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LETTER TO THE JOURNAL

Impact of pre-existing cardiometabolic diseases on metastatic cancer stage at diagnosis: a prospective multinational cohort study

Owing to shared risk factors between cardiometabolic diseases (CMDs) and cancer, coupled with population aging, the lifetime risk of an individual developing cancer after a CMD is increasing. Furthermore, biological mechanisms such as insulin resistance or inflammation may not only predispose individuals with CMD to an elevated risk of certain types of cancer but also to a diagnosis of cancer at an advanced stage [1, 2].

Cancer stage at diagnosis strongly correlates with cancer survival rates and impacts treatment decisions. Early cancer detection is key to improving cancer outcomes, especially for cancers with poor prognosis. Factors associated with a higher risk of an advanced-stage diagnosis may differ from those associated with cancer incidence. Previous studies support an association between advanced-stage cancer at diagnosis and certain patient characteristics, such as higher body mass index (BMI), older age, smoking, comorbidities, and cancer type. Studies examining the influence of comorbidities on cancer stage at diagnosis have suggested that a CMD requiring regular medical follow-up is associated with earlier cancer detection [3, 4]. However, studies have also suggested that overall participation rates in cancer screening programs may be lower among individuals with type 2 diabetes (T2D) or cardiovascular diseases (CVD), which may lead to later cancer detection and a more advanced stage at diagnosis [5].

A better understanding of how CMDs prior to cancer are associated with stage at cancer diagnosis may inform cancer screening recommendations. This study aimed to investigate whether having a pre-existing CMD is associated with late-stage cancer diagnosis and to identify potential modifiers of this association in the European Prospective Investigation into Cancer and Nutrition study (EPIC).

This multinational prospective cohort study included 11,945 individuals diagnosed with first primary cancer between 1992 and 2012. Of all the diagnosed cancers, 64.9% were localized, 35.1% were metastatic, 53.6% were diagnosed in women, and 4.8%, a, 7.1%, and 1.3% had a history of CVD, of T2D, and of both CVD and T2D, respectively (Supplementary Figure S1, Supplementary Table S1). In addition to overall cancer, breast and colorectal cancers (38.1% of all cancers) were also investigated separately because of the well-established population-based cancer screening programs for these two cancers at the time of cancer diagnosis in the countries included in this study (i.e., Denmark, Germany, Italy, Spain, Sweden, and the UK). Detailed methods are described in Supplementary Materials.

We found that the adjusted odds ratios (ORs) of developing metastatic cancer (vs. localized) comparing individuals with pre-existing CVD, T2D or both to those without a CMD prior to cancer were 0.92 (95% confidence interval [CI] = 0.65-1.01), 1.04 (95% CI = 0.83-1.18) and 1.06 (95% CI = 0.60-1.36), respectively (Figure 1). Among cancer patients diagnosed with cancers other than breast or colorectum (i.e., "other cancers"), the OR for the association between pre-existing T2D and metastatic cancer diagnosis was 1.12 (95% CI = 0.85-1.49), whereas no association was observed for pre-existing CVD (OR = 0.98; 95% CI = 0.67-1.15). Not adjusting for cancer site led to a substantial difference in estimates for other cancers, whereby individuals with pre-existing T2D as compared to individuals without a CMD had a higher risk of a late-stage diagnosis (OR = 1.26; 95% CI = 1.04-1.55) (Supplementary Figure S2). Among patients with breast and colorectal cancers, pre-existing CVD, as compared to no CMD, was almost inversely associated with a metastatic cancer diagnosis (OR of metastatic cancer = 0.71; 95% CI = 0.48-1.07).

List of abbreviations: BMI, body mass index; CI, confidence interval; CMD, cardiometabolic diseases; CVD, cardiovascular diseases; EPIC, European Prospective Investigation into Cancer and Nutrition study; OR, odds ratio; T2D, type 2 diabetes.

	Localized, *N* (%)	Metastatic, *N* (%)	OR (95% CI)
All cancers			
No comorbidities	6,758 (87.2)	3,608 (86.0)	Ref
CVD	368 (4.7)	202 (4.8)	0.92 (0.65-1.01)
T2D	522 (6.7)	326 (7.8)	1.04 (0.83-1.18)
CVD & T2D	104 (1.3)	57 (1.4)	1.06 (0.60-1.36)
Breast and colorectal cancers			
No comorbidities	2,622 (90.5)	1,498 (90.3)	Ref
CVD	86 (3.0)	45 (2.7)	0.71 (0.48-1.07)
T2D	165 (5.7)	100 (6.0)	0.91 (0.69-1.20)
CVD & T2D	24 (0.8)	15 (0.9)	0.99 (0.48-2.10)
Breast cancer			
No comorbidities	1,829 (93.1)	810 (93.3)	Ref
CVD	41 (2.1)	12 (1.4)	0.71 (0.35-1.41)
T2D	91 (4.6)	41 (4.7)	0.88 (0.59-1.33)
CVD & T2D	4 (0.2)	5 (0.6)	0.91 (0.68-2.52)
Colorectal cancer			
No comorbidities	793 (85.1)	688 (87.1)	Ref
CVD	45 (4.8)	33 (4.2)	0.69 (0.42-1.13)
T2D	74 (7.9)	59 (7.5)	0.93 (0.63-1.38)
CVD & T2D	20 (2.1)	10 (1.3)	0.68 (0.29-1.59)
Other cancers			
No comorbidities	4,136 (85.2)	2,110 (83.2)	Ref
CVD	282 (5.8)	157 (6.2)	0.98 (0.67-1.15)
T2D	357 (7.4)	226 (8.9)	1.12 (0.85-1.49)
CVD & T2D	80 (1.6)	42 (1.7)	1.09 (0.55-1.35)

