

# Influence of Height on Risk and Outcome of Patients with Early Breast Cancer: A Pooled Analysis of 4,925 Patients from 5 Randomized Trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)

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## Keywords

Early breast cancer · Height · Body mass index · Risk · Outcome · Austrian Breast and Colorectal Cancer Study Group · Disease-free survival · Overall survival

## Abstract

**Background:** Associations between height, cancer risk and worse outcome have been reported for several cancers including breast cancer. We hypothesized that in breast cancer clinical trials, tall women should be overrepresented and

might have worse prognosis. **Methods:** Data of 4,935 women, included from 1990 to 2010 in 5 trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG), were analyzed retrospectively. The primary objective was to determine differences in height distribution between the ABCSG cohort and the Austrian female population according to a cross-sectional health survey conducted by the Austrian Sta-

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tistic Center in 2006 and 2007. Secondary endpoints were disease-free survival (DFS) and overall survival (OS) in different height classes and differences of body mass index (BMI) distribution. **Results:** Breast cancer patients in the ABCSG cohort were only slightly but statistically significantly smaller compared to unselected Austrian adult females (mean 164.3 vs. 164.8 cm;  $p < 0.0001$ ) and significantly more patients were seen in the lower body height class (50 vs. 46%;  $p < 0.0001$ ) when using the median as a cutoff. However, after adjustment for age, the difference in body height between the two cohorts was no longer significant ( $p = 0.089$ ). DFS and OS in the two upper height groups ( $\geq 170$  cm) compared to the two lowest height groups ( $< 160$  cm) was not significantly different (5-year DFS: 84.7 vs. 83.0%; HR 0.91, 95% CI 0.73–1.13,  $p = 0.379$ ; 5-year OS: 94.8 vs. 91.7%; HR 0.74, 95% CI 0.55–1.00,  $p = 0.051$ ). The BMI of ABCSG patients was significantly higher than in the reference population (mean BMI 24.64 vs. 23.96;  $p < 0.0001$ ). **Conclusions:** Our results do not confirm previous findings that greater body height is associated with a higher breast cancer risk and worse outcome.

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## Background

Body constitution is thought to influence both incidence and treatment outcome of breast cancer. Obesity is an established risk factor for the development of cancer and is associated with worse prognosis and outcome after antineoplastic therapy [1, 2]. Besides body weight, body height was also shown to have an impact on cancer risk and treatment efficacy, with an increased risk in taller individuals [3–7]. In the Million Women Study, 1.3 million women without previous history of cancer were followed for cancer incidence for a median of 9.4 years [8]. The relative risk (RR) for developing 1 of 17 documented cancer types increased 1.16 per 10 cm body height. This was significant for 15 of 17 examined tumor types, including breast cancer (RR per 10 cm body height 1.17) [8].

In 2001, Gunnell et al. [9] reviewed 24 cohort and nested case-control studies, which reported a statistical association between height and breast cancer risk. In all but one of the studies, the RR in relation to increasing height was greater than 1 [3]. The reviewed studies were performed in different countries, which is of importance because epidemiologic analyses indicate that geographic patterns of cancer incidence and mortality are associated with variations in population height [9, 10].

Even birth length has been shown to represent a risk factor for breast cancer. In a review of 32 cohort and case-control studies, the association between birth size and breast cancer risk was analyzed. Among the 3 variables birth weight, head circumference, and birth length, length has been shown to be the strongest independent predictor

of risk [11]. However, in a prospective study of 453,023 women, birth weight did not add any further information to adult height as a predictor of cancer incidence [12].

The precise nature of the mechanisms underlying these observations remains unclear and speculative. One possible explanation might be that taller people have simply more cells (including stem cells) and, thus, a numerically greater “background” risk of mutations leading to malignant transformation [13]. This is, however, not fully applicable for breast cancer risk, since taller women do not mandatorily have bigger or denser breasts. Another reason could be that people with higher body height have significantly higher plasma levels of insulin-like growth factor 1 (IGF1), which has been linked to an increased risk for several cancer types, breast cancer included [14–17]. The hormonal environment is another key player in this context. Within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the risk for both hormone receptor (HR)-negative and HR-positive breast cancer was positively associated with standing height, leg length, and sitting height and inversely associated with an increasing age at menarche [18, 19]. Women who were tall and had an early menarche ( $\leq 13$  years) showed an almost 2-fold increased risk for HR-positive breast tumors, but no such increase in risk was observed for HR-negative breast cancer, suggesting a possible hormonal link [19].

