, stomach, ovarian, and bladder cancers (online supplemental table 7).

In this study, we also investigated the joint association between type 2 diabetes and cardiovascular disease and mortality in adults with cancer. Research in individuals with cancer compared with individuals with a combination of cancer and other chronic diseases is needed to improve our understanding of disease interactions. This knowledge is essential for personalised medicine to guide clinical practice and to improve the prognosis in this growing group of patients affected by multiple long term conditions.[7 39 40] Although we found little evidence for multiplicative interaction for all cause or cause specific mortality in adults with all cancers combined, we cannot exclude the possibility that type 2 diabetes and cardiovascular disease might interact in their associations with mortality for specific cancers (eg, ovarian cancer).

Another gap in our knowledge that we could investigate is the role of duration of pre-existing cardiometabolic comorbidities on mortality, which could be important for risk stratification.[6] We found no evidence for effect modification by duration of type 2 diabetes ($P_{interaction}$=0.73) with similar all cause mortality estimates for durations of <3 or ≥3 years, or ≥5 years. Duration of cardiovascular disease of ≥5 years was associated with slightly higher all cause mortality than duration of <5 years ($P_{interaction}$=0.24). Information on the management of cardiovascular disease and type 2 diabetes could also provide insights beyond the duration of comorbidity because, for example, metformin treatment has been reported to decrease all cause mortality in adults with endometrial cancer and diabetes.[41]

Three main hypotheses have been proposed to explain associations between pre-existing comorbidities and mortality in cancer survivors.[5] Firstly, comorbidity could directly affect all cause and non-cancer mortality similarly in cancer survivors and the general population. This hypothesis, however, might not entirely explain excess non-cancer mortality. For example, Sturgeon et al reported that adults with cancer (all sites) had an increased risk of dying from cardiovascular diseases than the general population.[42] A non-causal explanation for increased cancer specific mortality in the presence of a comorbidity is that those with cancer who die of a comorbid condition might be incorrectly categorised as dying from their cancer.[43] Secondly, patients with cancer and comorbidity might receive less effective cancer treatments, worsening cancer specific survival,[44–46] and might also have higher levels of toxicity from cancer treatments.[47] A third mechanism could be a direct effect of a comorbidity on progression of cancer.[5] In diabetes, for example, hyperinsulinaemia has been shown to affect progression of breast cancer.[48] Furthermore, in our previous work in the same study population, we showed that a history of type 2 diabetes was associated with a metastatic stage diagnosis of overall cancer other than colorectal or breast cancer.[49]

Strengths and limitations of this study

A main strength of our study was the availability of validated incident events of type 2 diabetes and cardiovascular disease, which should mean that our results are less susceptible to misclassification of these comorbidities. This method also allowed us to evaluate the duration of type 2 diabetes and cardiovascular diseases and their association with mortality in individuals with cancer. Also, we accounted for stage of cancer at diagnosis, lifestyle factors, and other comorbidities, such as obesity and hypertension. We also performed separate analyses for the 11 most frequent cancers.

Having no available information on the treatment of type 2 diabetes, cardiovascular disease, or cancer was a limitation of our study. Although stage of cancer at diagnosis could be a proxy for cancer treatment, the lack of effect modification by duration of type 2 diabetes or cardiovascular disease could indicate that these comorbidities were well controlled. To help interpret our findings in the context of possible unmeasured confounding from treatment or other risk factors for type 2 diabetes or cardiovascular disease (eg, cardiorespiratory fitness),[50] we computed E values.[27] We estimated that an unmeasured confounder would need to have a minimum strength of association with the variable and outcome of 1.51 (1.28 for lower 95% CI) to explain our weakest observed association (ie, a relative risk of 1.13, figure 2). Nevertheless, potential improvements in treatment for people with cardiometabolic comorbidities in the past 10 years (mortality follow-up ended in 2013) would imply that the relative risks in our study were overestimated. These improvements, however, were likely not substantial (eg, clinical investigations that tested the diabetes drug metformin as one of the most promising repurposed cancer therapeutics have been disappointing so far).[51]

Also, 28% and 40% of participants had missing information for hypertension at recruitment and cancer stage at diagnosis, respectively. In the complete case analysis, however, where we only considered participants with complete information, risk estimates were similar to our main results (online supplemental table 5). This finding suggests a low likelihood of bias because of missing information (eg, cancer stage). For 11% of eligible participants with cancer, information on type 2 diabetes was missing which, however, was comparable with the full cohort. Although the study population was mostly recruited from the general adult population, participants were likely more health conscious,[21] which warrants caution when generalising our observations. Also, the results by type of cancer must be interpreted with care, given the small sample size with imprecise confidence intervals. These and the joint analyses of type 2 diabetes and cardiovascular disease had low power, and we could not investigate cause specific mortality, which should be done in future studies.

