Maternal height and breast cancer risk: results from a study nested within the EPIC-Greece cohort

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Abstract

The positive association of adult height with breast cancer (BC) risk has been hypothesized to be partly accounted for by an association of this risk with maternal height (operating in utero to modify hormone effects). In a case-control study (271 BC patients and 791 controls) nested within the EPIC-Greece cohort, we applied mediation analysis to calculate the direct and indirect (through the woman's own height) effect of maternal height on BC risk. Per 5cm increase in maternal height and depending on its reference value: the indirect excess risk range was 2%-7%; the direct excess risk 6%-11%; and the total excess risk (direct and indirect effects) 8%-19%. The effect sizes consistently increased for higher reference categories of maternal height, but did not generally reach statistical significance, possibly due to the limited sample size.

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Height has been positively associated with breast cancer risk [1]. In 1990, Trichopoulos published a hypothesis implicating in utero exposures in breast cancer etiology [2], which has been supported by the effects of the in utero exposure to diethylstilbestrol (a synthetic estrogen) on offspring breast cancer risk [3], as well as studies showing a positive association of birth size (a proxy for in utero exposures) with this risk [4]. The underlying mechanism has been reported to rely on the effect of pregnancy growth hormones on the size of the fetus' mammary tissue-specific stem cell pool [5]. On the basis of the above, it has been hypothesized that the positive association of adult height with breast cancer risk may, to a certain extent, be accounted for by an association between maternal height (operating in utero to modify the effects of growth hormones on the fetal stem cell pool) and the risk of breast cancer. [6]

We conducted a case-control study nested within the Greek segment of the European Prospective Investigation into Cancer (EPIC) [7], to investigate whether maternal height is also associated with breast cancer risk and, if so, to which extent this association is mediated through the woman's own height. Anthropometric measurements (including height) were performed for all volunteers in EPIC-Greece at recruitment; for the present study, we additionally collected information on maternal height in a subsample of the women through telephone interviews conducted July- September 2012. We included both prevalent (192) and incident (244) breast cancer cases in the EPIC-Greece cohort and matched them to three control women, who had not developed any type of cancer. Matching criteria were age at recruitment (±1 year) and date of enrollment (±6 months). Cases and controls had to be alive at the time of interview on maternal height. The percentage of those who didn't answer declined to participate was 33% for the cases and we tried to find up to 3 controls for them (the percentage of non-repliers in controls was about the same with the cases, but we tried to substitute the non-repliers). After excluding 74 participants (6%) with missing information in any of the covariates used in our analyses, we ended up with 271 breast cancer cases (60 of them being only self-reported canes, all the others were confirmed through hospital records) and 791 controls (see Appendix for more details)..

Breast cancer cases were defined as those with a verified (through hospital discharge data or medical records) breast cancer diagnosis (International Classification of Diseases for Oncology code C50). Sociodemographic, lifestyle and reproductive history data were collected at recruitment in EPIC-Greece, through standard interviewer-administered questionnaires. Regarding maternal height, women were asked to classify their mother's height in comparison to

their own height in one of five categories: shorter by ≥8 cm, 3-7 cm shorter, approximately the same height (±2 cm), 3-7 cm taller, taller by ≥8 cm. They were also asked to give information of their mother's height in cm.

We applied causal mediation analysis methods for dichotomous outcomes [8] and we estimated the natural direct effect of maternal height on breast cancer risk, the natural indirect effect through the woman's own height, as well as the total effect (a combination of the two). Given that the outcome is dichotomous, natural direct and indirect effects were measured at the odds ratio (OR) scale, and the total effect was estimated by the multiplication of these two [8]. To derive the results from the mediation analysis, per 5 cm increase in maternal height (continuously), at different reference levels of this variable, we ran two models: a) logistic regression, to model the association of maternal height, woman's own height and other potential confounders with breast cancer risk; in this model, we allowed for interaction between maternal and woman's own height, and b) linear regression, applied only to controls, to model the dependence of a woman's own height on maternal height and the remaining potential confounders. Conditional natural direct, indirect and total effects of maternal height on breast cancer risk were estimated at the mean value of the confounders among controls. The potential (mediator-outcome) confounders we accounted for in our analysis were age at enrollment, body mass index, alcohol intake, energy intake, physical activity, number of children, age at menarche, smoking and menopausal status. Statistical analyses were conducted using the Stata Statistical Software, release 11 (StataCorp. 2009, StataCorp LP). For the mediation analysis, we used the *paramed* command.

