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Associations of adult-attained height and early life energy restriction with postmenopausal breast cancer risk according to estrogen and progesterone receptor status

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Adult-attained height is a marker for underlying mechanisms, such as cell growth, that may also influence postmenopausal breast cancer (BC) risk, perhaps specifically hormone-sensitive BC subtypes. Early life energy restriction may inhibit these mechanisms, resulting in shorter height and a reduced postmenopausal BC risk. Women (62,573) from the Netherlands Cohort Study completed a self-administered questionnaire in 1986 when 55–69 years old, and were followed-up for 20.3 years (case–cohort: $N_{subcohort}$ = 2,438; N_{cases} = 3,354). Cox multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated for BC risk overall and by estrogen and progesterone receptor subtypes in relation to height and early life energy restriction during the Hunger Winter, War Years, and Economic Depression. Although energy restriction can only influence longitudinal growth in women exposed before and/or during the growth spurt, it may also influence BC risk when occurring after the growth spurt, possibly through different growth processes. Therefore, Cox analyses were additionally conducted according to timing of energy restriction in relation to the growth spurt. Height was associated with an increased BC risk ($HR_{per\ 5cm}$ = 1.07, 95%CI:1.01–1.13), particularly hormone receptor-positive BC. Energy restriction before and/or during the growth spurt was associated with a decreased hormone receptor-positive BC risk. Energy restriction during the Hunger Winter increased the estrogen receptor-negative BC risk regardless of the timing of energy restriction. In conclusion, height and energy restriction before and/or during the growth spurt were both associated with hormone receptor-positive BC risk, in the direction as expected, indicating critical exposure windows for hormonal growth-related mechanisms.

Introduction

Based on meta-analyses from cohort studies, there is convincing evidence that postmenopausal breast cancer (BC) risk is increased by 7–11% for every 5 cm increase in adult-attained height.[1–3] This may be of particular relevance for the tallest population in the world, the population of the Netherlands,[4] which also has one of the highest BC rates worldwide.[5] While information on BC hormone receptor status is not always available, associations between adult-attained height and postmenopausal BC risk may exist particularly for the most commonly diagnosed breast cancer subtype, which is the estrogen receptor positive (ER+) subtype. Associations of adult-attained height with ER+ BC have been reported both in combination with PR+ BC[6,7] and when studied separately as an endpoint (i.e., no information on PR status was available).[8–10] Significantly increased ER+ BC relative risks have been reported in association with adult-attained height and null associations have been reported for ER-BC risk,[8,9] when ER status is studied regardless of PR status as an endpoint. Joint ER+PR+ BC status has been associated with increased relative risks in relation to adult-attained height,[6,7] whereas joint ER-PR- BC status has been associated both with increased relative risks[7] and null associations.[6] There is only one study that investigated adult-attained height in relation to PR+ tumors as a separate endpoint, which reported associations with nonsignificant increased relative risks for both PR+ and PR- BC status.[8] The inconclusive findings for adult-attained height and hormone-receptor negative subtypes, that is, both null associations and nonsignificantly increased relative risks, may be due to the fact that BCs with a negative hormone receptor status are less common, resulting in relatively less power to investigate these subtypes, and that information

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What's new?

Evidence suggests that postmenopausal breast cancer risk increases with height, while risk is reduced among individuals who experience reduced caloric intake in early life, which can result in shorter adult stature. In this investigation of women in the Netherlands Cohort Study, significant early-life energy restriction, either before or during the pubertal growth spurt, was associated specifically with a decreased risk of estrogen receptor-positive and progesterone receptor-positive postmenopausal breast cancer. Greater adult-attained height was significantly associated with increased hormone receptor-positive postmenopausal breast cancer risk. The findings highlight the influence of hormonal growth-related mechanisms on later postmenopausal breast cancer risk.

on PR BC status is less often available than ER BC status, limiting opportunities to investigate this. Yet, it is also plausible that there is a null association between adult-attained height and hormone receptor-negative BC.

Adult-attained height is a marker for mechanisms such as cell growth, which determine both adult-attained height and postmenopausal BC risk. These growth processes can be influenced by early life environmental exposures.[11,12] Therefore, when energy balance is disturbed in early life, for example, by energy restriction, this can have an effect on adult-attained height and postmenopausal BC risk later in life. In a recent meta-analysis of observational studies by our group, severe transient energy restriction during early life was associated with a 28% increased BC risk, though some of the underlying studies showed null results.[13] Conversely, moderate energy restriction during early life for a longer period of time, as studied in animal experimental models and human ecological studies, was generally inversely associated with BC risk.[13] Biologically, the latter seems plausible as continuous moderate early life energy restriction (pre- and peripubertal) may lead to decreased growth factor levels,[14] which in turn may result in a shorter stature[15–17] and a reduced postmenopausal BC risk.[18] Earlier and more rapid childhood and pubertal growth, for instance during catch-up growth, on the other hand, appear to increase postmenopausal BC risk.[19–22] In our meta-analysis, results from a sub analysis on energy restriction in women aged 10–20 years indicated a 21% increased BC risk compared to women not exposed during that age period. A comparison with the summary risk estimate in women aged 0–10 years was not possible, however, as this estimate could not be computed due to a high between-study heterogeneity.[13] One source of heterogeneity in results may be differences in distribution of hormone receptor subtypes among BC cases. To our knowledge, only one report has been published on the association between energy restriction and postmenopausal BC risk by ER+/- and PR+/- status, investigating combinations of ER+/- and PR+/- subtypes.[23] Results of our study showed that women exposed to the Chinese famine, particularly those exposed after birth (0–3 years), had an increased risk of ER-PR- BC, ER-PR+ BC, and ER+PR- BC, while no association was observed with ER+PR+ BC.

The Netherlands Cohort Study (NLCS), a prospective cohort study that includes 58,279 men and 62,573 women, has data available on height, early life energy restriction, ER+/- and PR+/- status of breast cancer cases during follow-up and other covariates. The long follow-up of 20.3 years enabled us to study the following aims with sufficient power. Firstly, we investigated the association of adult-attained height with overall postmenopausal BC risk and by ER+/- and PR+/- status of the tumor. Secondly, we examined the association of early life energy restriction with overall postmenopausal BC risk and by ER+/- and PR+/- status of the tumor. Considering that different growth processes may be at play during different periods in life, we additionally conducted these analyses according to timing of energy restriction in relation to the growth spurt. Energy restriction was hypothesized to be able to affect longitudinal growth only when exposure occurred before and/or during the growth spurt, but an effect on BC risk could also exist for exposure after the growth spurt, and not necessarily through a relationship between energy restriction and height. The association between adult-attained height and early life energy restriction with regard to breast cancer risk has been studied in the NLCS previously. A positive association between adult-attained height and breast cancer risk among postmenopausal women was observed, after 4.3 years of follow-up.[24] With regard to energy restriction, neither exposure to early life energy restriction regardless of timing of the growth spurt nor exposure to energy restriction during the adolescent growth spurt were associated with breast cancer risk after 6.3 years of follow-up.[25]

Methods

Study population and design

The Netherlands Cohort Study (NLCS) includes 58,279 men and 62,573 women, who were 55 to 69 years old at baseline in September 1986.[26] Participants completed a self-administered questionnaire at baseline on cancer risk factors. For efficiency reasons related to the processing of questionnaires and follow-up, the NLCS uses a case-cohort design in which cases are enumerated from the entire cohort and the person-time at risk is estimated from a subcohort. This subcohort, consisting of 5,000 men and women, was randomly selected immediately after baseline and independent of exposure. The follow-up for vital status and migration is performed through linkage to the Central Bureau of Genealogy and the municipal population registries (~100% completeness).[27] Cancer follow-up is