Studies restricting analyses to individuals with a chronic disease (ie, patients with cancer) can induce collider bias, when the variable (ie, type 2 diabetes and cardiovascular disease) itself is a cause of cancer (ie, the potential collider).[52] In our context, the evidence indicates that type 2 diabetes is a likely cause of several cancers, including breast, colorectal, and endometrial cancers,[9] whereas evidence is lacking that cardiovascular diseases increase the risk of cancer. Collider bias is the most likely explanation of the inverse association between type 2 diabetes and mortality in women diagnosed as having endometrial cancer (online supplemental table 7). In contrast, cardiovascular disease was not associated with mortality in these women. Investigating type 2 diabetes and cardiovascular disease head to head might therefore help in assessing the presence of collider bias in this research context.

Conclusions

In this multinational cohort study, cardiovascular diseases or type 2 diabetes before a diagnosis of cancer were each associated with increased all cause mortality, and cancer and cardiovascular disease specific mortality. No differences in mortality outcomes were found for duration of these comorbidities. Clinicians treating people with cancer are encouraged to optimally manage cardiometabolic comorbidities.

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Contributors HF conceived and designed the study, had primary responsibility for the final content of the manuscript, and had final responsibility in submitting the manuscript for publication. VD-B analysed the data. VV and HF supported data analysis. VD-B and HF wrote the manuscript. VD-B, VV, PF, and HF had full access to all of the data. All authors critically reviewed the manuscript for important intellectual content and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. HF is the guarantor. Transparency: The lead author (HF, the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Patient consent for publication Not applicable.

Ethics approval The study was conducted according to the principles of the Declaration of Helsinki. The European Prospective Investigation into Cancer and Nutrition (EPIC) study was approved by the ethical review boards of the International Agency for Research on Cancer (IARC, No 23-40) and the institutional review board of each participating EPIC center. Written informed consent was obtained from all study participants. Participants gave informed consent to participate in the study before taking part. Withdrawal from the study was possible at any time during follow-up. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data may be obtained from a third party and are not publicly available. Data access can be requested from https://epic.iarc.fr/access/index.php. The request will be assessed by the European Prospective Investigation into Cancer and Nutrition (EPIC) working groups and the EPIC steering committee. After approval by the EPIC steering committee, de-identified data will be made available. An agreement will be signed specifying the study protocol, variables, statistical analysis plan, researchers involved, and length of time that the data will be available. The study protocol and statistical analysis plan of this study was approved by the EPIC steering committee before the start of the analysis.