Noteworthy, Maehle et al. [18] reported that higher birth length is a negative prognostic factor for breast cancer outcome. This may reflect effects of factors stimulating both longitudinal body growth and metastatic tumor spread. In addition, a relationship between adult body height and breast cancer-related deaths has been described [3, 4].

Body mass index (BMI) is calculated from height and body weight, respectively. Increased BMI has been associated with increased cancer risk in many cancer types, including breast cancer [1, 2, 20]. Increased BMI is largely dominated by body weight mostly caused by an excess of fat tissue. The state of overweight and obesity is now considered a major contributor to cancerogenesis [1]. This is largely attributed to the proinflammatory condition provided by fat tissues and the cytokines released by macrophages therein as well as by significant alterations in the leptin pathway [2].

All these findings led us to hypothesize that in a comprehensive cohort of breast cancer patients, enrolled in Trials of the Austrian Breast and Colon Cancer Study Group (ABCSG), taller women could be overrepresented compared to the general Austrian female population and could have a shorter disease-free survival (DFS) and overall survival (OS) compared to shorter breast cancer patients. Furthermore, we wanted to demonstrate whether BMI had an effect in this regard.

**Table 1.** Mean and median age, height, weight, and BMI of patients included in the 5 evaluable ABCSG trials and of women included in the Austrian health survey

Characteristics		ABCSG trials (N = 4,935)	Austria (N = 3,624,274)
Age, years <sup>a</sup>	Median (range)	49 (23, 80)	43 (17, 87) <sup>a</sup>
	Mean (95% CI)	51 (50, 51)	47 (47,48) <sup>a</sup>
Height, cm	Median (range)	164 (130, 188)	164.4 (136.0, 190.0)
	Mean (95% CI)	164.3 (164.1, 164.4)	164.8 (164.6, 165.0)
Weight, kg <sup>b</sup>	Median (range)	67.0 (35.0, 140.0)	65.6 (38.0, 164.0)
	Mean (95% CI)	68.4 (68.1, 68.8)	67.1 (66.7, 67.4)
BMI <sup>b</sup>	Median (range)	24.5 (14.6, 53.3)	24.0 (14.4, 67.0)
	Mean (95% CI) <sup>c</sup>	24.6 (24.5, 24.8)	24.0 (23.9, 24.1)

CI, confidence interval; BMI, body mass index. <sup>a</sup> Data from the Austrian health survey did not include the exact age, but age classes of 5-year intervals. Therefore, the mid-values of the class intervals were used to calculate the median and the mean. <sup>b</sup> Weight and BMI were available for 4,928 patients in the ABCSG population. <sup>c</sup> Mean calculated after reciprocal transformation of the BMI values.

## Methods

### Participants

Preconditions for eligibility of trials and patients were the following: (1) height and weight were available, (2) data of included patients were available in digital form, and (3) trials were already closed for inclusion. Thus, breast cancer patients from the ABCSG (neo) adjuvant trials numbers 5, 6, 12, 14, and 24 were included, comprising in total 4,935 women. The control group of Austrian adult females was represented by a data set provided by the Austrian Statistic Center, containing the results of a cross-sectional health survey conducted in 2006 and 2007 using a computer-assisted personal interviewing (CAPI) system. In total, 25,130 persons older than 15 years were invited to participate in this survey and 15,474 people were finally interviewed for this survey, including 8,469 women.

### Trials

Three adjuvant (ABCSG 5, 6, and 12) and 2 neoadjuvant (ABCSG 14 and 24) trials, performed between 1990 and 2010, were available for this evaluation. Two of the studies investigated chemotherapeutic regimens only (ABCSG 14 and 24), 1 study both chemotherapy and endocrine treatment (ABCSG 5), and 2 studies investigated endocrine therapy alone (ABCSG 6 and 12). One study (ABCSG 6) included postmenopausal women only, 2 studies (ABCSG 5 and 12) premenopausal women only, and 2 trials (ABCSG 14 and 24) both pre- and postmenopausal breast cancer patients.

