Estimation of causal effects of menopausal hormone replacement therapy on BMI and breast cancer risk

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Résumé

This study aims to estimate the causal effects of menopausal hormone replacement therapy (HRT) on body mass index (BMI) and breast cancer (BC) risk using causal inference methods. We examined data from the E3N cohort, concentrating on 27,308 French women who had undergone menopause, were aged between 43 and 70 years, and had not used hormone replacement therapy (HRT) at baseline. We investigated the causal impacts of initiating HRT within 2-3 years post-baseline on body mass index (BMI) measured 4-6 years post-baseline, as well as on breast cancer incidence recorded by the end of the follow-up period (average duration of 13 years). The primary objective was to determine whether HRT exposure has a causal effect on post-exposure BMI and BC risk and to assess whether baseline BMI modifies these effects. Our methodological framework is based on Rubin's counterfactual causal model (Rubin, 1974), enabling us to estimate the average treatment effect of HRT on BMI and BC risk from observational data. This framework allows for a robust estimation of the overall average effects of HRT exposure, while also allowing subgroup analyses to examine potential heterogeneity in treatment effects (Yang et al., 2021). We employed stabilized weighting and double robust estimators, exploring various alternative models for the propensity score and outcome regression (Bang and Robins, 2005; Li et al., 2018). We also applied a recently introduced sensitivity analysis method to evaluate the robustness of our findings against potential violations of the unconfoundedness assumption. Our main analyses revealed no overall effect of HRT on post-treatment BMI (Risk Difference: 0.04 (-0.06;0.13)), but subgroup analyses showed a significant positive causal effect in women with low baseline BMI (Risk Difference: 0.18 (0.10;0.25)) and a negative effect in overweight women (Risk Difference: -0.18 (-0.40;0.02)). In line with previous findings (Fournier et al., 2014; Fornili et al., 2021), exposure to HRT was associated with an elevated BC risk (Risk Ratio: 1.34 (1.17;1.55)), with the magnitude of this risk varying across subgroups defined

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by baseline BMI. These findings, derived from a robust causal framework rather than estimations based on parametric models, enhance our understanding of the mechanisms by which HRT may influence BMI and BC development, thereby informing the ongoing debate regarding the benefits and risks of HRT in postmenopausal women.

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