Research Article

Cancer Epidemiology, Biomarkers & Prevention

Height, Sitting Height, and Leg Length in Relation with Breast Cancer Risk in the E3N Cohort

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Abstract

Background: If height is a well-established risk factor for breast cancer, leg length and sitting height are usually considered as better candidate biomarkers of growth hormone exposure than height, respectively, in pre- and postpuberty.

Methods: Risk of breast cancer associated with quartiles of height, sitting height, and leg length were estimated in the French E3N cohort ($N = 50{,}704$, including 2,065 breast cancer cases), stratified on both menopausal and hormone receptor statuses.

Results: Height was associated with an increased postmenopausal breast cancer risk [HR = 1.22 (1.06–1.41) when comparing extreme categories, $P_{trend} = 0.002$], which was exclusively driven by the association with leg length [HR = 1.21 (1.05–1.39), $P_{trend} = 0.013$] and not sitting height [HR = 1.03 (0.89–1.18), $P_{trend} = 0.379$]. Leg length was associated with an increased ER^+ breast cancer risk in postmenopausal [HR = 1.24 (1.06–1.46), $P_{trend} = 0.004$], whereas sitting height was associated with a borderline decreased ER^- premenopausal breast cancer risk [HR = 0.45 (0.20–1.01), $P_{trend} = 0.011$]. The positive associations observed in the overall population between leg length and breast cancer risk were actually restricted to women who had a short birth length [HR = 1.82 (1.22–2.72), $P_{trend} = 0.022$] and those with a low birth weight [HR = 1.43 (1.00–2.04), $P_{trend} = 0.054$].

Conclusion: The two components of height risk are differentially associated with breast cancer risk: leg length with an increased risk of postmenopausal ER^+ tumors and sitting height with a decreased risk of premenopausal ER^- tumors.

Impact: Future prospective studies should no longer consider height a single risk factor for breast cancer risk. *Cancer Epidemiol Biomarkers Prev; 21(7); 1171–5. ©2012 AACR.*

Introduction

Height is a well-established risk factor for breast cancer (1–3). Only 2 cohort studies (4, 5) showed that its effect was because of leg length rather than to sitting height. In parallel, the hypothesis that leg length is a better biomarker of childhood IGF-1 levels than sitting height or height has been recently criticized (6). These components of height have also been reported as potential confounders in the relationship between age at menarche and breast cancer risk (7).

To our knowledge, no study has ever provided results about the relationships between height, leg length, sitting height, and breast cancer risk, taking into account menopausal and hormone receptor statuses, and birth weight, birth length, and age at menarche. We used data from the French E3N cohort to evaluate these associations.

Material and Methods

Study population

The E3N cohort includes 98,995 women living in France and covered by a national health insurance program primarily comprising schoolteachers. Its design has previously been described (8). Briefly, participants were 40 to 65 years old when they first entered the cohort in 1990. At inclusion, they filled in a baseline questionnaire containing questions on established risk factors for breast cancer, including aspects of reproductive life, menopausal status, history of benign breast disease, breast cancer in first-degree relatives and a variety of lifestyle characteristics. Follow-up questionnaires were sent out approximately 2 to 3 years thereafter. Pathology reports were obtained for 93% of incident invasive breast cancer cases.

For this study, follow-up started in 1995, the date of return of the fourth questionnaire, when components of height were self-reported for the first time. Responders ($n = 65{,}989$) contributed person-years of follow-up until the date of any cancer diagnosis other than basal cell carcinoma, date of the last completed questionnaire, or

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date of mailing of the last available questionnaire (the ninth, sent in 2008), whichever occurred first. We excluded women with prevalent cancer (other than basal cell carcinoma; $n = 936$), those with no follow-up ($n = 1,312$), and women who did not provide information on height or sitting height ($n = 12,508$). Among the 2,594 breast cancer cases, we excluded cases with an unknown hormone receptor status ($n = 529$). During follow-up (accruing 600,674 person-years), 2,065 breast cancer cases were finally considered among 50,704 women. Median follow-up time was 6 years for women with breast cancer and 13 years for non–breast cancer cases.

