

Appendix

Study population

Though anthropometric measurements (including height) were performed and recorded for the volunteers in EPIC-Greece (11953 men/16619 women) [1], no information was recorded on the height of the participants' mothers. As collection of this information for all women recruited in EPIC-Greece was impractical, we conducted a matched case-control study nested within EPIC-Greece and collected information on maternal height in a subsample of the women in the cohort through telephone interviews. We included all breast cancer cases diagnosed either before or after their recruitment in the cohort. Each breast cancer case was matched 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. Of the 524 cases, 436 (96%) respectively, were alive at the time of the interview. The percentage of those who didn't answer or declined to participate was 33% (144 individuals) 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). We collected information from 1,136 women and, 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 (110 prevalent and 161 incident cases) and 791 controls. Moreover, 60 out of the 271 breast cancer cases were only self-reported cases and not confirmed through hospital records).

Data collection

Socio-demographic and lifestyle characteristics, such as educational level, physical activity, smoking status, as well as information related to age at menarche, menopausal status and parity, were recorded at enrollment in the EPIC-Greece cohort. Recording frequency and duration of participation in physical activities [1] allowed the calculation of a metabolic equivalent index (MET value) for each activity [2] and eventually of an overall MET x hour sum, indicating the amount of energy per kilogram of body weight expended during an average day by each participant. Dietary habits were also recorded at enrollment, with the use of a validated interviewer-administered semi-quantitative food frequency questionnaire [3]. Anthropometric measurements were undertaken using standardized procedures [4]. Body weight was measured to the nearest 100 g, and height was measured to the nearest 1 cm. Body mass index (BMI) was calculated as the ratio of weight over the square of height (in kg/m²). Data on maternal height were collected through telephone interviews conducted from July to September 2012. Women were asked to classify their mother's height in comparison to their own height in one of five categories: shorter by 8 cm or more, 3-7 cm shorter, approximately the same height (± 2 cm), 3-7 cm taller, taller by 8 cm or more. They were also asked to give an estimation of their mother's height in cm.

Table A1: Distribution of breast cancer patients and control women by sociodemographic, lifestyle, reproductive and anthropometric variables recorded at enrollment in the EPIC-Greece cohort, as well as by maternal height

	CASES (n=271)		CONTROLS (n=791)	
CONTINUOUS VARIABLES	mean	SD	mean	SD
Age (in years)	53.1	10.0	53.1	9.7
Body Mass Index (in kg/m ²)	28.5	5.0	28.7	5.0
Alcohol intake (in gr/day)	3.48	6.12	3.93	6.59
Energy intake (in kcal/day)	1885	560	1905	555
Physical activity (in METS*/day)	35.4	4.1	36.0	4.2
Number of children	1.94	1.08	2.03	1.10
Age at menarche (in years)	13.0	1.5	13.1	1.5
Woman's height (in m)	1.58	0.06	1.57	0.06
Maternal height (in m)	1.58	0.07	1.58	0.07
CATEGORICAL VARIABLES	n	%	n	%
Smoking status				
Never smokers	187	69	554	70
Former smokers	36	13	72	9
Current smokers	48	18	165	21
Menopausal status				
Pre- and peri menopausal	116	43	333	42
Post-menopausal	155	57	458	58

*Metabolic equivalents

Table A2: Logistic regression derived beta coefficients (95% Confidence Intervals) for breast cancer mutually adjusted for the indicated variables. First part model of mediation analysis from Table in the paper (regression of outcome on exposure, mediator and confounders)

	Log-odds ratio (i.e. beta coef)	95% Confidence Interval
Maternal height (per 5cm)	-0.81	(-2.86 to 1.25)
Own woman's height (per 5cm)	-0.82	(-2.93 to 1.30)
Maternal height*Woman's own height (per 5cm each)	0.03	(-0.04 to 0.09)
Age (in years)	0.00	(-0.02 to 0.03)
Smoking status		
Former vs never	0.32	(-0.14 to 0.78)
Current vs never	-0.23	(-0.63 to 0.17)
Body Mass Index (per 1 kg/m²)	-0.01	(-0.04 to 0.03)
Alcohol intake (per 1 gr/day)	-0.01	(-0.04 to 0.01)
Energy intake (per 200 Kcal/day)	-0.01	(-0.06 to 0.05)
Physical Activity (per 1 MET/day)	-0.03	(-0.07 to 0.00)
Menopausal status		
Post-menopausal vs pre/peri-menopausal	-0.08	(-0.50 to 0.34)
Number of children	-0.04	(-0.17 to 0.09)
Age at menarche (per 1 year)	-0.04	(-0.13 to 0.06)

Table A3: Linear regression-derived beta coefficients (95% Confidence Interval) for a woman's own height by maternal height controlling for the indicated variables; estimated among control women for 5 cm increase in the woman's own height. Second part model of mediation analysis Table in the paper (regression of exposure on mediator and confounders among controls)