Table 1. Overview of the overlap between hormone receptor subtypes of breast cancer in postmenopausal women of the Netherlands Cohort Study

	PR+ BC cases	PR- BC cases	BC cases with unknown PR status	
	N (%)	N (%)	N (%)	*Total number of BC cases by ER status*
ER+ BC cases	979 (97,0%)	308 (55,4%)	333 (18,6%)	1,620
ER- BC cases	30 (3,0%)	245 (44,1%)	89 (5,0%)	364
BC cases with unknown ER status	0 (0,0%)	3 (0,5%)	1,367 (76,4%)	1,370
Total number of BC cases by PR status	1,009	556	1,789	3,354

Abbreviation: BC, breast cancer; ER+, estrogen receptor positive; ER-, estrogen receptor negative; PR+, progesterone receptor positive; PR-, progesterone receptor negative.

performed through linkage to the population-based cancer registry and PALGA (Netherlands pathology database; >95% completeness).[28] Participants who reported a history of cancer at baseline (except skin cancer) were excluded leaving 4,774 subcohort members, of which 2,438 female subcohort members. A total of 3,354 postmenopausal BC cases were identified in the total cohort after 20.3 years of follow-up (September 17, 1986, until January 1, 2007) (ICD-O-3: C50). ER and PR receptor status was available for 59% and 47% of the cases, respectively, with 1,620 ER+ cases, 364 ER- cases, 1,009 PR+ cases, and 556 PR- cases (see Table 1 for an overview of the overlap between hormone receptor subtypes). If dietary data of participants were incomplete or inconsistent, these participants were excluded, leaving 2,248 female subcohort members

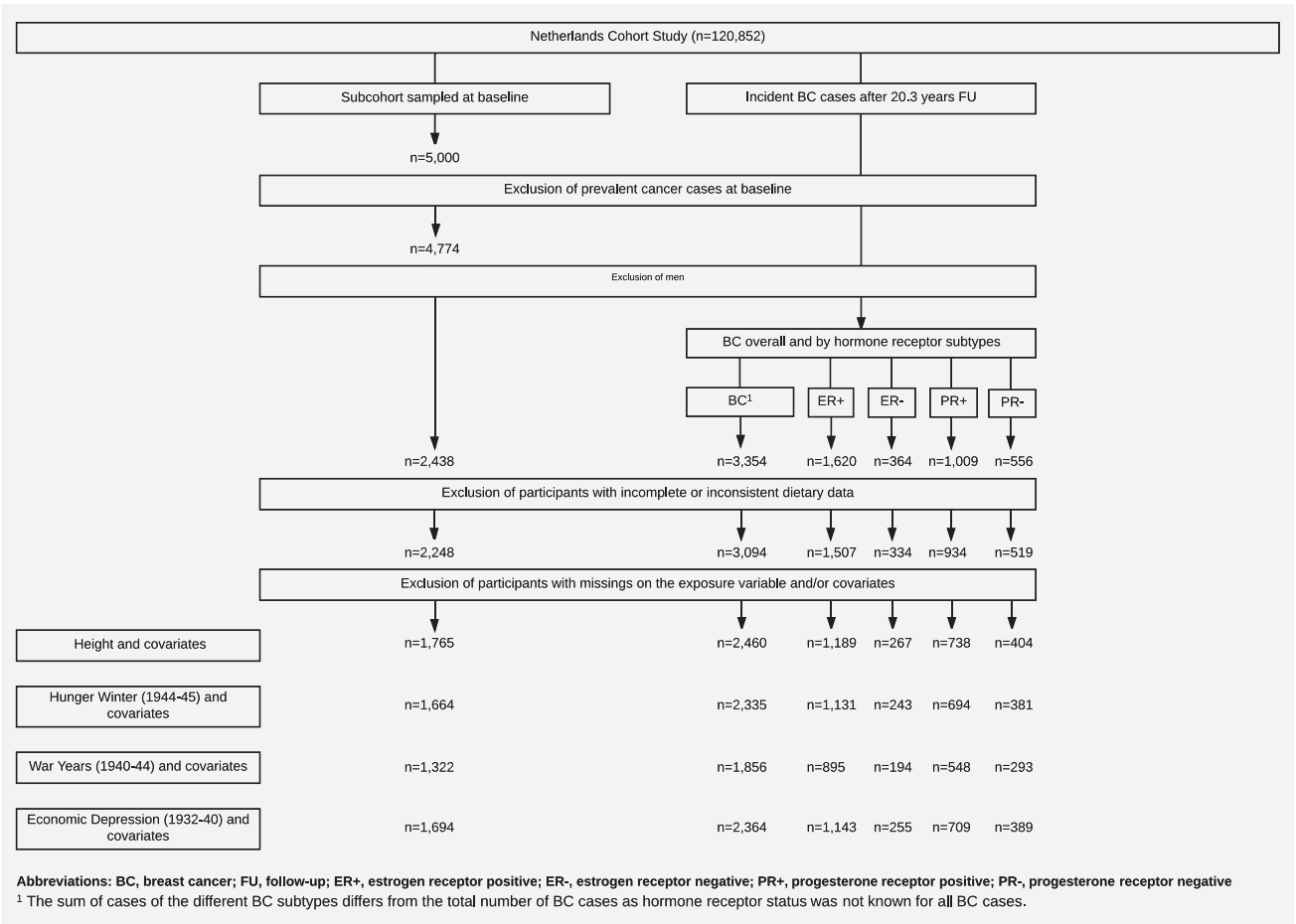

Figure 1. Flow diagram of available subcohort members and breast cancer cases among postmenopausal women in the Netherlands Cohort Study, 1986–2006.

and 3,094 postmenopausal BC cases, among which 1,507 ER+ cases, 334 ER- cases, 934 PR+ cases, and 519 PR- cases (see flow chart in Fig. 1).

Exposure assessment

Adult-attained height (cm) was self-reported on the baseline questionnaire. Height was defined as a continuous variable (per 5 cm increase) as well as a categorical variable in tertiles based on the distribution in the female subcohort. Early life energy restriction was measured through three proxy variables, as individual food intake data in early life of the cohort members were not available. The proxies covered three time periods in the Netherlands during which a part of the population experienced energy restriction, that is, the Hunger Winter (the winter of 1944–45), the War Years (1940–44), and the Economic Depression (1932–40). For the Hunger Winter, which was at its height between December 1944 and May 1945, place of residence was used to approximate exposure to energy restriction as individuals living in a western city, and to a lesser extent a western rural area, were exposed to (severe) energy restriction. During this time period, official daily rations *per capita* were between 400 and 800 kcal for women living in a western city.[29,30] In a follow-up study in the NLCS, female subcohort members were asked if they really had experienced hunger during the Hunger Winter. Of the women who reported severe hunger, 80% lived in a western city during this winter.[25] These results indicate that place of residence during the Hunger Winter is an adequate proxy for exposure to energy restriction. Place of residence was based on the reported residence during the winter of 1944–45 and classified into "living in a nonwestern area," "living in a western rural area," or "living in a western city." Also for the War Years, place of residence was used as a proxy for energy restriction. During the War Years, food rationing was introduced, and caloric intake was reduced to ~1,700 kcal/d during 1941–1943.[31] Between 1943 and 1944, the nutritional status of the Dutch population deteriorated, especially for those living in the cities.[25] Place of residence was based on the question to list the last 4 residences before baseline of the study, which resulted in a classification into "living in an urban area" (defined as a town with at least 40,000 residents) or "living in a rural area" in 1942 (the midpoint of the War Years 1940–44). For the Economic Depression, employment status of the father was used to approximate exposure to energy restriction. Several surveys showed that having an unemployed father indicated that the number of calories available was less and the variation in the individual's food pattern was limited compared to families with an employed father.[25,32] Father's employment status was dichotomized into participants whose father had a job during the years of the Economic Depression or worked intermittingly ("employed") and cohort members with fathers without a job during these years ("unemployed").[33] Information on covariates that were considered potential confounders on the basis of previous research was also available from the baseline questionnaire.