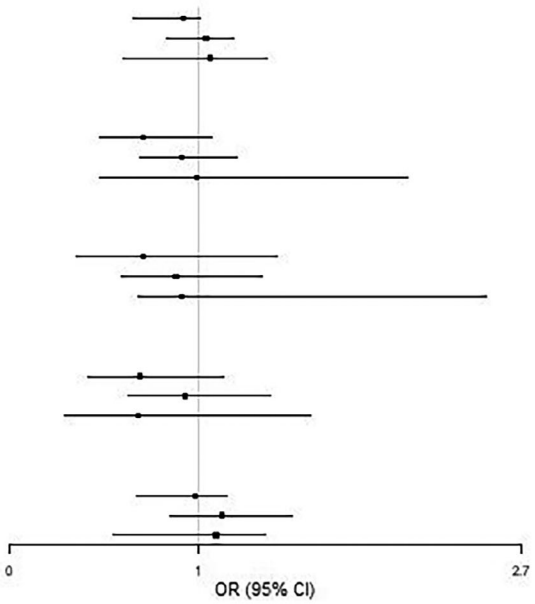

FIGURE 1 Association of pre-existing cardiometabolic comorbidities with metastatic stage at cancer diagnosis by population-based cancer screening program availability in EPIC. Models were adjusted for country, age at cancer diagnosis, sex, physical activity, BMI, alcohol intake, smoking status, education level, cancer site and self-reported hypertension at baseline. Model for breast cancer was only computed in women and further adjusted for menopausal status. Other cancers include bladder, kidney, lung, pancreatic, stomach, thyroid, cervix uteri, corpus uteri, ovarian, prostate, malignant melanoma, skin, urethral, hematologic, brain, anogenital, upper aerodigestive tract, and small intestine cancers, and leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma. Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition study; OR, odds ratio; CI confidence interval; CVD cardiovascular diseases; T2D, type 2 diabetes.

Point estimates were similar for both breast and colorectal cancer-specific analysis (Figure 1).

A few differences in associations across pre-defined subgroups of the study population were observed. There was suggestive evidence that associations between CMD status and metastatic cancer diagnosis were more pronounced among the younger age group (30-65 years) compared to the older age group (≥ 66 years), both for breast and colorectal cancers ($P = 0.008$) and other cancers (p-interaction = 0.017). There was evidence for effect modification by smoking status for other cancers ($P = 0.032$). The positive association between T2D status and diagnosis of metastatic other cancers was stronger in never smokers (OR: 1.60; 95% CI 1.04-2.46) than in former/current smokers (OR: 1.21; 95% CI 0.96-1.54) (Supplementary Table S2). This could be explained by fewer surveillance opportunities for non-smokers compared to individuals who smoked [6].

Our study supports prior findings as reviewed by Boakye et al. [7], who reported that T2D was associated with a higher risk of late-stage diagnosis of all cancers combined, whereas myocardial infarction was inversely associated with a late-stage diagnosis. We also found important differences. First, the positive association between T2D and a late-stage diagnosis was restricted to cancers not covered by population-based screening programs. Furthermore, the observation that this association became stronger when not adjusting for cancer type suggests that adults with T2D have a higher risk of cancers that are more frequently diagnosed at metastatic stages. In contrast, the suggestive inverse association between CVD and a late-stage diagnosis was restricted to cancers with population-wide screening (i.e., breast and colorectal cancers in our study). Second, there was evidence for effect modification of these associations by age group and smoking status.

Mechanisms by which chronic diseases might interfere with a timely cancer diagnosis include competing demands, whereby a chronic disease with high care complexity may delay cancer diagnosis due to masking of or undetected symptoms. It has also been suggested that patients with a high frequency of visits to health services may be reluctant to undergo additional diagnostic tests by health professionals. Lastly, biological mechanisms affecting cancer progression, such as hyperinsulinemia, inflammation pathways or shared risk factors, may explain the relation between CMDs and late-stage cancer diagnosis [1, 8]. In contrast, mechanisms facilitating a timely cancer diagnosis include more frequent contact with healthcare services, thereby providing surveillance opportunities to discuss possible cancer symptoms and second, some

treatments for chronic diseases may reduce the risk of progression to metastatic disease (e.g., aspirin and colorectal cancer) [1, 9].