Statistical analysis

Sitting height was self-reported. Women were asked to sit up right on a hard seat, buttocks, and scapulas against the wall, to measure their height using a tape measure with an angle bracket placed on their heads, and then to subtract the seat height. Height and sitting height measurements were previously validated (9), with correlation coefficients between self-report and measurements by a technician of 0.94 and 0.56, respectively. Leg length was calculated as the difference between the height and sitting height. Cox proportional hazards regression models with age as the time scale were used to estimate HR and 95% confidence intervals (CI). Both the hypotheses of the estrogen pathway in breast cancerogenesis and the differential effect of pre- and postpubertal growth were tested by including interaction terms between the components of height and menopausal status, use of MHT, body mass index, and birth length and weight. Trends were tested by including the ordinal variable in multivariate models with median values of each quartile.

Results

Population characteristics

Main mean characteristics are tabulated in Table 1. Anthropometric characteristics were very similar between cases and noncases. In noncases, mean height was 161.7 cm (SD = 5.7), mean sitting height was 84.7 cm (SD = 4.1), and mean leg length 76.9 cm (SD = 4.9). During follow-up, 2,065 breast cancer cases were diagnosed: 306 in premenopause and 1,759 in postmenopause.

Table 1. Main baseline characteristics of the study population, E3N cohort ($N = 50,704$)

	Cases ($N = 2,065$) Mean (STD) or N (%)	Noncases ($N = 48,639$) Mean (STD) or N (%)
Age	54.5 (6.3)	54.4 (6.7)
Height (cm)	162.0 (5.7)	161.7 (5.7)
Sitting height (cm)	84.8 (4.2)	84.7 (4.1)
Leg length (cm)	77.2 (4.9)	76.9 (4.9)
Birth weight		
Low (≤2,490 g)	252 (12.3)	6,010 (12.5)
Medium (2,490–4,000 g)	1,367 (66.3)	31,308 (64.2)
Large (>4,000 g)	231 (11.3)	5,462 (11.3)
Missing	215 (10.1)	5,859 (12.0)
Birth length		
Short (≤47 cm)	196 (9.2)	4,655 (9.6)
Medium (47–51 cm)	1,378 (67.0)	31,732 (65.2)
Large (>51 cm)	144 (7.0)	3,013 (6.2)
Missing	347 (16.8)	9,239 (19.0)
Body shape at menarche		
Lean	1,221 (59.1)	27,162 (55.9)
Medium	470 (22.8)	11,316 (23.3)
Large	374 (18.1)	10,161 (20.8)
Age at menarche	12.7 (1.3)	12.8 (1.4)
Menopausal status		
Premenopause	716 (34.7)	17,887 (36.8)
Postmenopause	1,349 (65.3)	30,748 (63.2)

Height and breast cancer risk in the overall population and according to menopausal status

As an interaction between height and menopausal status was observed ($P = 0.092$), analyses are presented in the overall, pre- and postmenopausal populations (Table 2). Because age-adjusted and fully adjusted estimates did not differ materially, we decided to comment only those pertaining to fully adjusted models. Compared with short women (<158 cm), tall women (≥165 cm) were at significantly increased risk [HR = 1.16 (1.02–1.31)]. A significant trend was also observed ($P = 0.007$). This association was restricted to postmenopausal women [HR = 1.22 (1.06–1.41)] for the highest quartile, $P_{trend} = 0.002$ in postmenopause and HR = 0.86 (0.61–1.20), $P_{trend} = 0.504$ in premenopause.

Components of height and breast cancer risk

The positive association with height in the overall and postmenopause populations was driven by leg length. Women in the highest category (≥80 cm) were at increased risk, in the overall population [HR = 1.17 (1.03–1.33)] and in postmenopause [HR = 1.21 (1.05–1.39)], with P for trends equal to 0.013 in both populations. No association was observed for sitting height.

Hormone receptor status

Among the 306 premenopausal breast cancer, 235 were ER^+. Among the 1,759 cases in postmenopause, 1,456 were ER^+. When stratifying breast cancer risk according to the estrogen receptor (ER) status (Table 3), the above described associations were confirmed for ER^+ tumors only. HRs in the third and fourth quartiles were, respectively, 1.17 (1.00–1.37) and 1.28 (1.11–1.48) for height and 1.16 (1.01–1.34) and 1.22 (1.06–1.41) for leg length in the overall population. Results were similar in postmenopausal women. Trends for height were also observed both in the overall ER^+ ($P < 0.001$) and postmenopausal ER^+ ($P < 0.001$) populations, as were trends for leg length ($P = 0.003$ and 0.004, respectively).