Statistical analyses

We calculated the mean adult-attained height for each category of the three proxies for early life energy restriction in those female subcohort members exposed to energy restriction before and/or during the growth spurt, since we only expected an effect of energy restriction on mean adult-attained height in this subgroup of women. The historic events that are associated to the three proxies took place in three different periods in time and thus affected cohort members at different ages (12–28 years for the Hunger Winter, 7–28 years for the War Years, and 0–23 years for the Economic Depression). The growth spurt was defined as two years before the self-reported age at menarche until one year after the reported age at menarche. Furthermore, in a sensitivity analysis, we restricted the analyses for the Hunger Winter and the War Years to individuals from the middle provinces of the Netherlands. We did so, because there was virtually no exposure to energy restriction in the northern and southern provinces during both time periods, as these are mostly nonwestern and rural areas, and, at the same time, these provinces are characterized by, on average, the tallest and shortest people in the country, respectively.[4] Including individuals from these provinces in the analyses, therefore, can mask the relationship between energy restriction and height, if present. Cox proportional hazards analysis was used to estimate both age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for postmenopausal BC risk overall and by ER+/- and PR+/- status. In the multivariable-adjusted models, we adjusted for potential confounders that were selected *a priori* on the basis of that these were risk factors in the literature. To account for the additional variance introduced by sampling the subcohort from the entire cohort, standard errors were estimated using the robust Huber-White sandwich estimator.[34] The proportional hazards assumption was tested using the scaled Schoenfeld residuals and by visual inspection of the -log(−log) transformed hazard curves.[35]

In the multivariable-adjusted models for height and postmenopausal BC risk, the following *a priori* selected potential confounders were included on the basis of that these are potential risk factors for postmenopausal BC: age at baseline (y), energy intake (kcal/d), baseline nonoccupational physical activity ($\leq$30 min/d, >30- $\leq$60 min/d, >60–90 min/d, >90 min/d), smoking status (never, former, current), smoking frequency (numbers of cigarettes per day; continuous, centered), and smoking duration (number of years; continuous, centered), alcohol intake (0, 0.1–29, $\geq$30 g/d), level of education (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/ university), family history of BC (no, yes), history of benign breast disease (no, yes), age at menarche (y), age at menopause (y), age at first childbirth (nulliparous, >25y, $\leq$ 25y), parity (*n* children), oral contraceptive use (never, ever), and postmenopausal hormone-replacement therapy (never, ever). After excluding

participants without (complete) information on height and/or the covariates, 1,765 subcohort members and 2,460 postmenopausal BC cases were left for analysis (see Fig. 1).

Considering that (most) other studies that have investigated the height-BC association have not adjusted for body mass index (BMI) (kg/m^2) or weight (kg), our primary model will not include BMI or weight, enabling comparison of our results with those in the literature. BMI approximates body fatness, though may do so differentially depending on age and height, with a positive correlation between height and BMI in young populations and an inverse correlation in older populations.[36,37] Since the NLCS comprises an older population, we conducted two additional sensitivity analyses to investigate whether including either BMI or weight as additional continuous covariates in the models for height changed the associations.

In the multivariable-adjusted models for early life energy restriction and postmenopausal BC risk, the following *a priori* selected potential confounders were included on the basis of that these are potential risk factors for postmenopausal BC: age at baseline (y), BMI (kg/m^2), energy intake (kcal/d), baseline nonoccupational physical activity ($\leq$30 min/d, >30- $\leq$ 60 min/d, >60–90 min/d, >90 min/d), smoking status (never, former, current), smoking frequency (numbers of cigarettes per day; continuous, centered), smoking duration (number of years; continuous, centered), alcohol intake (0, 0.1–29, $\geq$30 g/d), level of education (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/ university), family history of BC (no, yes), history of benign breast disease (no, yes), age at menopause (y), age at first childbirth (nulliparous, >25y, $\leq$ 25y), parity (*n* children), oral contraceptive use (never, ever), and postmenopausal hormone-replacement therapy (never, ever). In a sensitivity analysis, we checked whether additional adjustment for adult-attained height and age at menarche changed the results because these are also important risk factors for postmenopausal BC. However, early life energy restriction may also influence adult-attained height and age at menarche and these could thus also act as intermediate factors. After excluding participants without (complete) information on energy restriction and/or the primary covariates of interest, 1,664 subcohort members and 2,335 postmenopausal BC cases were left for analysis for the Hunger Winter, 1,322 subcohort members and 1,856 postmenopausal BC cases left for analysis for the War Years, and 1,694 subcohort members and 2,364 postmenopausal BC cases for the Economic Depression (see Fig. 1).

Results

Table 2 shows baseline characteristics of the female subcohort members and postmenopausal BC cases overall and by hormone receptor subtypes. Postmenopausal BC cases, in particular ER+ and PR+ cases, more often reported a family history of BC compared to subcohort members. Additionally, postmenopausal BC cases more often reported a history of benign breast disease compared to subcohort members.

Mean adult-attained height according to early life energy restriction. Table 3 shows the mean adult-attained height by exposure to early life energy restriction in female subcohort members who were exposed to energy restriction before and/or during the growth spurt, and when further restricting to female subcohort members living in the middle provinces of the Netherlands. There were no differences in height between female subcohort members who were and those who were not exposed to energy restriction before and/or during the growth spurt as a result of the Hunger Winter or the War Years. Further restriction of the analyses to those living in the middle provinces of the Netherlands did not change this finding. During the Economic Depression, most of the women from the cohort were younger (0–23 years) and most (94.4%) were before or in their growth spurt. Female subcohort members who were exposed to energy restriction during the Economic Depression before or during their growth spurt were statistically significantly shorter than those without this exposure (163.8 cm *versus* 165.5 cm, respectively).

Adult-attained height and postmenopausal BC risk. Table 4 shows the associations between adult-attained height and postmenopausal BC risk overall and by hormone receptor subtypes. Height was associated with a significantly increased risk of postmenopausal BC overall ($HR_{per\ 5\ cm}$ = 1.07, 95% CI: 1.01–1.13). In particular, height was positively associated with ER+ BC risk ($HR_{per\ 5\ cm}$ = 1.08, 95% CI: 1.01–1.15) and, though borderline significant, with PR+ BC risk ($HR_{per\ 5\ cm}$ = 1.07, 95% CI: 0.99–1.16), but not with ER- BC risk ($HR_{per\ 5\ cm}$: 1.03, 95% CI: 0.92–1.16) or PR- BC risk ($HR_{per\ 5\ cm}$ = 1.05, 95% CI: 0.95–1.16). Including either BMI or weight, both as additional continuous covariates, in the models for height did not change the associations (data not shown).

Supporting Information Table 1 shows the associations between adult-attained height and postmenopausal BC risk by combinations of hormone receptor subtypes. Height was only borderline significantly associated with an increased ER+PR+ BC risk ($HR_{per\ 5\ cm}$ = 1.07, 95% CI: 0.99–1.16) and an increased ER+PR- BC risk ($HR_{per\ 5\ cm}$ = 1.12, 95% CI: 0.99–1.28), though the number of cases was rather low for other combinations, especially ER-PR+ BC.