In detail, ABCSG 5 compared adjuvant endocrine treatment (tamoxifen and goserelin) in premenopausal patients with estrogen receptor (ER)-positive breast cancer with adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) [21]. ABCSG 6 compared tamoxifen with tamoxifen plus aminoglutethimide as adjuvant treatment in postmenopausal breast cancer patients with hormone receptor-positive disease [22]. In ABCSG 12, tamoxifen plus goserelin and anastrozole plus goserelin were compared in premenopausal women and the effect of zoledronic acid was investigated [23]. ABCSG 14 investigated the effect of 3 versus 6 cycles of neoadjuvant epirubicin and docetaxel plus granulocyte colony-stimulating factor (G-CSF) on pathologic complete remission rate [24]. ABCSG 24 compared epirubicin, docetaxel, and capecitabine plus G-CSF with epirubicin and docetaxel plus G-CSF as neoadjuvant treatment for early breast cancer [25].

### Procedures

The primary aim of this analysis was to determine a difference in height distribution between the ABCSG cohort and the Austrian female population. As secondary endpoints, we defined long-term outcome in different height classes and different classes of BMI of the ABCSG breast cancer cohort. Height of participants was determined in centimeters and weight in kilograms at study entry. Analogous to the Million Women Study [8], patients were divided into 6 height categories: <155 cm, 155–159.9 cm, 160–164.9 cm, 165–169.9 cm, 170–174.9 cm, and ≥175 cm. BMI was classified according to the classification of the World Health Organisation (WHO) into 4 categories: underweight (<18.5), normal weight (18.5–24.99), overweight (≥25), and obese (≥30).

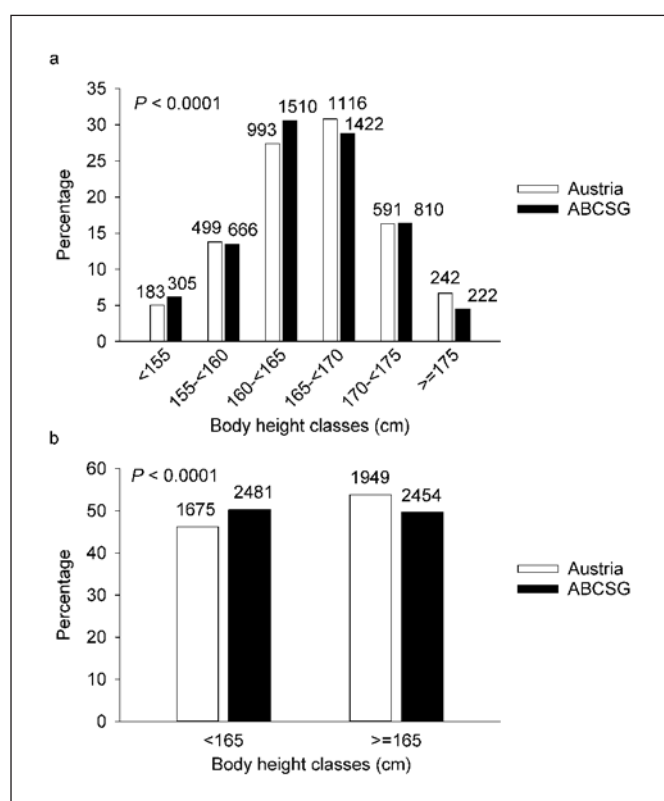
### Statistical Methods

The sample of the cross-sectional health survey was spatially stratified in order to achieve an equal size for each supply region to obtain sampling errors and thus results of equal accuracy. The stratification was carried out according to the 32 health care regions, as defined in the Austrian Structural Plan for Health, that is, the same number of people from the population of each care region was included in the sample. To account for a possible bias caused by stratifications, the data from the Austrian health survey were weighted based on the number of citizens of the regions grouped by 5-year age classes and gender. These sampling weights were taken into account for the estimation of frequencies and statistical parameters using dedicated survey procedures. Differences in the body height and BMI class distribution of ABCSG patients and normal Austrian adult females were analyzed using the Rao-Scott  $\chi^2$  test. In a first step, no adjustment for age was made. In addition, body height was categorized into 2 height classes: above and below the median height of 165 cm. To test for differences between the 2 populations in terms of continuous body height, BMI values, and age (based on mid-values of class intervals), analysis of variance (ANOVA) was used. Since body height data differed slightly but significantly from the normal distribution, results were confirmed by using a nonparametric Kruskal-Wallis test. Because there was no change with respect to inference, only results from ANOVA are given. For BMI data, reciprocal transformation has been used to approximate a normal distribution. An analysis of covariance (ANCOVA) with midpoints of the age classes as covariable was

