Dietary insulinemic potential and survival after breast cancer diagnosis

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Background and Aims

Hyperinsulinemia may promote the growth and metastasis of breast cancers by activating the insulin/insulin-like growth factor 1 signaling pathways. Whether the insulinemic potential of the diet contributes to breast cancer prognosis has not been examined previously. Here, we focused on a food-based **empirical dietary index for hyperinsulinemia (EDIH)**, an index previously designed as most predictive of fasting plasma C-peptide.

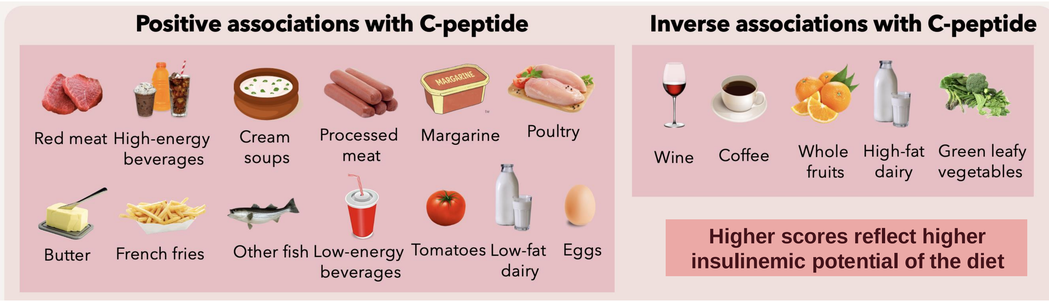
We aimed to investigate whether EDIH (at different time settings) is associated with overall and breast cancer-specific mortality.

Results

- Participants were followed up for a **median of 12 years after breast cancer diagnosis**.
- We documented **1,120 deaths due to breast cancer** and **2,762 all-cause deaths.**

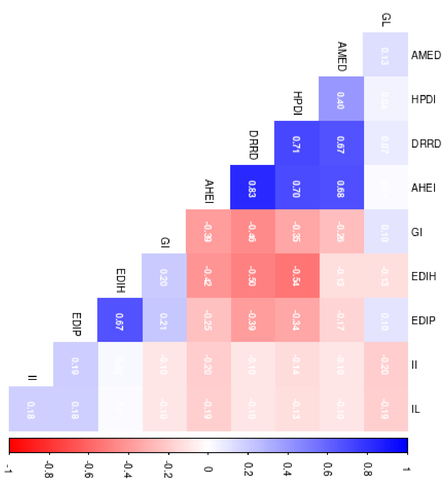
Methods

- EDIH was derived (Br J Nutr. 2016;116:1787-1798) based on **39 predefined food groups** from food frequency questionnaires (FFQs) **using stepwise linear regression models** to identify a dietary pattern most **predictive of circulating C-peptide concentrations** beyond the postprandial state and which captures factors that also influence insulin resistance (e.g., coffee).
- EDIH might capture the **influence of the whole diet on insulin concentrations**.
- EDIH is comprised of **18 food groups**; 13 were positively associated with C-peptide, five inversely.



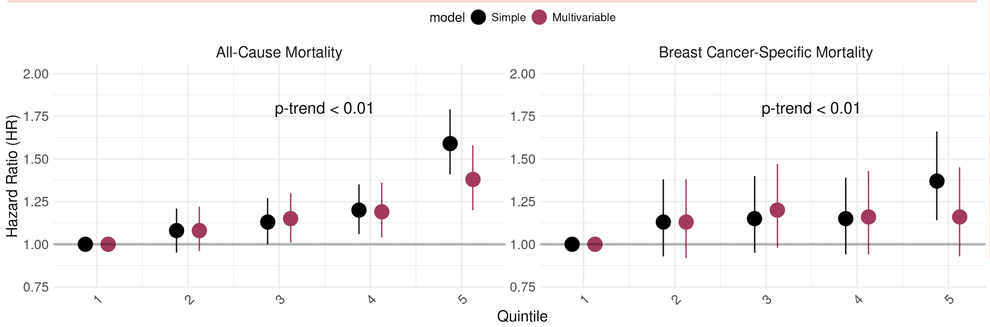
- For **9,640 women with stage I-III breast cancer** from NHS and NHSII, we calculated the **cumulative average EDIH**, using repeated measures of post-diagnostic diet from FFQs.
- We also considered the **pre-diagnostic EDIH score** (using the last FFQ reported before diagnosis), the **first postdiagnostic EDIH score**, as well as a **simple updated EDIH score**.
- Information on **diet and other factors** was repeatedly measured in validated questionnaires every two to four years.
- **Deaths** were ascertained by report from family members or by searching the National Death Index.
- Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models.