Early life energy restriction and postmenopausal BC risk. Table 5 shows the associations between exposure to early life energy restriction and postmenopausal BC risk overall and by hormone receptor subtypes, including stratification on exposure to energy restriction before and/or during the growth spurt *versus* after the growth spurt. Exposure to energy restriction before and/or during the growth spurt could potentially have an effect on longitudinal growth and, particularly in this group, exposure to energy restriction was associated

Table 2. Baseline characteristics of female subcohort members and postmenopausal BC cases overall and by hormone receptor subtypes in the Netherlands Cohort Study[1]

	Subcohort		Postmenopausal BC cases		ER+		ER−		PR+		PR−	
	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)
Height, cm	165.2 (6.2)		165.8 (6.5)		165.9 (6.5)		165.3 (6.7)		165.8 (6.4)		165.7 (6.6)	
Residence during Hunger Winter (1944-45)[2]												
Nonwestern		56.6		55.1		55.6		47.7		62.4		57.7
Western rural		15.0		16.3		15.4		21.2		13.9		15.0
Western city		28.4		28.6		29.0		31.1		23.7		27.3
Residence during War years (1940–1944)[2]												
Rural area in 1942		46.8		47.1		43.8		44.8		47.2		44.3
Urban area in 1942		53.2		52.9		56.2		55.2		52.8		55.7
Job status father during Economic Depression (1932–1940)[2]												
Employed		88.5		90.2		90.1		87.9		90.8		90.6
Unemployed		11.5		9.8		9.9		12.1		9.2		9.4
Age at baseline, y	61.4 (4.3)		61.3 (4.1)		61.3 (4.2)		61.0 (3.9)		61.3 (4.2)		60.9 (3.9)	
Adult BMI, kg/m^2	25.1 (3.6)		25.4 (3.4)		25.4 (3.3)		24.9 (3.4)		25.5 (3.4)		25.1 (3.3)	
Energy intake, kcal/d	1,686 (397)		1,688 (399)		1,683 (398)		1,691 (416)		1,681 (397)		1,729 (413)	
Baseline nonoccupational physical activity, min/d[2]												
≤30		25.0		27.9		26.9		28.6		27.8		26.9
30–≤60		31.2		31.8		32.0		24.9		31.5		30.4
› 60–90		22.4		21.1		21.0		24.6		20.5		22.0
› 90		21.4		19.2		20.1		21.9		20.2		20.7
Cigarette smoking[2]												
Never		58.4		56.4		56.1		53.6		57.2		54.7
Former		20.6		22.6		22.7		23.0		23.8		20.6
Current		21.0		21.0		21.2		23.4		19.0		24.7
Number of cigarettes per day[3]	4.6 (7.7)		5.0 (8.0)		5.0 (8.1)		5.6 (8.4)		4.6 (7.7)		5.3 (8.3)	
Years of smoking[3]	11.4 (15.8)		11.8 (15.9)		12.0 (16.1)		12.7 (16.2)		11.4 (15.7)		12.7 (16.4)	
Alcohol intake, g/d[2]												
0		32.3		30.3		30.6		31.6		31.8		28.8
0.1–29		64.2		64.7		65.2		63.5		64.5		65.8
≥30		3.5		5.0		4.2		4.9		3.7		5.4
Level of education[2]												
Primary school		33.5		32.5		31.7		35.0		31.5		35.1
Lower vocational school		23.2		21.6		22.2		19.0		21.5		19.4
Intermediate vocational/high school		34.5		36.8		37.6		36.6		37.7		37.7

(Continues)

Table 2. Continued

	Subcohort		Postmenopausal BC cases		ER+		ER−		PR+		PR−	
	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)	Mean (SD)	(%)
Higher vocational school/ university		8.8		9.1		8.5		9.4		9.3		7.8
Family history of BC[2]												
No		91.3		85.8		85.9		88.6		84.7		89.2
Yes		8.7		14.2		14.1		11.4		15.3		10.8
History of benign breast disease[2]												
No		92.3		87.5		88.8		88.0		88.8		88.2
Yes		7.7		12.5		11.2		12.0		11.2		11.8
Age at menarche, y	13.7 (1.8)		13.5 (1.7)		13.5 (1.8)		13.4 (1.7)		13.4 (1.7)		13.6 (1.8)	
Age at menopause, y	48.7 (4.5)		49.1 (4.3)		49.0 (4.4)		48.6 (4.3)		48.8 (4.5)		49.1 (4.2)	
Age at first childbirth[2], y												
Nulliparous		18.0		19.4		18.7		17.7		18.2		17.5
< 25		22.9		21.3		20.8		24.8		21.4		21.2
≥ 25		59.1		59.3		60.5		57.5		60.4		61.3
Parity[2], n children												
Nulliparous		18.0		19.4		18.7		17.7		18.2		17.5
1 child		8.3		8.9		9.2		8.7		9.8		7.3
2 children		21.2		23.7		24.0		22.1		23.1		23.3
≥ 3 children		52.5		48.0		48.1		51.5		48.9		51.9
Oral contraceptive use[2]												
Never		75.0		75.0		76.1		72.2		77.7		72.2
Ever		25.0		25.0		23.9		7.8		22.3		27.8
Postmenopausal hormone replacement therapy[2]												
No		6.8		86.4		86.0		87.7		84.8		86.6
Yes		13.2		13.6		14.0		12.3		15.2		13.4

Abbreviations: BC, breast cancer; BMI, body mass index; ER+, estrogen receptor positive; ER-, estrogen receptor negative; PR+, progesterone receptor positive; PR-, progesterone receptor negative; SD, standard deviation.
[1]Participants with incomplete or inconsistent dietary data were excluded.
[2]Sums of categories differ because of missing values on the particular variable.
[3]Among former and current smokers only.

Table 3. Mean and SD of adult-attained height by exposure to early life energy restriction in all female subcohort members in the Netherlands Cohort Study, when restricting to those who were exposed to energy restriction before and/or during the growth spurt[1], and when additionally restricting to those living in the middle provinces of the Netherlands

	All women		Women with energy restriction before/during the growth spurt		Women with energy restriction before/during the growth spurt who lived in the middle provinces of the Netherlands	
Proxies for early life energy restriction	N	Mean height in cm (SD)	N	Mean height in cm (SD)	N	Mean height in cm (SD)
Residence during Hunger Winter (1944–1945)						
Nonwestern	1,150	165.5 (6.3)	206	165.9 (6.6)	44	165.0 (6.7)
Western rural	306	165.6 (6.0)	57	164.9 (5.6)	57	164.9 (5.6)
Western city	583	165.4 (5.8)	108	166.5 (5.7)	108	166.5 (5.7)
p-Value[2]		0.91		0.32		0.18
Residence during War Years (1940–44)						
Rural area in 1942	753	165.6 (6.0)	267	165.4 (6.1)	114	165.0 (5.7)
Urban area in 1942	858	165.1 (6.0)	294	165.5 (5.9)	201	165.9 (5.6)
p-Value[2]		0.11		0.79		0.14
Job status father during Economic Depression (1932–1940)						
Employed	1,836	165.5 (6.1)	1,736	165.5 (6.1)	-[3]	-[3]
Unemployed	240	163.6 (6.8)	222	163.8 (6.6)	-[3]	-[3]
p-Value[2]		<0.0001		0.0001		