Table 2. Univariate and multivariate models for height, sitting height, and leg length associations with breast cancer risk in the overall, pre-, and postmenopausal population, E3N cohort ($N = 50{,}704$)

	Overall population			Premenopausal women			Postmenopausal women		
	N	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	*N*	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	*N*	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Height (cm)									
<158	453	1 (ref)	1 (ref)	69	1 (ref)	1 (ref)	384	1 (ref)	1 (ref)
158–162	509	0.96 (0.85–1.09)	0.96 (0.84–1.09)	77	0.94 (0.68–1.30)	0.82 (0.59–1.15)	432	0.98 (0.85–1.12)	0.98 (0.85–1.12)
162–165	390	1.07 (0.93–1.23)	1.07 (0.93–1.23)	50	0.75 (0.52–1.08)	0.78 (0.53–1.14)	340	1.14 (0.98–1.32)	1.13 (0.97–1.32)
≥165	713	1.14 (1.02–1.29)	1.15 (1.01–1.31)	110	0.89 (0.66–1.21)	0.88 (0.63–1.23)	603	1.20 (1.06–1.37)	1.22 (1.06–1.40)
P_{trend}		0.006	0.008		0.422	0.576		0.001	0.002
Sitting height (cm)									
<82	368	1 (ref)	1 (ref)	40	1 (ref)	1 (ref)	328	1 (ref)	1 (ref)
82–85	536	0.98 (0.86–1.12)	0.97 (0.85–1.11)	81	1.35 (0.92–1.98)	1.19 (0.81–1.76)	455	0.96 (0.83–1.10)	0.94 (0.81–1.08)
85–87	466	1.02 (0.89–1.17)	1.00 (0.87–1.15)	70	1.04 (0.70–1.53)	0.93 (0.62–1.39)	396	1.02 (0.88–1.18)	0.99 (0.85–1.15)
≥87	695	1.04 (0.91–1.18)	1.02 (0.89–1.16)	115	1.07 (0.74–1.53)	1.02 (0.70–1.49)	580	1.05 (0.92–1.21)	1.03 (0.89–1.18)
P_{trend}		0.411	0.64		0.674	0.723		0.253	0.37
Leg length (cm)									
<74	457	1 (ref)	1 (ref)	72	1 (ref)	1 (ref)	385	1 (ref)	1 (ref)
74–77	501	1.06 (0.94–1.21)	1.06 (0.93–1.21)	81	1.07 (0.78–1.48)	1.03 (0.74–1.44)	420	1.06 (0.93–1.22)	1.06 (0.92–1.21)
77–80	495	1.11 (0.97–1.26)	1.11 (0.97–1.27)	73	0.97 (0.70–1.34)	1.05 (0.74–1.47)	422	1.13 (0.98–1.30)	1.13 (0.98–1.30)
≥80	612	1.16 (1.02–1.31)	1.17 (1.03–1.33)	80	0.97 (0.70–1.33)	1.00 (0.71–1.40)	532	1.19 (1.05–1.36)	1.20 (1.05–1.38)
P_{trend}		0.015	0.015		0.702	0.982		0.005	0.02

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for (1) non updated variables: education level (undergraduate/graduate or postgraduate), total physical activity (MET-h/wk), age at menarche (year), nulliparity (yes/no) age at first full-term pregnancy (before/after 30 years), breastfeeding (yes/no/unknown), age at menarche (year), age at menopause (year for postmenopausal women only), birth height (short, medium, large) and birth weight (low, medium, and large; (2) variables considered as time dependent: menopausal status (yes/no), use of oral contraceptives (current/non-user), family history of breast cancer (yes/no), mammography during the previous follow-up period (yes/no/unknown), history of benign breast disease (never/ever), use of oral progestagens alone before menopause (current/non-user), use of menopausal hormone therapy (MHT, current/non-user for postmenopausal women only).

With regard to ER^- tumors, an inverse association was observed for height which was restricted to premenopausal women (HR = 0.33[0.14–0.77 and 0.35[0.18–0.70], respectively, for the third and fourth quartile). A negative significant trend was observed ($P = 0.003$). A negative trend was also observed for sitting height ($P = 0.011$) but not for leg length ($P = 0.365$).