Figure 1. Spearman correlations coefficients between cumulative average dietary patterns in the pooled data of NHS and NHSII.



Abbreviations: **AHEI**: Alternate Healthy Eating Index; **AMED**: Alternate Mediterranean Diet score; **DRRD**: Diabetes Risk Reduction Score; **EDIH**: Empirical Dietary Index for Hyperinsulinemia; **EDIP**: Empirical Dietary Inflammatory Pattern; **HPDI**: healthful plant-based diet index; **II**: Insulin Index; **IL**: Insulin load.

Figure 2. Multivariable HRs and 95% CIs for the association between **quintiles of cumulative average post-diagnostic EDIH** and **mortality outcomes among breast cancer survivors** using pooled data from NHS (follow-up from 1984-2016) and NHSII (follow-up from 1991-2017).



Simple model: Adjusted for age at diagnosis and calendar year of diagnosis.

Multivariable-adjusted model: Adjusted for age at diagnosis, calendar year of diagnosis, pre-diagnostic menopausal status, age at menarche, pre-diagnostic parity, pre-diagnostic family history of breast cancer in a first degree relative, pre-diagnostic personal history of benign breast disease, pre-diagnostic oral contraceptive use, pre-diagnostic menopausal hormone therapy use, pre-diagnostic BMI, cumulative average post-diagnostic BMI changes from pre- to post-diagnosis, post-diagnostic cigarette smoking, post-diagnostic aspirin use, cumulative average post-diagnostic physical activity, cumulative average post-diagnostic total energy intake, cumulative average post-diagnostic alcohol intake, disease stage, tumor estrogen receptor status, self-reported radiotherapy, chemotherapy, hormonal treatment and post-diagnostic census tract neighborhood socioeconomic status score.

Further adjustment for other well-known dietary indices (e.g., DRRD, AHEI-2010, aMED, hPDI, and EDIP) did not change the associations between EDIH and subsequent risk of death from all-cause among breast cancer survivors.

Table 1. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for the **association between quintiles of EDIH score at four different settings** and **all-cause mortality among breast cancer survivors** using pooled data from NHS (1984-2016) and NHSII (1991-2017).

EDIH score	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend
Last pre-diagnosis						
Multivariable-adjusted model	1 (ref.)	1.00 (0.89, 1.13)	1.10 (0.97, 1.24)	1.11 (0.98, 1.26)	1.21 (1.06, 1.38)	<0.001
First post-diagnosis						
Multivariable-adjusted model	1 (ref.)	1.07 (0.95, 1.20)	1.10 (0.97, 1.24)	1.27 (1.11, 1.43)	1.27 (1.11, 1.46)	<0.001
Simple updated						
Multivariable-adjusted model	1 (ref.)	1.05 (0.92, 1.19)	1.05 (0.92, 1.19)	1.05 (0.92, 1.19)	1.13 (0.99, 1.30)	0.08
Cumulative average (Figure 2)						
Multivariable-adjusted model	1 (ref.)	1.08 (0.96, 1.22)	1.15 (1.01, 1.30)	1.19 (1.04, 1.36)	1.38 (1.20, 1.58)	<0.001

Subgroup analyses for the association between quintiles of cumulative average post-diagnostic EDIH score and mortality among breast cancer survivors

- We did not identify statistically significant effect modification of the associations between post-diagnosis cumulative average EDIH score and breast cancer-specific mortality by **tumor ER or IR status, menopausal status at diagnosis, BMI, or physical activity** (P-interaction≥0.05).
- Although there was **no significant effect modification of the association between EDIH and all-cause cancer mortality by BMI at diagnosis**, the strength of the association appeared to be **more pronounced among women with a BMI between 25 and 30 kg/m²** ($HR_{Q5vs.Q1}$,139; 95% CI, 1.09, 1.78; P-trend=0.01) and **those with a BMI ≥30 kg/m²**($HR_{Q5vs.Q1}$,1.66; 95% CI, 1.17, 2.35; P-trend=0.002).

Conclusions

In this large prospective study of breast cancer survivors, higher hyperinsulinemic dietary scores (reflecting higher dietary insulinemic potential) were associated with higher risk of all-cause, but not breast cancer-specific, mortality. Thus, dietary recommendations emphasizing the importance of avoiding high insulinemic dietary patterns (i.e., processed meat and red meat) and prioritizing low insulinemic dietary patterns (i.e., coffee, whole fruit and green-leafy vegetables) as components of a healthy diet may improve overall survival.

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