Abbreviation: SD, standard deviation.
[1]The growth spurt was defined as: 2 years before reported age of menarche till 1 year after reported age of menarche.
[2]Testing for significant differences in mean height between categories of the proxies for early life energy restriction was performed using a t-test in case of two categories and ANOVA in case of more than two categories, with $p < 0.05$ considered statistically significant.
[3]For the Economic Depression, the analyses were not restricted to individuals from the middle provinces of the Netherlands as exposure to energy restriction during this time period was not based on place of residence.

with a decreased risk of postmenopausal BC, particularly ER+ BC and PR+ BC. This result was observed across all three proxies. More specifically, women residing in a western city during the Hunger Winter compared to women residing in a nonwestern area had a significantly decreased risk of ER+ BC and PR+ BC (HR = 0.49; 95% CI: 0.28–0.88; HR = 0.23; 95% CI: 0.10–0.54, respectively). Women living in an urban area during the War Years compared to women living in a rural area had a (non)significantly decreased risk of ER+ BC and PR+ BC (HR = 0.72; 95% CI: 0.51–1.01; HR = 0.59; 95% CI: 0.39–0.89, respectively). Women with an unemployed father during the Economic Depression compared to women with an employed father had a nonsignificantly decreased risk of ER+ BC and PR+ BC (HR = 0.89; 95% CI: 0.68–1.17; HR = 0.76; 95% CI: 0.54–1.07, respectively). The risk of ER- BC was significantly increased for women residing in a western city during the Hunger Winter compared to women residing in a nonwestern area without stratification on timing of exposure to energy restriction in relation to women's growth spurt (HR = 1.54; 95% CI: 1.11–2.12). This increased risk of ER- BC also seemed independent of whether exposure to energy restriction was before and/or during or after the growth spurt, as both hazard ratios were increased, although the first was not statistically significantly increased (HR = 1.82; 95% CI: 0.69–4.78 and HR = 1.51; 95% CI: 1.06–2.17, respectively). This nonsignificant finding for women exposed before and/or during the growth spurt may be due to a low number of cases in this subgroup. Except for the association of exposure to energy restriction during the Hunger Winter when exposed after the growth spurt with increased ER- BC risk, no significant associations were observed between exposure to energy restriction after the growth spurt with regard to the other proxies of energy restriction, that is, the War Years and Economic Depression and other subtypes of BC. Additional adjustment for adult-attained height and age at menarche did not change these results (data not shown).

Supporting Information Table 2 shows the associations between exposure to early life energy restriction and postmenopausal BC risk by combinations of hormone receptor subtypes, including stratification on timing of exposure in relation to the growth spurt. Again, when restricting to those women who were exposed to energy restriction before and/or

Table 4. Hazard ratios and 95% confidence intervals for the association between adult-attained height and postmenopausal BC risk overall and by hormone receptor subtypes in the Netherlands Cohort Study, 1986–2006

		Postmenopausal BC			ER+			ER-			PR+			PR-		
	PY	N	HR[1]	95%CI	N	HR[1]	95%CI	N	HR[1]	95%CI	N	HR[1]	95%CI	N	HR[1]	95%CI
Height (cm)[2]																
Tertile 1 (range: 132–163 cm)	11,424	830	1	ref	396	1	ref	105	1	ref	249	1		147	1	ref
Tertile 2 (range: 164–168 cm)	10,609	864	1.12	(0.96–1.31)	424	1.15	(0.96–1.39)	86	0.88	(0.64–1.22)	266	1.15	(0.93–1.44)	130	0.94	(0.72–1.23)
Tertile 3 (range: 169–198 cm)	8,595	766	1.23	(1.04–1.45)	369	1.25	(1.03–1.52)	76	0.97	(0.69–1.37)	223	1.19	(0.94–1.50)	127	1.14	(0.86–1.51)
p for trend			0.02			0.02			0.81			0.13			0.41	
Continuous per 5 cm	30,629	2,460	1.07	(1.01–1.13)	1,189	1.08	(1.01–1.15)	267	1.03	(0.92–1.16)	738	1.07	(0.99–1.16)	404	1.05	(0.95–1.16)

Abbreviations: BC, breast cancer; CI, confidence interval; ER+, estrogen receptor positive; ER-, estrogen receptor negative; HR, hazard ratio; PR+, progesterone receptor positive; PR-, progesterone receptor negative; PY, person-years.

[1]Adjusted for age (y), energy intake (kcal/d), baseline nonoccupational physical activity (≤30 min/d, >30- ≤ 60 min/d, >60–90 min/d, >90 min/d), smoking status (never, former, current), smoking frequency and smoking duration (number of cigarettes per day and number of years, respectively; continuous, centered), alcohol intake (0, 0.1–29, ≥30 g/d), level of education (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/ university), family history of BC (no, yes), history of benign breast disease (no, yes), age at menarche (y), age at menopause (y), age at first childbirth (nulliparous, >25y, ≤ 25y), parity (n children), oral contraceptive use (never, ever),and postmenopausal hormone-replacement therapy (never, ever).

[2]Tertiles were based on the distribution in the subcohort.

during the growth spurt, the period during which exposure to energy restriction could potentially have had an effect on longitudinal growth, early life energy restriction was (borderline) significantly associated with a decreased risk of ER+PR+ BC, which was consistently observed across all three proxies (HR = 0.23; 95% CI: 0.10–0.54 for women living in a western city during the Hunger Winter compared to women residing in a nonwestern area; HR = 0.60; 95% CI: 0.39–0.91 for women living in an urban area during the War Years compared to women living in a rural area; and HR = 0.74; 95% CI: 0.53–1.04 for women with an unemployed father during the Economic Depression compared to women with an employed father). The three remaining combinations of hormone receptor subtypes showed no significant associations with any of the energy restriction exposures considered. However, it should be kept in mind that the number of cases was rather low, especially for ER-PR+ BC and ER-PR- BC; resulting in unstable HRs and we refrained from presenting these when the number of cases in the exposure or reference category was less than five.

Discussion

In our study, height was significantly positively associated with BC risk, in particular with hormone receptor-positive BC subtypes. Of the three exposures to energy restriction investigated, that is, exposure to energy restriction during the Economic Depression, War Years, and Hunger Winter, only exposure to energy restriction during the Economic Depression was related to a shorter stature in female subcohort members who were before and/or during their growth spurt, and thus relatively young (0–23 years). Nevertheless, energy restriction during all three periods of exposure provided it occurred before and/or during the growth spurt was associated with a significantly decreased risk of hormone receptor-positive BC subtypes. Interestingly, exposure to energy restriction during the Hunger Winter was also associated with an increased ER- BC risk, which seemed independent of timing of exposure to energy restriction in relation to women's growth spurt.