**Table 2.** Characteristics of the patients included in the 5 evaluable ABCSG trials

Characteristics		ABCSG trials (N = 4,935)	
		n	%
Menopausal status	Pre- or perimenopausal	3,053	61.9
	Postmenopausal	1,882	38.1
Tumor stage	T1	2,862	57.0
	T2	1,834	37.2
	T3	206	4.2
	T4	31	0.6
	Unknown	2	<0.1
Nodes	Negative	2,986	60.5
	Positive	1,949	39.5
Tumor grading	G1	611	12.4
	G2	2,879	58.3
	G3	1,267	25.7
	Unknown	178	3.6
ER status	Negative	257	5.2
	Positive	3,761	76.2
	Unknown	917	18.6
PgR status	Negative	609	12.3
	Positive	3,404	68.0
	Unknown	922	18.7
HR status	Negative (ER- and PgR-)	270	5.5
	Positive	4,263	86.4
	Unknown	402	8.1
HER2 <sup>a</sup>	Negative	388	7.8
	Positive	181	3.7
	Unknown	4,366	88.5
Histology	Ductal invasive	3,012	61.0
	Lobular invasive	553	11.2
	Other subtypes	561	11.4
	Unknown	809	16.4
Type of surgery	Breast conserving	3,327	67.4
	Mastectomy	1,572	31.9
	Other	18	0.4
	Unknown	18	0.4
(Neo)adjuvant chemotherapy	Yes	897	18.2
	No	1,514	30.7
	Not applicable	1,530	31.0
	Unknown	994	20.1
(Neo)adjuvant trastuzumab if HER2-positive <sup>b</sup>	Yes	45	24.9
	No	136	75.1
Adjuvant endocrine therapy if HR-positive <sup>c</sup>	Yes	3,333	78.2
	No	930	21.8
pCR <sup>d</sup> in case of neoadjuvant therapy <sup>e</sup>	Yes	138	17.2
	No	646	80.6
	Unknown	18	2.2

ER, estrogen receptor; PgR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response. <sup>a</sup> HER2 was documented in ABCSG 14 and ABCSG 24 only. <sup>b</sup> Percentages per 181 HER2-positive patients. <sup>c</sup> Percentages per 4,263 HR-positive patients. <sup>d</sup> Defined as no invasive tumor in breast irrespective of lymph node involvement (pT0/is). <sup>e</sup> Percentages per 802 patients who received neoadjuvant therapy.



**Fig. 1.** Differences in body height distribution between the ABCSG cohort and the Austrian female population in 6 (a) and 2 (b) height classes. The numbers of females on top of the bars of the Austrian population have to be multiplied by 1,000.

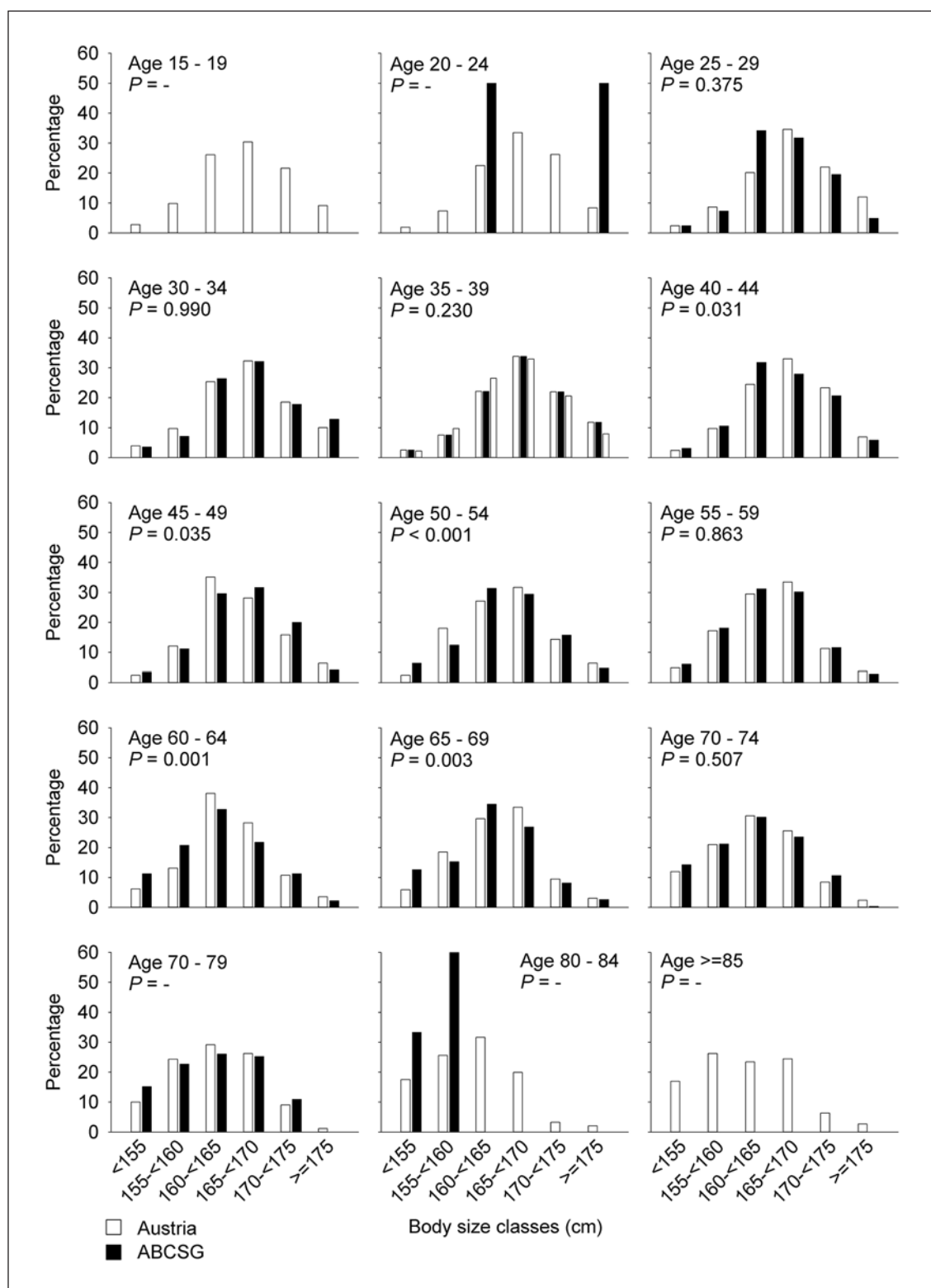
calculated to adjust for the effect of age on the body height and BMI-population relationship.