	Beta	95% Confidence Interval
Maternal height (per 5cm)	0.40	(0.35 to 0.46)
Age (in years)	-0.02	(-0.03 to -0.01)
Smoking status		
Former vs never	0.43	(0.17 to 0.68)
Current vs never	0.20	(0.01 to 0.40)
Body Mass Index (per 1 kg/m²)	-0.04	(-0.05 to -0.02)
Alcohol intake (per 1 gr/day)	0.01	(0.00 to 0.02)
Energy intake (per 100 Kcal/day)	0.01	(-0.02 to 0.04)
Physical Activity (per 1 MET/day)	-0.01	(-0.03 to 0.01)
Menopausal status		
Post-menopausal vs pre/peri-menopausal	0.07	(-0.15 to 0.28)
Number of children	-0.04	(-0.11 to 0.02)
Age at menarche (per 1 year)	-0.02	(-0.07 to 0.03)
Constant	21.30	(19.21 to 23.38)

Sensitivity analyses

Table A4: 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*, among participants 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%)

Maternal height	Natural Direct Effects OR (95% CI)	Natural Indirect Effects OR (95% CI)	Total Effects OR (95% CI)
From 150 to 155cm	1.08 (0.95-1.22)	1.01 (0.95-1.08)	1.09 (0.96-1.23)
From 155 to 160cm	1.10 (0.97-1.25)	1.03 (0.97-1.09)	1.13 (1.01-1.27)
From 160 to 165cm	1.12 (0.98-1.28)	1.05 (0.98-1.12)	1.18 (1.03-1.35)
From 165 to 170cm	1.15 (0.99-1.33)	1.07 (0.99-1.16)	1.23 (1.03-1.47)
From 170 to 175cm	1.17 (0.99-1.39)	1.09 (0.98-1.21)	1.28 (1.02-1.61)

* Adjusted for: age at enrollment (in years), body mass index (in kg/m²), 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)

Table A5: 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*, for incident breast cancer cases and the corresponding controls

Maternal height	Natural Direct Effects OR (95% CI)	Natural Indirect Effects OR (95% CI)	Total Effects OR (95% CI)
From 150 to 155cm	1.10 (0.94-1.29)	1.00 (0.91-1.09)	1.10 (0.94-1.28)
From 155 to 160cm	1.12 (0.96-1.30)	1.01 (0.93-1.10)	1.13 (0.99-1.30)
From 160 to 165cm	1.13 (0.96-1.33)	1.03 (0.93-1.13)	1.16 (0.98-1.37)
From 165 to 170cm	1.15 (0.96-1.38)	1.04 (0.92-1.17)	1.19 (0.92-1.50)
From 170 to 175cm	1.17 (0.95-1.44)	1.05 (0.91-1.23)	1.23 (0.91-1.65)

* Adjusted for: age at enrollment (in years), body mass index (in kg/m²), 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)

Table A6: 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* among post-menopausal women only

Maternal height	Natural Direct Effects OR (95% CI)	Natural Indirect Effects OR (95% CI)	Total Effects OR (95% CI)
From 150 to 155cm	1.04 (0.89-1.21)	1.02 (0.94-1.10)	1.06 (0.92-1.22)
From 155 to 160cm	1.05 (0.90-1.22)	1.03 (0.96-1.10)	1.08 (0.94-1.24)
From 160 to 165cm	1.06 (0.90-1.25)	1.04 (0.95-1.12)	1.09 (0.92-1.30)
From 165 to 170cm	1.07 (0.89-1.28)	1.04 (0.94-1.15)	1.11 (0.89-1.39)
From 170 to 175cm	1.07 (0.87-1.32)	1.05 (0.92-1.19)	1.13 (0.85-1.50)

* Adjusted for: age at enrollment (in years), body mass index (in kg/m²), 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)

Table A7: 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, without adjusting for any of the potential confounders (see Table A1)

Maternal height	Natural Direct Effects OR (95% CI)	Natural Indirect Effects OR (95% CI)	Total Effects OR (95% CI)
From 150 to 155cm	1.05 (0.93-1.19)	1.02 (0.96-1.09)	1.08 (0.96-1.21)
From 155 to 160cm	1.07 (0.95-1.20)	1.04 (0.98-1.10)	1.11 (1.00-1.23)
From 160 to 165cm	1.09 (0.96-1.23)	1.06 (0.99-1.13)	1.15 (1.01-1.31)
From 165 to 170cm	1.11 (0.96-1.28)	1.07 (0.98-1.17)	1.19 (0.98-1.37)
From 170 to 175cm	1.13 (0.96-1.33)	1.09 (0.97-1.21)	1.22 (0.97-1.54)

Table A8: 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*, among confirmed breast cancer cases and the corresponding controls (841 of the 1062 of the participants, i.e. 79%)

Maternal height	Natural Direct Effects OR (95% CI)	Natural Indirect Effects OR (95% CI)	Total Effects OR (95% CI)
From 150 to 155cm	1.09 (0.95-1.25)	0.99 (0.92-1.07)	1.08 (0.95-1.24)
From 155 to 160cm	1.12 (0.98-1.28)	1.01 (0.95-1.08)	1.14 (1.01-1.28)
From 160 to 165cm	1.15 (1.00-1.33)	1.04 (0.96-1.12)	1.19 (1.03-1.37)
From 165 to 170cm	1.18 (1.01-1.38)	1.06 (0.97-1.16)	1.25 (1.03-1.51)
From 170 to 175cm	1.21 (1.01-1.45)	1.08 (0.97-1.21)	1.31 (1.02-1.67)

* Adjusted for: age at enrollment (in years), body mass index (in kg/m²), 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)

References

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