Research letter

Nutrition

Causal effects of genetically predicted cooked vegetable intake on breast cancer risk and survival: a Mendelian randomisation study

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Breast cancer (BC) has emerged as the most prevalent malignant tumour among women. Among the lifestyle factors associated with BC risk and survival, dietary patterns have become a prominent focus of research. Plant-based diets, in particular, have garnered attention due to their potential health benefits [1, 2]. Despite extensive observational studies suggesting an inverse association between vegetable consumption and BC risk [3], the evidence remains inconsistent. Mendelian randomisation (MR), an analytical approach that uses genetic variants as instrumental variables (IVs) to mimic a randomised controlled trial, was used to assess the genetically inferred causal effects of cooked vegetable intake (CVI) on BC risk and 15-year survival.

Methods. We used a two-sample MR analysis of genome-wide association studies (GWAS) summary statistics from the IEU OpenGWAS platform (GWAS ID: ebi-a-GCST90096907; N = 435,417; SNPs = 5,733,790). Instruments were constructed using independent single nucleotide polymorphisms (SNPs) associated with each trait at $p < 1 \times 10^{-7}$ and F-statistics > 10. BC risk and molecular subtype data were derived from the Breast Cancer Association Consortium (BCAC). Survival data were obtained from a cohort of 91,686 women with primary invasive BC (any stage) aged ≥ 18 years at diagnosis, with 15 years of follow-up and documented survival status (Supplementary Table SI). Analyses were restricted to the OncoArray dataset. To minimise confounding bias, exposure (CVI) and outcome (BC risk/survival) datasets were derived from independent GWAS sources.

The primary analysis was performed using the inverse variance-weighted (IVW) method with a multiplicative random-effects model, which synthesises Wald ratio estimates from each SNP to derive an overall causal effect. A p-value of < 0.05 was considered statistically significant. Cochran's Q statistic was used to assess heterogeneity among the SNPs. MR-Egger regression was used to assess directional pleiotropy through its intercept term. The MR-PRESSO test was used to identify and correct for pleiotropy by detecting and removing outliers. A leave-one-out analysis was performed to evaluate whether the overall causal estimate was disproportionately driven by any single, influential SNP.

Results. ***Causal effect of CVI on overall BC risk.*** All SNPs selected for MR analysis are listed in Supplementary Table SII. The results showed no significant causal association between CVI and overall BC risk (β = –0.27,

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95% CI: –8.07 to 2.52, $p \geq 0.05$) or across molecular subtypes, including luminal A (β = –0.56, 95% CI: –1.56 to 2.67, $p = 0.61$), luminal B (β = 1.92, 95% CI: –3.54 to 7.39, $p = 0.49$), luminal B HER2-negative (β = 1.27, 95% CI: –2.34 to 4.88, $p = 0.49$), HER2-enriched (β = 0.57, 95% CI: –6.81 to 7.95, $p = 0.88$), and triple-negative BC (β = –2.19, 95% CI: –5.91 to 1.53, $p = 0.25$) (Supplementary Table SIII).

Causal effect of CVI on 15-year BC survival. Genetically predicted higher CVI showed a protective causal association with 15-year survival in the overall BC cohort (β = –4.94, 95% CI: –9.50 to –0.39, $p = 0.033$). Significant associations were also observed in subgroup (e) (HR+/HER2– tumours: β = –7.98, 95% CI: –15.85 to –0.10, $p = 0.047$) and subgroup (k) (tamoxifen-treated patients: β = –16.52, 95% CI: –27.54 to –5.50, $p = 0.003$) (Figures 1 A–C), whereas no statistically significant associations were found in the other subgroups (all $p \geq 0.05$) (Supplementary Table SIV). Sensitivity analyses confirmed the robustness of these findings. After outlier removal using MR-PRESSO, Cochran's Q test and the MR-Egger intercept test revealed no significant heterogeneity or directional pleiotropy (both $p > 0.05$) (Supplementary Figures S1, S2).

Discussion. This two-sample MR study provides novel evidence that although genetically predicted CVI does not have a significant causal effect on BC incidence, it may confer survival benefits to patients with primary invasive disease. Specifically, protective effects were observed in individuals with HR+/HER2– tumours and in those receiving tamoxifen treatment, highlighting potential interactions between dietary components and endocrine-related therapeutic pathways.