The risk of recurrence in terms of DFS and OS in the 2 height classes with the tallest patients was compared to the 2 height classes with the shortest patients using the log-rank test stratified by type of therapy (tamoxifen, anastrozole, CMF). Hazard ratios with confidence intervals were computed using univariate, stratified Cox proportional hazards models. These analyses were restricted to the adjuvant trials (5, 6, and 12). Patients from the ABCSG 6 trial were censored at 60 months because they were allowed to switch to another trial. Multivariate Cox proportional hazards regression model stratified by the type of therapy was applied to adjust for tumor stage, nodal stage, tumor grading, hormone receptor status, and BMI. No significant deviation from the proportionality assumption was observed for the univariate and the multivariate models. Analyses were performed using statistical software SAS<sup>®</sup> v9.3 and v9.4 (SAS Institute, Cary, NC, USA).

## Results

In our analysis, 4,935 breast cancer patients from 5 different ABCSG trials were included. Patient characteristics are provided in Table 1 and Table 2. The control group consisted of a data set of 8,469 women registered in the Austrian health survey from 2006/2007 (conducted by Statistik Austria) and was chosen as representative for the Austrian



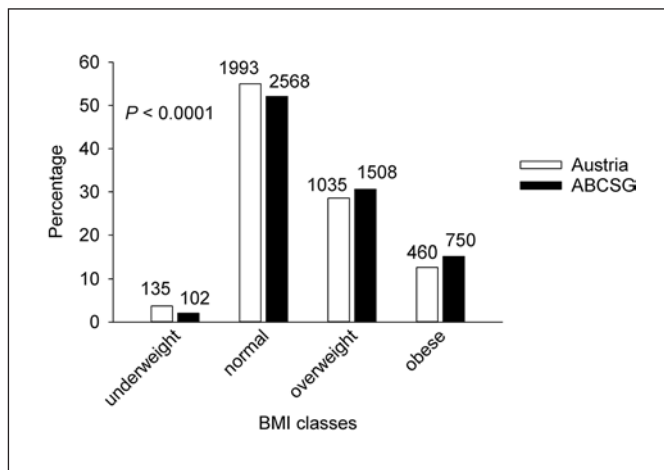


**Fig. 2.** Differences in body height distribution between the ABCSG cohort and the Austrian female population per age classes.

female population (Table 1). The projected population size based on the weights of the survey was 3,624,274 females.