Studies investigating specific comorbidities and stage at diagnosis are scarce for cancers other than breast and colorectal cancers [7]. Nevertheless, patients with newly diagnosed T2D or hyperinsulinemia have been recommended for pancreatic and liver cancer screening since the presence of pre-existing disease may mask other diseases and thus lead to late cancer presentation [10]. Such recommendations for screening are supported by our findings. For other cancer sites, such as respiratory or hematologic cancers, studies have not shown an impact of pre-existing CMD on cancer stage at diagnosis [7].

Strengths of our study include the use of validated CMD diagnoses, including data on the duration of the comorbidity. Furthermore, the availability of data on a wide range of dietary and lifestyle variables enabled comprehensive adjustment for confounders. Limitations of our study include the lack of data on CVD/T2D management, lack of repeated assessment of confounders (e.g., lifestyle factors), and the limited sample size, which did not allow analyses for less frequent cancers (Supplementary Table S3). Study participants were invited from the general adult population in most study centers apart from some centers in Italy and Spain (blood donors), Utrecht and Florence (women invited for a local population-based breast cancer screening program), and Oxford (half of the recruited participants did not eat meat). Generalizing observed results beyond our study population should therefore be done with caution.

In this prospective multinational cohort study, cancer patients with pre-existing CVD, T2D or both were overall not more likely to be diagnosed with late-stage cancer. Further studies are needed to confirm the suggestive positive association between T2D vs. no CMD and late-stage cancer among patients with cancers not included in population-based screening.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Conceived and designed the study: Heinz Freisling. Analyzed the data: Anna Jansana. Supported data analysis: Carine Biessy, Vivian Viallon. Wrote the manuscript: Anna Jansana, Heinz Freisling. Has primary responsibility for the final content of the manuscript: Heinz Freisling. Critically reviewed the manuscript for important intellectual content and approved the final version: Anna Jansana, Aviane Auguste, Marina Kvaskoff, Carine Biessy, Agnès Fournier, Emma Fontvieille, Laia Peruchet-Noray, Reynalda Cordova, Kristina Elin Nielsen Petersen, Anne Tjønneland, Verena Katzke, Rudolf Kaaks, Fulvio Riccieri, Salvatore Panico, Paolo Contiero, Maria-Jose Sánchez, Jesus Castilla, Marta Crous-Bou, Alicia Heath, Elom Kouassivi Aglago, Elisabete Weiderpass, Marc James Gunter, Pietro Ferrari, Elio Riboli, Vivian Viallon, Heinz Freisling.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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DATA AVAILABILITY STATEMENT

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. For information on how to apply to gain access to EPIC data and/or biospecimens, please follow the instructions: http://epic.iarc.fr/access/index.php.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for the European Prospective Investigation into Cancer and Nutrition (EPIC) study was obtained from the International Agency for Research on Cancer and the ethical review boards of the participating institutes (permit number: IEC-10-07-2017). All participants provided written informed consent.

CONSENT FOR PUBLICATION

Not applicable.

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 they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/ World Health Organization.

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REFERENCES

1. Renzi C, Kaushal A, Emery J, Hamilton W, Neal RD, Rachet B, et al. Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms. Nat Rev Clin Oncol. 2019;16(12):746–61.
2. Sattar N, Gill JMR, Alazawi W. Improving prevention strategies for cardiometabolic disease. Nat Med. 2020;26(3):320–5.
3. Zaborowski AM, Abdile A, Adamina M, Aigner F, d'Allens L, Allmer C, et al. Characteristics of Early-Onset vs Late-Onset Colorectal Cancer: A Review. JAMA Surg. 2021;156(9):865–74.
4. Mobley LR, Tangka FKL, Berkowitz Z, Miller J, Hall IJ, Wu M, Sabatino SA. Geographic Disparities in Late-Stage Breast Cancer Diagnosis Rates and Their Persistence Over Time. J Womens Health (Larchmt). 2021;30(6):807–15.
5. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin. 2016;66(4):337–50.
6. Gabler M, Geier S, Mayerhoff L, Rathmann W. Cardiovascular disease prevalence in type 2 diabetes - an analysis of a large German statutory health insurance database. BMC Public Health. 2021;21(1):328.
7. Boakye D, Günther K, Niedermaier T, Haug U, Ahrens W, Nagrani R. Associations between comorbidities and advanced stage diagnosis of lung, breast, colorectal, and prostate cancer: A systematic review and meta-analysis. Cancer Epidemiol. 2021;75:102054.
8. Qiang JK, Sutradhar R, Giannakeas V, Bhatia D, Singh S, Lipscombe LL. Impact of diabetes on colorectal cancer stage and mortality risk: a population-based cohort study. Diabetologia. 2020;63(5):944–53.
9. von Wagner C, Cadar D, Hackett RA, Demakakos P, Beeken RJ, Cooper Bailey S, et al. Type 2 diabetes and colorectal cancer screening: Findings from the English Longitudinal Study of Ageing. J Med Screen. 2020;27(1):25–30.
10. Li P, Hu Y, Scelo G, Myrskylä M, Martikainen P. Pre-existing psychological disorders, diabetes, and pancreatic cancer: A population-based study of 38,952 Finns. Cancer Epidemiol. 2023;82:102307.

SUPPORTING INFORMATION

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