Although some studies suggest that plant-based diets reduce BC risk [4], our MR analysis did not support a causal role for CVI. This discrepancy may stem from (1) the relatively low proportion of cooked vegetables in total dietary intake, (2) insufficient duration of dietary intervention to influence carcinogenesis, and (3) variability in the bioavailability of specific components, such as isoflavones [5]. Notably, the protective effects of soy isoflavones (phytoestrogens) reported in postmenopausal women may differ from our findings due to variations in the vegetable types and intake levels examined [6, 7].

The survival benefits of CVI may be attributable to phytoestrogen-mediated regulation of oestrogen receptor (ER) pathways [8, 9]. For instance, the significant association observed in the tamoxifen-treated subgroup (k) suggests that isoflavones synergistically inhibit ER signalling. Similarly, the protective trend in the aromatase inhibitor-treated subgroup (l) may reflect isoflavones' potential to suppress oestrogen synthesis. However, in younger patients, high-grade tumours, or aggressive subtypes (e.g. triple-negative BC), dietary benefits may be overshadowed by adverse prognostic features.

A novel finding of this study is the pivotal role of the rs12629972 SNP (located in the intronic region of *RARB*) in survival outcomes. Although *RARB* expression showed no significant correlation with BC survival in the GEPIA2 database (Supplementary Figure S3), this SNP may influence tumour cell differentiation or treatment response by modulating retinoic acid (RA) signalling [10]. Potential underlying mechanisms include modifying the RA receptor activity to enhance endocrine therapy sensitivity and epigenetic regulation of downstream target genes [11]. Functional studies are required to validate these hypotheses.

The MR design minimised the confounding inherent to observational studies, and the multidimensional sensitivity analyses supported its robustness. Nonetheless, several limitations warrant caution: (1) the self-reported dietary data may incur recall bias and measurement error, without capturing overall dietary patterns or intervention duration; (2) the limited IVs yielded borderline F-statistics, potentially attenuating causal estimates; (3) European-ancestry restriction limits generalisability; and (4) the genetic associations require experimental and clinical validation.

In conclusion, this study provides genetic evidence supporting CVI as a potential nutritional intervention for BC patients. For HR+/HER2– patients and those receiving endocrine therapy, increasing the intake of phytoestrogen-rich vegetables may improve prognosis. In addition, rs12629972 may serve as a biomarker to guide personalised therapeutic strategies.