In agreement with previous studies,[1–3] we observed a 7% increased risk in postmenopausal BC per 5 cm increase in adult-attained height. Previously in the NLCS, after 4.3 years of follow-up, the association between adult-attained height and breast cancer risk has also been studied and a positive association was reported, however results were not stratified by hormone receptor-defined subtypes among postmenopausal women.[24] Regarding hormone receptor status, a recent meta-analysis reported that a positive association between adult-attained height and BC risk was primarily limited to hormone receptor-positive BC, both ER+ and PR+ BC separately as well as combined ER+ and PR+ status.[38] A borderline significant positive association was observed between adult-attained height and PR- BC.[38] While this meta-analysis did not distinguish between premenopausal and postmenopausal BC cases

Table 5. Hazard ratios and 95% confidence intervals for the association between exposure to early life energy restriction and postmenopausal BC risk overall and by hormone receptor subtypes, including stratification by timing of the growth spurt[1] in the Netherlands Cohort Study, 1986–2006

	Postmenopausal BC risk											
	All women				Women with energy restriction before/during the growth spurt				Women with energy restriction after the growth spurt			
Proxies for energy restriction by cancer endpoint	PY	N	HR[2]	95%CI	PY	N	HR[2]	95%CI	PY	N	HR[2]	95%CI
Postmenopausal BC												
Residence during Hunger Winter (1944–45)												
Nonwestern	16,549	1,280	1	(ref)	3,042	204	1	(ref)	13,507	1,076	1	(ref)
Western rural	4,150	377	1.18	(0.97–1.44)	791	65	1.50	(0.90–2.51)	3,359	312	1.14	(0.92–1.42)
Western city	8,250	678	1.03	(0.88–1.20)	1,603	101	0.68	(0.43–1.08)	6,647	577	1.09	(0.91–1.29)
Residence during War Years (1940–44)												
Rural area in 1942	10,540	859	1	(ref)	3,899	305	1	(ref)	6,641	554	1	(ref)
Urban area in 1942	12,387	997	0.93	(0.79–1.10)	4,705	313	0.72	(0.54–0.97)	7,681	684	1.06	(0.87–1.31)
Job status father during Economic Depression (1932–40)												
Employed	26,247	2,146	1	(ref)	25,078	2,029	1	(ref)	1,169	117	1	(ref)
Unemployed	3,151	218	0.82	(0.66–1.02)	2,900	206	0.86	(0.68–1.08)	251	12	0.33	(0.10–1.09)
ER+												
Residence during Hunger Winter (1944–45)												
Nonwestern	16,549	624	1	(ref)	3,042	109	1	(ref)	13,507	515	1	(ref)
Western rural	4,150	181	1.17	(0.93–1.48)	791	35	1.51	(0.82–2.77)	3,359	146	1.12	(0.87–1.46)
Western city	8,250	326	1.02	(0.85–1.24)	1,603	42	0.49	(0.28–0.88)	6,647	284	1.12	(0.91–1.38)
Residence during War Years (1940–44)												
Rural area in 1942	10,540	394	1	(ref)	3,899	154	1	(ref)	6,641	240	1	(ref)
Urban area in 1942	12,387	501	1.05	(0.87–1.28)	4,705	153	0.72	(0.51–1.01)	7,681	348	1.29	(1.00–1.67)
Job status father during Economic Depression (1932–40)												
Employed	26,247	1,037	1	(ref)	25,078	981	1	(ref)	1,169	56	1	(ref)
Unemployed	3,151	106	0.83	(0.64–1.09)	2,900	102	0.89	(0.68–1.17)	251	4	–[3]	–[3]
ER-												
Residence during Hunger Winter (1944–45)												
Nonwestern	16,549	108	1	(ref)	3,042	20	1	(ref)	13,507	88	1	(ref)
Western rural	4,150	53	2.10	(1.44–3.08)	791	4	–[3]	–[3]	3,359	49	2.24	(1.49–3.38)
Western city	8,250	82	1.54	(1.11–2.12)	1,603	17	1.82	(0.69–4.78)	6,647	65	1.51	(1.06–2.17)
Residence during War Years (1940–44)												
Rural area in 1942	10,540	82	1	(ref)	3,899	25	1	(ref)	6,641	57	1	(ref)

(Continues)

Table 5. Continued

Proxies for energy restriction by cancer endpoint	Postmenopausal BC risk											
	All women				Women with energy restriction before/ during the growth spurt				Women with energy restriction after the growth spurt			
	PY	N	HR[2]	95%CI	PY	N	HR[2]	95%CI	PY	N	HR[2]	95%CI
Urban area in 1942	12,387	112	1.05	(0.75–1.48)	4,705	40	1.07	(0.60–1.92)	7,681	72	1.07	(0.69–1.65)
Job status father during Economic Depression (1932–40)												
Employed	26,247	222	1	(ref)	25,078	212	1	(ref)	1,169	10	1	(ref)
Unemployed	3,151	33	1.23	(0.81–1.86)	2,900	31	1.24	(0.81–1.92)	251	2	–[3]	–[3]
PR+												
Residence during Hunger Winter (1944–45)												
Nonwestern	16,549	431	1	(ref)	3,042	75	1	(ref)	13,507	356	1	(ref)
Western rural	4,150	96	0.88	(0.66–1.17)	791	17	1.04	(0.49–2.23)	3,359	79	0.85	(0.62–1.17)
Western city	8,250	167	0.74	(0.59–0.93)	1,603	17	0.23	(0.10–0.54)	6,647	150	0.83	(0.65–1.07)
Residence during War Years (1940–44)												
Rural area in 1942	10,540	257	1	(ref)	3,899	102	1	(ref)	6,641	155	1	(ref)
Urban area in 1942	12,387	291	0.93	(0.73–1.18)	4,705	88	0.59	(0.39–0.89)	7,681	203	1.16	(0.85–1.58)
Job status father during Economic Depression (1932–40)												
Employed	26,247	652	1	(ref)	25,078	612	1	(ref)	1,169	40	1	(ref)
Unemployed	3,151	57	0.71	(0.51–0.98)	2,900	55	0.76	(0.54–1.07)	251	2	–[3]	–[3]
PR-												
Residence during Hunger Winter (1944–45)												
Nonwestern	16,549	213	1	(ref)	3,042	40	1	(ref)	13,507	173	1	(ref)
Western rural	4,150	61	1.22	(0.88–1.70)	791	12	1.68	(0.69–4.07)	3,359	49	1.16	(0.80–1.69)
Western city	8,250	107	1.02	(0.77–1.34)	1,603	23	1.05	(0.51–2.19)	6,647	84	1.00	(0.74–1.37)
Residence during War Years (1940–44)												
Rural area in 1942	10,540	125	1	(ref)	3,899	46	1	(ref)	6,641	79	1	(ref)
Urban area in 1942	12,387	168	1.08	(0.80–1.44)	4,705	59	0.90	(0.55–1.48)	7,681	109	1.25	(0.85–1.82)
Job status father during Economic Depression (1932–40)												
Employed	26,247	353	1	(ref)	25,078	339	1	(ref)	1,169	14	1	(ref)
Unemployed	3,151	36	0.84	(0.57–1.26)	2,900	36	0.92	(0.61–1.38)	251	0	–[3]	–[3]

Abbreviations: BC, breast cancer; CI, confidence interval; ER+, estrogen receptor positive; ER-, estrogen receptor negative; HR, hazard ratio; PR+, progesterone receptor positive; PR-, progesterone receptor negative; PY, person-years.

[1]The growth spurt was defined as: 2 years before reported age of menarche till 1 year after reported age of menarche.

[2]Adjusted for age (y), BMI (kg/m^2), energy intake (kcal/d), baseline nonoccupational physical activity ($\leq$30 min/d, ›30- $\leq$ 60 min/d, ›60–90 min/d, ›90 min/d), smoking status (never, former, current), smoking frequency and smoking duration (number of cigarettes per day and number of years, respectively; continuous, centered), alcohol intake (0, 0.1–29, $\geq$30 g/d), level of education (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/ university), family history of BC (no, yes), history of benign breast disease (no, yes), age at menopause (y), age at first childbirth (nulliparous, ›25y, $\leq$ 25y), parity (n children), oral contraceptive use (never, ever), and postmenopausal hormone-replacement therapy (never, ever).

[3]Estimate not shown because of a too low number of cases.

and ER status was only known for 8.7% of the cases and PR status for 5.4% of the cases (compared to 59% and 47% of the cases, respectively, in our study), it is in support of our finding that adult-attained height may be particularly associated with hormone receptor-positive BC subtypes. Such an association points to the involvement of hormone-related growth-mechanisms in the height-BC association.