We observed a significant association between body height categories and population; however, the direction

of this correlation was opposite to our hypothesis: ABCSG breast cancer patients had a slightly, but statistically significantly, lower mean body height compared to the Austrian adult female population (164.3 vs. 164.8 cm,  $p <$



**Fig. 3.** Differences in BMI distribution between the ABCSG cohort and the Austrian female population in 4 BMI classes. The numbers of females on top of the bars of the Austrian population have to be multiplied by 1,000.

0.0001; Fig. 1a). When categorized into 2 height classes, according to the median height of the whole population (165 cm), significantly more ABCSG patients were seen in the lower body height class and significantly fewer ABCSG patients in the higher body height class than expected by chance ( $p < 0.0001$ ; Fig. 1b).

Age had a weak but significant effect ( $R^2 = 0.086$ ;  $p < 0.0001$ ) on body height. After adjusting for age, the difference between Austrian adult females and ABCSG patients with respect to body height was not significant anymore (ANCOVA:  $F = 2.90$ ,  $p = 0.089$ ). Significant differences in terms of frequency distributions across height classes occurred in the age classes 40–44, 45–49, 50–54, 60–64, and 65–69 years (Fig. 2). Significant differences in terms of height comparisons were found in the age classes 35–39, 40–44, 60–64, and 65–69 years. In these height classes, body height was lower for ABCSG patients compared to Austrian adult females. The mean difference was 0.53 cm.

We observed a significant difference between the breast cancer population and the control group with respect to BMI as well. Compared to Austrian adult females, the mean BMI of ABCSG patients was significantly higher (24.64 vs. 23.96,  $p < 0.0001$ ). These results were independent of the effect of age (Fig. 3).

The median follow-up in the combined analysis of the trials ABCSG 5, 6, and 12 was 73.1 months (95% CI 71.7–82.3). The risk of an event in the 2 height classes with the tallest patients ( $\geq 170$  cm) compared to the 2 classes with the shortest patients ( $< 160$  cm) was not significantly different for DFS (log-rank, 5-year DFS: 84.7 vs. 83.0%; HR 0.91, 95% CI 0.73–1.13,  $p = 0.379$ ; multivariate Cox model: HR 0.88, 95% CI 0.69–1.12,  $p = 0.281$ ). For OS, a borderline significance was reached with an absolute differ-

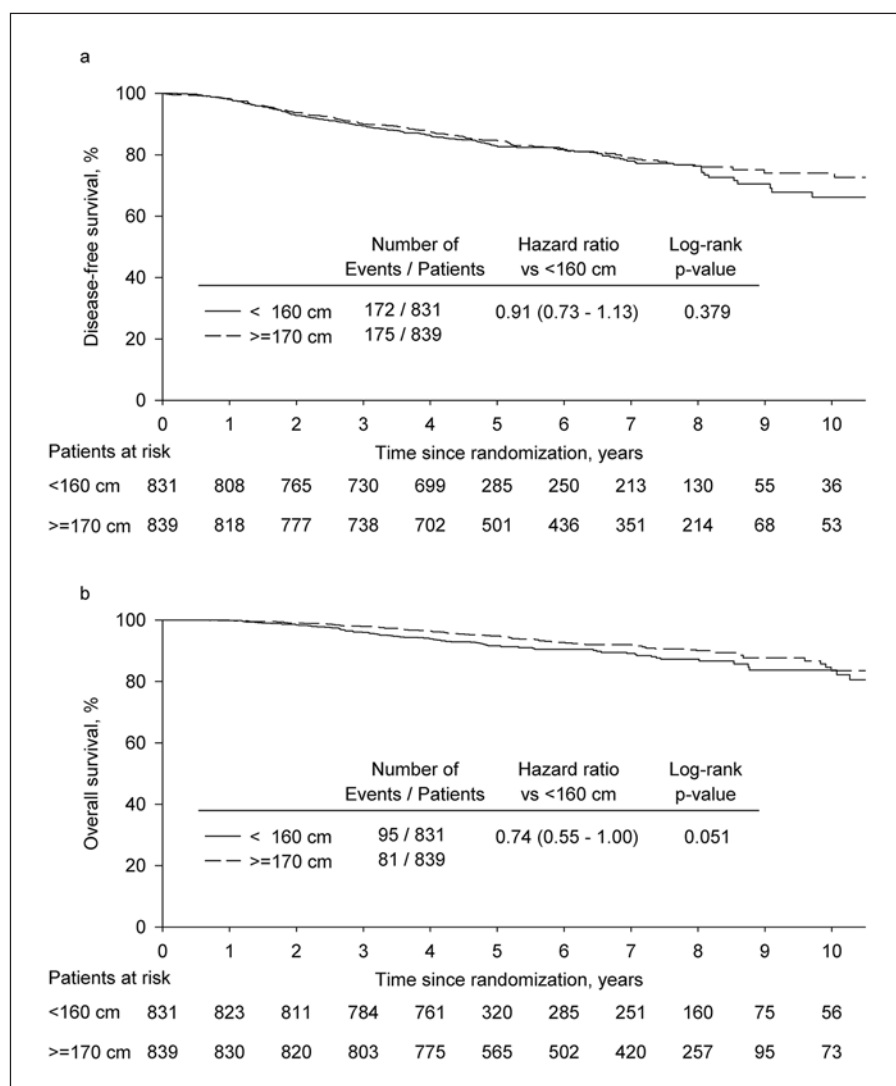
ence in 5-year OS of 3.1% (log-rank, 5-year OS: 94.8 vs. 91.7%; HR 0.74, 95% CI 0.55–1.00,  $p = 0.051$ ; multivariate Cox model: HR 0.73, 95% CI 0.51–1.04,  $p = 0.080$ ; Fig. 4).