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REFERENCES

1 World Health Organization. Noncommunicable diseases country profiles 2018. 2018. Available: https://www.who.int/publications/i/item/9789241514620
2 Fowler H, Belot A, Ellis L, *et al*. Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. BMC Cancer 2020;20:2. 10.1186/s12885-019-6472-9
3 Ogle KS, Swanson GM, Woods N, *et al*. Cancer and comorbidity: redefining chronic diseases. Cancer 2000;88:653–63. 10.1002/(sici)1097-0142(20000201)88:3<653::aid-cncr24>3.0.co;2-1
4 Loeppenthin K, Dalton SO, Johansen C, *et al*. Total burden of disease in cancer patients at diagnosis-a Danish nationwide study of multimorbidity and redeemed medication. Br J Cancer 2020;123:1033–40. 10.1038/s41416-020-0950-3
5 Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin 2016;66:337–50. 10.3322/caac.21342
6 Søgaard M, Thomsen RW, Bossen KS, *et al*. The impact of comorbidity on cancer survival: a review. Clin Epidemiol 2013;5:3–29. 10.2147/CLEP.S47150
7 Wallace E, Salisbury C, Guthrie B, *et al*. Managing patients with multimorbidity in primary care. BMJ 2015;350:h176. 10.1136/bmj.h176
8 Hu JX, Thomas CE, Brunak S. Network biology concepts in complex disease comorbidities. Nat Rev Genet 2016;17:615–29. 10.1038/nrg.2016.87
9 Tsilidis KK, Kasimis JC, Lopez DS, *et al*. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607. 10.1136/bmj.g7607
10 Abudawood M. Diabetes and cancer: A comprehensive review. J Res Med Sci 2019;24:94. 10.4103/jrms.JRMS_242_19
11 Barone BB, Yeh H-C, Snyder CF, *et al*. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754–64. 10.1001/jama.2008.824
12 Mehta LS, Watson KE, Barac A, *et al*. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. Circulation 2018;137:e30–66. 10.1161/CIR.0000000000000556
13 Batra A, Sheka D, Kong S, *et al*. Impact of pre-existing cardiovascular disease on treatment patterns and survival outcomes in patients with lung cancer. BMC Cancer 2020;20:1004. 10.1186/s12885-020-07487-9
14 Navi BB, Iadecola C. Ischemic stroke in cancer patients: A review of an underappreciated pathology. Ann Neurol 2018;83:873–83. 10.1002/ana.25227
15 Ameri P, Canepa M, Anker MS, *et al*. Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. Eur J Heart Fail 2018;20:879–87. 10.1002/ejhf.1165
16 Simon MS, Hastert TA, Barac A, *et al*. Cardiometabolic risk factors and survival after cancer in the Women's Health Initiative. Cancer 2021;127:598–608. 10.1002/cncr.33295
17 Tseng C-M, Wang H-H, Wang W-L, *et al*. Prognostic Impact of Diabetes Mellitus on Overall Survival in a Nationwide Population-Based Cohort of Patients With Pancreatic Cancer. Endocr Pract 2020;26:707–13. 10.4158/EP-2019-0565
18 Riboli E, Kaaks R. The EPIC Project: Rationale and study design. Int J Epidemiol 1997;26. 10.1093/ije/26.suppl_1.S6
19 Danesh J, Saracci R, Berglund G, *et al*. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. Eur J Epidemiol 2007;22:129–41. 10.1007/s10654-006-9096-8
20 Langenberg C, Sharp S, Forouhi NG, *et al*. Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. Diabetologia 2011;54:2272–82. 10.1007/s00125-011-2182-9
21 Riboli E, Hunt KJ, Slimani N, *et al*. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24. 10.1079/PHN2002394
22 Buckland G, González CA, Agudo A, *et al*. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am J Epidemiol 2009;170:1518–29. 10.1093/aje/kwp282
23 Christakoudi S, Kakourou A, Markozannes G, *et al*. Blood pressure and risk of cancer in the European Prospective Investigation into Cancer and Nutrition. Intl Journal of Cancer 2020;146:2680–93. 10.1002/ijc.32576
24 National Cancer Institute. Surveillance epidemiology and end result program. SEER data reporting tools. seer cause of death recode 1969+ (03/01/2018). Available: https://seer.cancer.gov/codrecode/1969_d03012018/index.html [accessed 07 Dec 2020]
25 Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133:601–9. 10.1161/CIRCULATIONAHA.115.017719
26 Wareham NJ, Jakes RW, Rennie KL, *et al*. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–13. 10.1079/PHN2002439
27 Mathur MB, Ding P, Riddell CA, *et al*. Web Site and R Package for Computing E-values. Epidemiology 2018;29:e45–7. 10.1097/EDE.0000000000000864
28 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403. 10.1016/j.ejca.2012.12.027