Influence of birth weight and height

An interaction between birth length and leg length was observed ($P = 0.066$). We thus, stratified our data by birth length and birth weight (not tabulated). The positive association between height, leg length, and breast cancer risk was restricted to women with a short birth length [HR = 1.78 (1.11–2.83) for the last category of height, $P_{trend} = 0.033$, HR = 1.82 (1.22–2.72) for the last category of leg length, $P_{trend} = 0.022$]. The association with leg length was restricted to women with a low birth weight [HR = 1.43 (1.00–2.04) for the last category and $P_{trend} = 0.0538$]. No other association was significant.

Discussion

In this study, we found a positive association between height and postmenopausal breast cancer risk, driven by leg length. No association between height or its components and overall premenopausal breast cancer risk has been observed. Leg length was associated with an increased risk of ER^+ breast cancer risk in postmenopausal, restricted to women who had a short birth length or a low birth weight, whereas sitting height was associated with a decreased ER^- premenopausal breast cancer risk.

There is evidence that height is associated with breast cancer risk in the literature (1, 2, 4, 10, 11). The absence of association in our study between height and premenopausal breast cancer risk may be attributed to small numbers in this category or to a limited height range in our cohort, with few tall women (12). Height is a biomarker of nutrition and growth factors in childhood (13–16). Although the interest of these variables was recently discussed (6), leg length and sitting height are considered more closely associated to growth hormone exposure than height, respectively, before and after menarche (1, 10).

Leg length has been suggested to be a privileged marker of exposures early in life, as it is particularly sensitive to environmental factors and diet in early childhood (17). In addition, leg length might be a more accurate and stable measure over time than height alone, as height loss in postmenopausal women is typically confined to the axial

Table 3. Multivariate models for height, sitting height, and leg length associations with breast cancer risk in the overall, pre- and postmenopausal population, stratified by estrogen receptor status, E3N cohort ($N = 50{,}704$)

	Overall population[a]				Premenopausal women[a]				Postmenopausal women[a]			
		ER^+		ER^-		ER^+		ER^-		ER^+		ER^-
	N	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)
Height (cm)												
<158	350	1	103	1	45	1	24	1	305	1	79	1
158–162	419	1.04 (0.90–1.20)	90	0.71 (0.53–0.95)	57	0.95 (0.64–1.43)	20	0.54 (0.29–1.01)	362	1.05 (0.89–1.25)	70	0.67 (0.47–0.95)
162–165	323	1.17 (1.00–1.37)	67	0.75 (0.55–1.04)	41	1.00 (0.64–1.57)	9	0.33 (0.14–0.77)	282	1.19 (1.00–1.43)	58	0.78 (0.53–1.13)
≥165	599	1.28 (1.11–1.48)	114	0.75 (0.56–1.00)	92	1.15 (0.77–1.71)	18	0.35 (0.18–0.70)	507	1.33 (1.13–1.57)	96	0.85 (0.61–1.19)
P_{trend}		<0.001		0.098		0.372		0.003		<0.001		0.589
Sitting height (cm)												
<82	293	1	75	1	29	1	11	1	264	1	64	1
82–85	430	0.99 (0.85–1.14)	106	0.91 (0.68–1.23)	57	1.16 (0.73–1.84)	24	1.21 (0.58–2.53)	373	0.99 (0.83–1.17)	82	0.86 (0.61–1.22)
85–87	387	1.05 (0.90–1.23)	79	0.78 (0.57–1.07)	50	0.91 (0.57–1.47)	20	0.88 (0.41–1.90)	337	1.02 (0.86–1.22)	59	0.72 (0.49–1.06)
≥87	581	1.08 (0.94–1.26)	114	0.76 (0.56–1.03)	99	1.23 (0.79–1.89)	16	0.45 (0.20–1.01)	482	1.10 (0.93–1.30)	98	0.86 (0.61–1.22)
P_{trend}		0.158		0.055		0.370		0.011		0.186		0.416
Leg length (cm)												
<74	365	1	92	1	51	1	21	1	314	1	71	1
74–77	404	1.08 (0.94–1.25)	97	1.00 (0.75–1.34)	62	1.12 (0.76–1.64)	19	0.77 (0.40–1.47)	342	1.01 (0.85–1.19)	78	1.03 (0.73–1.45)
77–80	411	1.16 (1.01–1.34)	84	0.92 (0.68–1.24)	60	1.20 (0.81–1.77)	13	0.61 (0.30–1.26)	351	1.07 (0.90–1.26)	71	0.93 (0.65–1.33)
≥ 80	511	1.22 (1.06–1.41)	101	0.96 (0.72–1.29)	62	1.07 (0.72–1.59)	18	0.76 (0.38–1.49)	449	1.24 (1.06–1.46)	83	0.98 (0.69–1.39)
P_{trend}		0.003		0.697		0.712		0.365		0.004		0.781