## Discussion

In this retrospective data analysis of 4,935 breast cancer patients included in clinical trials of the ABCSG, we found a significant difference in height distribution between the ABCSG population and the Austrian adult female population. In these studies, premenopausal as well as postmenopausal women were included and treated in neoadjuvant or adjuvant intention with endocrine therapy and/or chemotherapy according to their risk profile. Since up to 33% of all Austrian breast cancer patients are included in ABCSG trials, the ABCSG trial collective is a representative population sample enabling the planned comparison.

In contrast to our hypothesis, the ABCSG population was significantly shorter than the normal Austrian adult female population ( $p < 0.0001$ ). According to the literature, taller women should be overrepresented in cancer cohorts because of the widely described positive correlation between cancer risk and height. This association brought up in large epidemiologic comparisons was not confirmed by our data. After adjusting for age, however, the difference in height between the ABCSG population and the general population was not statistically significant anymore ( $p = 0.089$ ). Age is one potential confounding factor as it may be related to both height (the general adult population gets taller over the years in many countries [26]) and incidence of cancer (higher age is associated with higher incidence of cancer [27]). Interestingly, the Million Women Study stratified all analyses by age and adjusted – among others – for socioeconomic status and BMI. Nevertheless, a significant association between height and cancer risk was found [8].

It should be considered that our patient population was exclusively built up by patients enrolled into clinical trials and presents, therefore, a very homogenous group with regard to the inclusion criteria and the risk factor distribution. Probably, much stronger risk factors for breast cancer carcinogenesis, such as the hormonal environment, mask the influence of increased cell turnover mediated by growth factors or the larger cell amount in taller individuals. In the EPIC cohort, the highest risk for ER/progesterone receptor (PR)+ breast cancer was found in tall women who had an early menarche ( $\leq 13$  years). Their risk was almost 2-fold increased in comparison to the group with a late menarche and short stature. For ER–/PR– breast cancer, this association appeared to be less strong. The menopause, in turn, seems to influence the “height effect” on the risk for ER+/PR+ breast cancer



**Fig. 4.** Kaplan-Meier plots for disease-free survival (**a**) and overall survival (**b**) of patients  $\geq 170$  cm ( $N = 839$ ) versus patients  $< 160$  cm ( $N = 831$ ) from the trials ABCSG 5, 6, and 12.

as well, since a stronger correlation in postmenopausal women was observed in the EPIC cohort [19]. Unfortunately, other known risk factors for breast cancer development, such as socioeconomic status, region of residence, age at menarche, parity, age at first delivery, use of hormone replacement therapy, physical activity, smoking status, and alcohol consumption, were not recorded in the included trials. This is certainly, besides the retrospective design, one of the major limitations of this analysis.

Our second hypothesis was that taller patients with early breast cancer should have a shorter DFS and OS compared to shorter patients. Besides evaluating the effect of body height alone, our results were adjusted for age, tumor stage, nodal stage, tumor grading, hormone receptor status of estrogen and progesterone, and BMI. Again, our hypothesis was not confirmed. There was no statistical difference in univariate and multivariate analysis for DFS and OS, respectively. The univariate log-rank test for OS showed a borderline significance (HR 0.74,

95% CI 0.55–1.00,  $p = 0.051$ ), however, with a trend toward better prognosis for taller breast cancer patients, opposite to our initial hypothesis.