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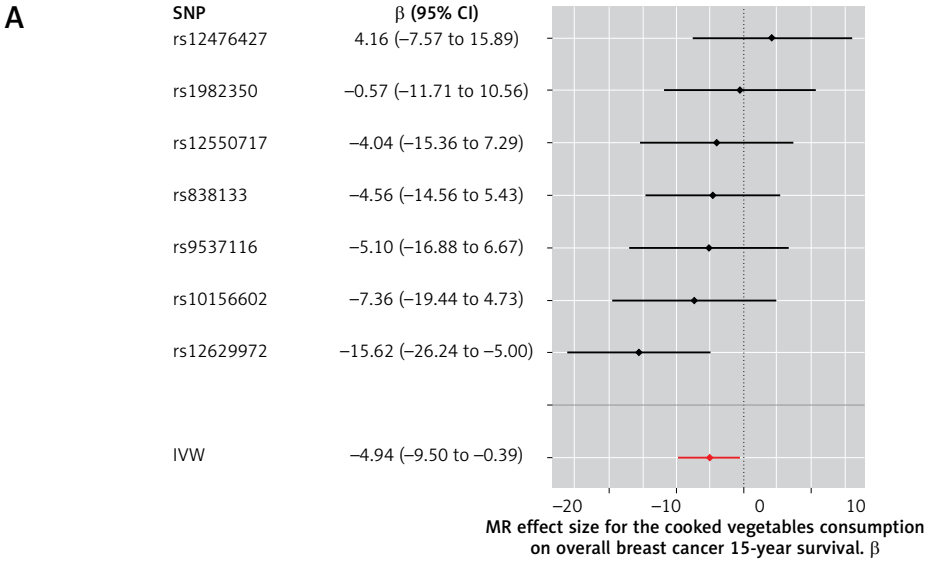
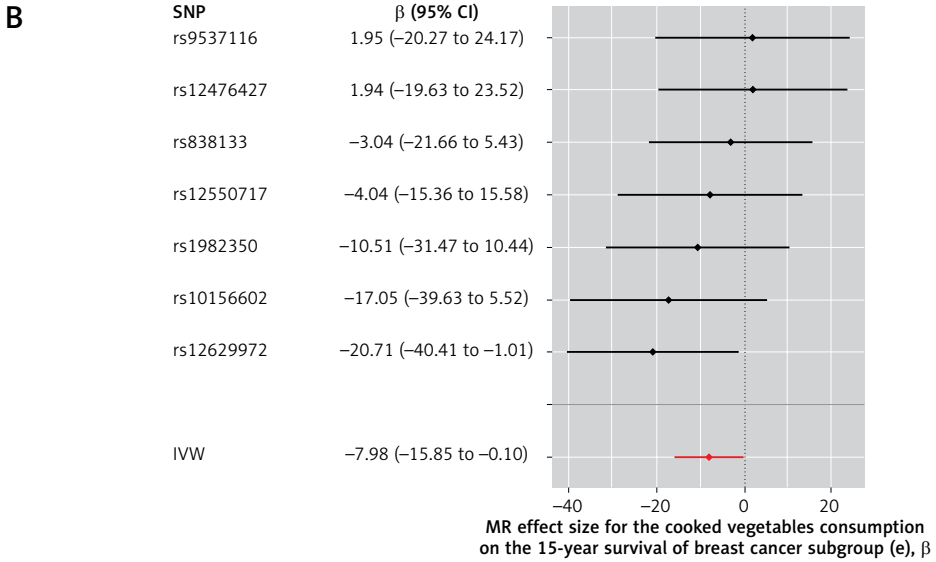
Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.





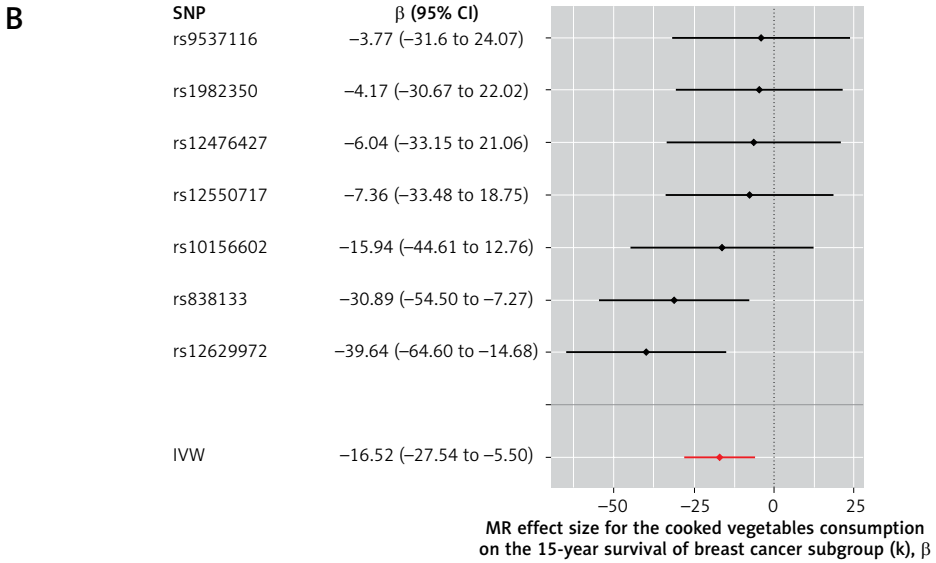


Figure 1. Forest plot of individual and combined SNP MR-estimated effect sizes. **A** – Effects of cooked vegetable intake on 15-year overall survival in breast cancer patients; error bars indicate 95% CIs. **B** – Effects on 15-year survival in breast cancer subgroup (e). **C** – Effects on 15-year survival in breast cancer subgroup (k)

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