[a] Models were adjusted for (1) nonupdated variables: education level (undergraduate/graduate or postgraduate), total physical activity (MET-h/wk), age at menarche (year), nulliparity (yes/no) age at first full-term pregnancy (before/after 30 years), breastfeeding (yes/no/unknown), family history of breast cancer (yes/no) age at menopause (year for postmenopausal women only), birth length (short: ≤2,490 g/medium: 2,490–4,000 g/high: >4,000g), birth weight (low: ≤47cm/medium: 47–51 cm/large: >51 cm) and body shape at menarche (lean, medium, large; (2) variables considered as time-dependent: use of oral contraceptives (current/non-user), menopausal status (yes/no), mammography during the previous follow-up period (yes/no/unknown), history of benign breast disease (never/ever), use of oral progestagens alone before menopause (current/non-user), use of menopausal hormone therapy (MHT, current/non-user for postmenopausal women only).

skeleton (18)-–mainly because of changes in the spinal vertebral bodies by osteoporosis and disk spaces (19). Our results also indicate that the overall association between height—or leg length-–and breast cancer risk are restricted to women with short birth length or low birth weight, which is in agreement with De Stavola and colleagues (2) who found that women with a catch-up growth during childhood—which is also associated with nutritional exposures (17)-–were at particularly increased risk of breast cancer. Catch-up growth has also already been associated with diet during childhood or adolescence. Our results can also be explained by the increased IGF-I levels, acting as a potential cancer promoter, observed in prepubertal children with low birth weight and postnatal catch-up growth (20). IGF-1 levels can act as a potential cancer promoter by inhibiting apoptosis and increasing the differentiation of cells (21), particularly of ER^+ subtype (22). But the association between IGF-1 levels in childhood and IGF-1 levels at adulthood is discussed (23). Another hypothesis involves insulinoresistance and diabetes: low birth weight and postnatal catch-up growth are associated with later-life risk of insulinoresistance and type 2 diabetes (24), which have been shown to increase risk of postmenopausal breast cancer, particularly of the ER^+ subtype (25). We had no biologic hypothesis supporting the decreased risk of ER^- premenopausal breast cancer with increasing sitting height, and to our knowledge, no other study has ever analyzed this relationship before.

Strengths and limits of the study

Anthropometric information was self-reported. A validation study proved them reliable (9): with correlation coefficients between self-reported and measured values of height and sitting height of, respectively, 0.94 and 0.56. Even if the correlation coefficient for sitting height was low as compared with the one for height, no absolute difference exceeded 1.1 cm, so that a categorization in quartiles made the risk of misclassification bias unlikely. Another limitation is the potential limited power in some categories and the limited variability of height in the cohort, which might be insufficient to detect small associations.

A major strength was our ability to stratify the analyses by menopausal status, ER status, birth length, and weight for the first time in a prospective study.

Conclusion

In our study, a large leg length was found to be a risk factor for breast cancer, but only for women who had a short birth length. Moreover, leg length seemed to be a risk factor only for ER^+ tumors in postmenopause, whereas a large sitting height was associated with a decreased risk of ER^- premenopausal tumors. These results provided evidence that the relationship between height and breast cancer risk can no longer be interpreted as a simple single association.

Disclosure of Potential Conflicts of Interest

The study sponsors had no role in the design of the study, analysis or interpretation of data, writing of the manuscript or the decision to submit the manuscript for publication.

Authors' Contributions

Conception and design: G. Fagherazzi, F. Clavel-Chapelon, S. Mesrine
Development of methodology: G. Fagherazzi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Clavel-Chapelon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Fagherazzi, A. Vilier, M.-C. Boutron-Ruault, S. Mesrine
Writing, review, and/or revision of the manuscript: G. Fagherazzi, M.-C. Boutron-Ruault, S. Mesrine
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Clavel-Chapelon
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