In the Table, the (conditional) natural direct, indirect and total effects of maternal height on breast cancer risk are expressed as ORs per 5 cm increase in maternal height, at different reference levels of maternal height. Hence, per 5cm increase in maternal height and depending on the reference value of maternal height: the indirect excess risk ranges from 2% to 7%; the direct excess risk ranges from 6% to 11%; for the total effect, combining both direct and indirect effects, the excess risk is in the range of 8% - 19%. The effect size of the association, overall, as well as through either the direct or the indirect route, appears to be higher as maternal height increases, as a reflection of a positive exposure-mediator interaction (see Appendix, table A2). When we repeated the analyses: a) among individuals for whom the information on height collected in categories was consisted with that provided as exact height (1001 of the 1062 of the participants, i.e. 94%), b) for incident breast cancer cases only (i.e. after excluding prevalent cases and their corresponding controls c) among postmenopausal women, d) with no adjustment for any of the potential confounders, and e) among the confirmed cases and the corresponding controls; the results remained practically unchanged, but slightly more pronounced associations in scenarios a) and e), i.e. when we analyzed more valid data (see Appendix, table A4-A8). Notwithstanding their consistency in sensitivity analyses, our results did not generally reach statistical significance, possibly due to our limited sample size.

The results are suggestive of a direct effect of maternal height on breast cancer risk, as well as an indirect effect (mediated through a woman's own height). The underlying mechanism of the early life origins of breast cancer hypothesis [2] has been reported to rely on the effect of pregnancy growth hormones on the size of the fetal mammary tissue-specific stem cell pool [5]. Interestingly so, it has been reported in cohorts of Caucasian and Asian women, that the

associations of pregnancy growth-enhancing hormones - notably maternal estriol, as well as cord blood insulin-like growth factor 1 (IGF-1) and IGF-2 - with birth size were mostly evident among the offspring of taller mothers [9]. On the basis of these associations, maternal height appears to play a role in the intrauterine origin of breast cancer. It can, thus, be inferred that among taller mothers, maternal size does not impose constraints on fetal growth, thus allowing growth-enhancing pregnancy hormones to exercise their growth potential and be positively associated with birth size and, thus, the risk of breast cancer [6]. In 2015, Vatten and colleagues studied a cohort of women in Norway and reported a positive association of birth length with breast cancer risk, which was stronger among women whose mothers were relatively tall (median or taller) compared to women whose mothers were relatively short (below median) at childbearing [10]. The results of the Norwegian cohort are in line with the results reported in our study in supporting a role of maternal height in breast cancer aetiology.

Strengths of our study include its being nested within the established and well-described EPIC-Greece cohort [7] and the novel approach of causal mediation analysis. Regarding the limitations, maternal height had to rely on recall data and misclassification cannot be excluded; nevertheless, it is unlikely that this misclassification was differential. We also included prevalent breast cancer cases, as both the exposure and the mediator are not affected by prevalent events, i.e. reverse causation is not an issue. Moreover, we did not include in the analyses individuals who were deceased at the time of interviews about maternal height or refused to participate; however, it is reasonable to assume that those participants were missing at random. Regarding the mediation analysis, the criticism expressed about the assumption that no effect of the exposure confounds the mediator-outcome relation (the cross-world independence assumption) could

apply also to our study [8]. Additionally, we could not adjust for the exposure-mediator or the exposure-outcome confounders (e.g. mother's socioeconomic status), but it is unlikely that this would have greatly affected our results. Finally, the study population was of moderate size and the numbers were adequate to generate strongly suggestive, though not statistically significant results.

In conclusion, we found evidence in support of a role of maternal height, both direct and indirect through a woman's own height, in breast cancer etiology. If replicated, our results will allow us to move one step forward in our understanding of the early life origins of breast cancer and, perhaps also, the early life origins of other cancers that have been positively associated with adult height.

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Table: Conditional natural direct, indirect and total effects of maternal height on breast cancer risk, expressed as odds ratios (95% confidence intervals) per 5 cm increase in maternal height, at different reference levels of maternal height*

Maternal height	**Natural Direct Effects** OR (95% CI)	**Natural Indirect Effects** OR (95% CI)	**Total Effects** OR (95% CI)
From 150 to 155cm	1.06 (0.94-1.19)	1.02 (0.96-1.09)	1.08 (0.96-1.21)
From 155 to 160cm	1.07 (0.95-1.21)	1.03 (0.98-1.09)	1.11 (1.00-1.23)
From 160 to 165cm	1.08 (0.96-1.23)	1.05 (0.98-1.11)	1.13 (1.00-1.29)
From 165 to 170cm	1.10 (0.95-1.26)	1.06 (0.98-1.14)	1.16 (0.98-1.37)
From 170 to 175cm	1.11 (0.95-1.30)	1.07 (0.97-1.18)	1.19 (0.96-1.47)

* Adjusted for: age at enrollment (in years), body mass index (in kg/m^2), alcohol intake (in gr/day), energy intake (in kcal/day), physical activity (in METS/day), number of children, age at menarche (in years), smoking status (never, former and current smokers; categorically) and menopausal status (pre- and peri- menopausal versus post-menopausal women)