Only energy restriction during the Economic Depression before and/or after the growth spurt had an effect on the mean adult-attained height, that is, having an unemployed father during the Economic Depression resulted in a shorter stature compared to having an employed father. Exposure to energy restriction during the Hunger Winter or the War Years before and/or after the growth spurt was not associated with adult-attained height. We had foremost expected an effect of energy restriction on height for energy restriction during the Hunger Winter as this was the most extreme exposure. However exposure to the Hunger Winter, although severe, occurred relatively late in early life and was of relatively short duration, possibly enabling catch-up growth to take place.[39] The timing of exposure to early life energy restriction may be of importance in relation to it having a potential influence on adult-attained height, as the women were younger (0–23 years) during the Economic Depression as compared to the other exposures (12–28 years during the Hunger Winter and 7–28 years during the War Years).

With regard to energy restriction, previously the NLCS examined the association between early life energy restriction and breast cancer risk after 6.3 years of follow-up and did not observe any associations, neither with regard to the timing of the growth spurt. This may have to do with the lower number of cases. In addition, associations were not examined by hormone receptor-defined subtypes.[25] In the current study, even though not all proxies of energy restriction influenced adult-attained height, all three proxies for energy restriction were associated with a (significantly) decreased risk of ER+ BC and PR+ BC in women who were exposed to energy restriction before and/or during the growth spurt, the group in which a potential effect on longitudinal growth was expected. The finding that both height and energy restriction, when occurring during a period in life in which adult-attained height is determined, are particularly associated with hormone receptor-positive BC risk supports the idea that common hormone-related growth-mechanisms may be involved. These findings also underline the notion that timing of exposure to early life energy restriction is an important factor to consider when studying BC risk.

The only study investigating energy restriction in relation to BC risk by hormone receptor subtypes reported an increased risk of ER-PR- BC, ER-PR+ BC, and ER+PR- BC, particularly in those exposed after birth (aged 0–3 years), while no association was reported for ER+PR+ BC. It should be noted, however, that the energy restriction (i.e., China's Great famine) was quite extreme in this study as almost everyone experienced severe hunger during this famine and over 3% of the total population died as a result of the famine.[40,41] For early life energy restriction during the Hunger Winter, during which many women living in a western city also experienced severe hunger, we also observed an increased ER- BC risk, which seemed independent of timing of exposure to energy restriction with regard to the growth spurt. We speculate on the basis of these findings that this increased risk may in part have to do with the nature of the exposure, as both findings relate to severe energy restriction. Based on animal experimental models, we expected to find a decreased postmenopausal BC risk[42] that might be dose-dependent, though evidence also exists for a transition phase of the energy restriction effect: there may be a reversal of the effect from an increased to a decreased life- and health span at some level of energy restriction.[43,44] Energy intake reduction up to 65% improves the life- and health span in rodents, most noticeably by reducing the incidence of multiple forms of cancer. Yet, it has been suggested that an energy intake reduction of more than 65% may not impose the same health benefits regarding longevity.[13] With regard to early life energy restriction in animal models, the number of studies on energy intake reduction of more than 65% has been limited. The effects of extreme *versus* more moderate energy restriction on cancer risk are not clear yet but it is possible that the effects may differ with respect to the risk of (subtypes of) postmenopausal BC. However, residual confounding such as stress,[45] malnutrition and comorbidities related to these severe famines[46–48] may also be partly responsible for the observed positive associations.

Strengths of the present study include the population-based prospective design and long follow-up, yielding large case numbers and making selection and information bias unlikely. Importantly, the elaborate available baseline information enabled us to adjust for a large set of relevant confounders, such as a number of reproductive factors, which are relevant for studying associations of adult-attained height and early life energy restriction with postmenopausal BC risk. In addition, information on ER+/- and PR+/- BC status in the NLCS was available for a relatively high percentage of BC cases (59% and 47%, respectively) and given the relatively large number of cases, we were able to conduct analyses on separate as well as combined ER+/- and PR+/-BC endpoints. Although the number of cases in some subgroup analyses were still small, this is the largest study to-date. We acknowledge that the frequency and method of receptor status testing may have differed over the course of the follow-up. Potential misclassification of the outcome was most likely independent of the exposures studied, and thus may have attenuated results if present. Despite this limitation, that is also not unique to our study, taking into account heterogeneity between hormone receptor subtypes was shown to be of importance given that the observed associations with both adult-attained height

and early life energy restriction differed for hormone receptor-positive and hormone receptor-negative BC subtypes. In the meta-analysis by our group, we were only able to investigate the risk of BC overall and observed a 28% increased BC risk for severe transient early life energy restriction.[13] Since the distribution of hormone receptor subtypes among BC cases may differ between study populations, and because associations with energy restriction seem to differ for the different BC subtypes, this may have affected the strength and direction of the observed association of early life energy restriction with the risk of BC overall in our meta-analysis. With regard to early life energy restriction, it should be mentioned that this is a unique exposure available within only a few cohorts worldwide.[13] Proxy measures were used to estimate energy restriction since information on individual food intake for the NLCS cohort was not available for the three periods of energy restriction, which may have resulted in some exposure misclassification. Nevertheless, any misclassification is likely to be nondifferential, as individuals were still at risk for cancer at baseline when reporting on energy restriction *via* the proxy measures, which makes attenuation of hazard ratios most likely.

In conclusion, adult-attained height and early life energy restriction before and/or during the growth spurt were both associated with hormone receptor-positive BC risk, in the direction as expected, indicating critical exposure windows for hormonal growth-related mechanisms related to BC.