29 Minlikeeva AN, Freudenheim JL, Eng KH, *et al*. History of Comorbidities and Survival of Ovarian Cancer Patients, Results from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2017;26:1470–3. 10.1158/1055-9965.EPI-17-0367
30 Raina P, Gilsing A, Freisling H, *et al*. The Combined Effect of Cancer and Cardiometabolic Conditions on the Mortality Burden in Older Adults. J Gerontol A Biol Sci Med Sci 2019;74:366–72. 10.1093/gerona/gly053
31 Patnaik JL, Byers T, Diguiseppi C, *et al*. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011;103:1101–11. 10.1093/jnci/djr188
32 Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Co-Morbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev 2016;25:1029–36. 10.1158/1055-9965.EPI-16-0133
33 Cai H, Xu Z, Xu T, *et al*. Diabetes mellitus is associated with elevated risk of mortality amongst patients with prostate cancer: a meta-analysis of 11 cohort studies. Diabetes Metab Res Rev 2015;31:336–43. 10.1002/dmrr.2582
34 Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e5602. 10.1097/MD.0000000000005602
35 O'Neill C, Donnelly DW, Harbinson M, *et al*. Survival of cancer patients with pre-existing heart disease. BMC Cancer 2022;22:847. 10.1186/s12885-022-09944-z
36 Youn J-C, Chung W-B, Ezekowitz JA, *et al*. Cardiovascular disease burden in adult patients with cancer: An 11-year nationwide population-based cohort study. Int J Cardiol 2020;317:167–73. 10.1016/j.ijcard.2020.04.080
37 Liu D, Ma Z, Yang J, *et al*. Prevalence and prognosis significance of cardiovascular disease in cancer patients: a population-based study. Aging (Milano) 2019;11:7948–60. 10.18632/aging.102301
38 Bertero E, Robusto F, Rulli E, *et al*. Cancer Incidence and Mortality According to Pre-Existing Heart Failure in a Community-Based Cohort. JACC CardioOncol 2022;4:98–109. 10.1016/j.jaccao.2021.11.007
39 Guisado-Clavero M, Violán C, López-Jimenez T, *et al*. Medication patterns in older adults with multimorbidity: a cluster analysis of primary care patients. BMC Fam Pract 2019;20:82. 10.1186/s12875-019-0969-9
40 Sathanapally H, Sidhu M, Fahami R, *et al*. Priorities of patients with multimorbidity and of clinicians regarding treatment and health outcomes: a systematic mixed studies review. BMJ Open 2020;10:e033445. 10.1136/bmjopen-2019-033445
41 Perez-Lopez FR, Pasupuleti V, Gianuzzi X, *et al*. Systematic review and meta-analysis of the effect of metformin treatment on overall mortality rates in women with endometrial cancer and type 2 diabetes mellitus. Maturitas 2017;101:6–11. 10.1016/j.maturitas.2017.04.001
42 Sturgeon KM, Deng L, Bluethmann SM, *et al*. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40:3889–97. 10.1093/eurheartj/ehz766
43 Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol 2010;39:598–610. 10.1093/ije/dyp392
44 Koene RJ, Prizment AE, Blaes A, *et al*. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation 2016;133:1104–14. 10.1161/CIRCULATIONAHA.115.020406
45 Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. Cardiovasc Res 2019;115:844–53. 10.1093/cvr/cvz035
46 Renehan AG, Yeh H-C, Johnson JA, *et al*. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia 2012;55:1619–32. 10.1007/s00125-012-2526-0
47 Lee L, Cheung WY, Atkinson E, *et al*. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. J Clin Oncol 2011;29:106–17. 10.1200/JCO.2010.31.3049
48 Goodwin PJ. Obesity and Breast Cancer Outcomes: How Much Evidence Is Needed to Change Practice? JCO 2016;34:646–8. 10.1200/JCO.2015.64.7503
49 Jansana A, Auguste A, Kvaskoff M, *et al*. Impact of pre-existing cardiometabolic diseases on metastatic cancer stage at diagnosis: a prospective multinational cohort study. Cancer Commun 2024;44:593–7. 10.1002/cac2.12526

50 Sparks JR, Wang X, Lavie CJ, *et al*. Cardiorespiratory Fitness as a Predictor of Non-Cardiovascular Disease and Non-Cancer Mortality in Men. Mayo Clin Proc 2024;99:1261–70. 10.1016/j.mayocp.2023.11.024
51 Lord SR, Harris AL. Is it still worth pursuing the repurposing of metformin as a cancer therapeutic? Br J Cancer 2023;128:958–66. 10.1038/s41416-023-02204-2
52 Digitale JC, Martin JN, Glidden DV, *et al*. Key concepts in clinical epidemiology: collider-conditioning bias. J Clin Epidemiol 2023;161:152–6. 10.1016/j.jclinepi.2023.07.004

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