References

1. Wirén S, Häggström C, Ulmer H, et al. Pooled cohort study on height and risk of cancer and cancer death. *Cancer Causes Control* 2014;25: 151–9. https://doi.org/10.1007/s10552-013-0317-7.
2. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. 2010.
3. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 2000;152:514–27.
4. Schönbeck Y, Talma H, van Dommelen P, et al. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. *Pediatr Res* 2013;73:371–7. https://doi.org/10.1038/pr.2012.189.
5. Cousminer DL, Berry DJ, Timpson NJ, et al. Genome-wide association and longitudinal analyses reveal genetic loci linking pubertal height growth, pubertal timing and childhood adiposity. *Hum Mol Genet* 2013;22:2735–47. https://doi.org/10.1093/hmg/ddt104.
6. Canchola AJ, Anton-Culver H, Bernstein L, et al. Body size and the risk of postmenopausal breast cancer subtypes in the California teachers study cohort. *Cancer Causes Control* 2012;23:473–85. https://doi.org/10.1007/s10552-012-9897-x.
7. Ritte R, Lukanova A, Tjønneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. *Int J Cancer* 2013;132:2619–29. https://doi.org/10.1002/ijc.27913.
8. Borgquist S, Jirstrom K, Anagnostaki L, et al. Anthropometric factors in relation to different tumor biological subgroups of postmenopausal breast cancer. *Int J Cancer* 2009;124: 402–11. https://doi.org/10.1002/ijc.23850.
9. Fagherazzi G, Vilier A, Boutron-Ruault MC, et al. Height, sitting height, and leg length in relation with breast cancer risk in the E3N cohort. *Cancer Epidemiol Biomarkers Prev* 2012;21: 1171–5. https://doi.org/10.1158/1055-9965.EPI-12-0130.
10. Bertrand KA, Gerlovin H, Bethea TN, et al. Pubertal growth and adult height in relation to breast cancer risk in African American women. *Int J Cancer* 2017;141:2462–70. https://doi.org/10.1002/ijc.31019.
11. Ruder EH, Dorgan JF, Kranz S, et al. Examining breast cancer growth and lifestyle risk factors: early life, childhood, and adolescence. *Clin Breast Cancer* 2008;8:334–42. https://doi.org/10.3816/CBC.2008.n.038.
12. Okasha M, McCarron P, Gunnell D, et al. Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res Treat* 2003;78:223–76.
13. Elands RJ, Simons CC, van Dongen M, et al. A systematic literature review and meta-regression analysis on early-life energy restriction and cancer risk in humans. *Plos One* 2016;11: e0158003. https://doi.org/10.1371/journal.pone.0158003.
14. Elias SG, Keinan-Boker L, Peeter EH, et al. Long term consequences of the 1944-1945 Dutch famine on the insulin-like growth factor axis. *Int J Cancer* 2004;108:628–30. https://doi.org/10.1002/ijc.11584.
15. Dahlmann N, Petersen K. Influences of environmental conditions during infancy on final body stature. *Pediatr Res* 1977;11:695–700. https://doi.org/10.1203/00006450-197705000-00014.
16. Angell-Andersen E, Tretli S, Bjerknes R, et al. The association between nutritional conditions during world war II and childhood anthropometric variables in the Nordic countries. *Ann Hum Biol* 2004;31:342–55. https://doi.org/10.1080/03014460410001685304.
17. Brundtland GH, Liestol K, Walloe L. Height, weight and menarcheal age of Oslo schoolchildren during the last 60 years. *Ann Hum Biol* 1980;7: 307–22.
18. Nilsen TI, Vatten LJ. Adult height and risk of breast cancer: a possible effect of early nutrition. *Br J Cancer* 2001;85:959–61. https://doi.org/10.1038/sj.bjc.6691946.
19. Li CI, Littman AJ, White E. Relationship between age maximum height is attained, age at menarche, and age at first full-term birth and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2007;16: 2144–9. https://doi.org/10.1158/1055-9965.EPI-07-0242.
20. Ahlgren M, Melbye M, Wohlfahrt J, et al. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 2004;351:1619–26. https://doi.org/10.1056/NEJMoa040576.
21. Velie EM, Nechuta S, Osuch JR. Lifetime reproductive and anthropometric risk factors for breast cancer in postmenopausal women. *Breast Dis* 2005;24:17–35.
22. De Stavola BL, dos Santos Silva I, McCormack V, et al. Childhood growth and breast cancer. *Am J Epidemiol* 2004;159:671–82.
23. Alimujiang A, Mo M, Liu Y, et al. The association between China's great famine and risk of breast cancer according to hormone receptor status: a hospital-based study. *Breast Cancer Res Treat* 2016;160:361–9. https://doi.org/10.1007/s10549-016-3994-6.
24. van den Brandt PA, Dirx MJ, Ronckers CM, et al. Height, weight weight change, and postmenopausal breast cancer risk: The Netherlands cohort study. *Cancer Causes Control* 1997;8:39–47.
25. Dirx MJ, van den Brandt PA, Goldbohm RA, et al. Diet in adolescence and the risk of breast cancer: results of The Netherlands cohort study. *Cancer Causes Control* 1999;10:189–99.
26. van den Brandt PA, Goldbohm RA, Van 'T Veer P, et al. A large-scale prospective cohort study on diet and cancer in The Netherlands. *J Clin Epidemiol* 1990;43:285–95.
27. Goldbohm RA, van den Brandt PA, Dorant E. Estimation of the coverage of Dutch municipalities by cancer registries and PALGA based on hospital discharge data. *Tijdschr Soc Gezondheidsz* 1994;72:80–4.
28. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol* 2007;29: 19–24.
29. Burger GSH, Drummond J. Malnutrition and starvation in Western Netherlands, September 1944 to July 1945. Part I and II. *The Hague, the Netherlands: General State Printing Office* 1948.
30. Trienekens G Tussen ons volk en de honger. De voedelvoorziening, 1940–45. (English translation: Between our nation and the hunger. The food supply, 1940–45). *Utrecht, the Netherlands: Stichting Matrijs* (1985).
31. Breunis J The Annals of the American Academy of Political and Social Science, Vol. 245, The Netherlands during German Occupation (May, 1946), pp. 87–92.

32. Paternoster L, Howe LD, Tiling K, et al. Adult height variants affect birth length and growth rate in children. *Hum Mol Genet* 2011;20:4069–75. https://doi.org/10.1093/hmg/ddr309.
33. Schouten LJ, van Dijk BA, Lumey LH, et al. Energy restriction during childhood and early adulthood and ovarian cancer risk. *Plos One* 2011;6:e27960. https://doi.org/10.1371/journal.pone.0027960.
34. Barlow WE. Robust variance estimation for the case-cohort design. *Biometrics* 1994;50:1064–72.
35. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; 69:239–41.
36. Sperrin M, Marshall AD, Higgins V, et al. Body mass index relates weight to height differently in women and older adults: serial cross-sectional surveys in England (1992-2011). *J Public Health (Oxf)* 2016;38:607–13. https://doi.org/10.1093/pubmed/fdv067.
37. Drøyvold WB, Nilsen TI, Krüger O, et al. Change in height, weight and body mass index: longitudinal data from the HUNT study in Norway. *Int J Obes (Lond)* 2006;30:935–9. https://doi.org/10.1038/sj.ijo.0803178.
38. Zhang B, Shu O, Delahanty RJ, et al. Height and breast cancer risk: evidence from prospective studies and Mendelian randomization. *J Natl Cancer Inst* 2015;107:1–17. https://doi.org/10.1093/jnci/djv219.
39. Widén E, Ripatti S, Cousminer DL, et al. Distinct variants at LIN28B influence growth in height from birth to adulthood. *Am J Hum Genet* 2010; 86:773–82. https://doi.org/10.1016/j.ajhg.2010.03.010.
40. Kane P. The demography of famine. *Genus* 1987; 43:43–58.
41. Song S. Mortality consequences of the 1959-1961 great leap forward famine in China: debilitation, selection, and mortality crossovers. *Soc Sci Med* 2010;71:551–8. https://doi.org/10.1016/j.socscimed.2010.04.034.
42. Dirx MJ, Zeegers MP, Dagnelie PC, et al. Energy restriction and the risk of spontaneous mammary tumors in mice: a meta-analysis. *Int J Cancer* 2003; 106:766–70. https://doi.org/10.1002/ijc.11277.
43. Roberts SB, Speakman J. Update on human calorie restriction research. *Adv Nutr* 2013;4:563–4. https://doi.org/10.3945/an.113.004317.
44. Speakman JR, Mitchell SE. Caloric restriction. *Mol Aspects Med* 2011;32:159–221. https://doi.org/10.1016/j.mam.2011.07.001.
45. Vin-Raviv N, Dekel R, Barchana M, et al. World war II-related post-traumatic stress disorder and breast cancer risk among Israeli women: a case-control study. *Int Psychogeriatr* 2014;26:499–508. https://doi.org/10.1017/S1041610213002081.
46. Bercovich E, Keinan-Boker L, Shasha SM. Long-term health effects in adults born during the holocaust. *Isr Med Assoc J* 2014;16:203–7.
47. Koupil I, Shestov DB, Sparén P, et al. Blood pressure, hypertension and mortality from circulatory disease in men and women who survived the siege of Leningrad. *Eur J Epidemiol* 2007;22:223–34. https://doi.org/10.1007/s10654-007-9113-6.
48. Huang C, Li Z, Wang M, et al. Early life exposure to the 1959-1961 Chinese famine has long-term health consequences. *J Nutr* 2010;140:1874–8. https://doi.org/10.3945/jn.110.121293.