High BMI is an established and widely described risk factor for the development of many different cancer sites [2]. This applies in particular to breast cancer. In accordance with these findings, we could detect an overrepresentation of women with higher BMI in the ABCSG cohort compared to the Austrian female population. This risk factor is of special interest since overweight or obesity at the time of diagnosis seems to be a poor prognostic factor associated with nodal involvement as well as increased disease-specific and overall mortality [28–30]. Furthermore, a reduced efficacy of adjuvant aromatase inhibitor therapy was reported for obese postmenopausal women, suggesting a certain under-dosage in these women [31, 32]. Unfortunately, adjustment for socioeconomic status, which is strongly related to BMI [33], was not possible in our analysis.

## Conclusions

Our results did not confirm previous findings that greater body height significantly increases breast cancer risk or deteriorates prognosis of this disease. Further studies are warranted to confirm the results of this retrospective data analysis. The hypothesis of a predominance of women with higher BMI in the early breast cancer cohort compared to the general female population was clearly supported in our study cohort.

## Statement of Ethics

All procedures performed in the 5 included studies were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All 5 studies were approved by ethics committees and institutional review boards in all participating institutions. Written informed consent was obtained from all study participants. For this retrospective analysis, no additional informed consent was obtained.

## Conflict of Interest Statement

Verena Sagaster declares the following relations: Employment: none; Leadership: none; Stock or other Ownership: none; Honoraria: none; Consulting or Advisory Role: Bayer, Novartis, Eli Lilly; Speakers Bureau: none; Research Funding: none; Patents, Royalties, Other Intellectual Property: none; Expert Testimony: none; Travel, Accommodation, Expenses: none; Other Relationships: none.

Florian Fitzal declares the following relations: Employment: none; Leadership: none; Stock or other Ownership: none; Honoraria: none; Consulting or Advisory Role: Pfizer, Roche; Speakers Bureau: none; Research Funding: Novartis, Pfizer, Roche, AstraZeneca, Comesa, Bondimed, Nanostring; Patents, Royalties, Other Intellectual Property: none; Expert Testimony: none; Travel, Accommodation, Expenses: Novartis, Pfizer, Roche, AstraZeneca, Comesa, Bondimed, Nanostring; Other Relationships: none.

Yelena Devyatko declares the following relations: Employment: none; Leadership: none; Stock or other Ownership: none; Honoraria: none; Consulting or Advisory Role: none; Speakers Bureau: none; Research Funding: none; Patents, Royalties, Other Intellectual Property: none; Expert Testimony: none; Travel, Accommodation, Expenses: Roche; Other Relationships: none.

Georg Pfeiler declares the following relations: Employment: none; Leadership: none; Stock or other Ownership: none; Honoraria: Amgen, Lilly, Roche, AstraZeneca, Novartis, Accord, Pfizer; Consulting or Advisory Role: Amgen, Lilly, Roche, AstraZeneca, Novartis, Accord, Pfizer; Speakers Bureau: none; Research Funding: none; Patents, Royalties, Other Intellectual Property: none; Expert Testimony: none; Travel, Accommodation, Expenses: none; Other Relationships: none.

Michael Gnant declares the following relations: Employment: Snadotz; Leadership: none; Stock or other Ownership: none; Honoraria: Amgen, AstraZeneca, Celgene, Eli Lilly, Invectys, Pfizer, Nansotring, Novartis, Roche, Medison; Consulting or Advisory Role: AstraZeneca, Eli Lilly; Speakers Bureau: none; Research Funding: none; Patents, Royalties, Other Intellectual Property: none; Expert Testimony: none; Travel, Accommodation, Expenses:

es: Amgen, AstraZeneca, Eli Lilly, Ipsen, Pfizer, Roche, Medison; Other Relationships: none.

All other authors declare that they do not have any conflicts of interest in direct or indirect relationship with this research.

## Funding Sources

This retrospective analysis was funded by the ABCSG. The design of the study, the collection, interpretation, and analysis of the data, the preparation of this report, or the decision to publish were not influenced by the funding source of the 5 clinical trials.

The corresponding author had full access to all data. C.F. had access to the raw data of all studies. The corresponding author assumes the final responsibility for the decision to submit for publication.

## Author Contributions

Conceptualization: R.G.: ideas; formulation or evolution of overarching research goals and aims. Data curation: C.F.: management activities to annotate (produce dataset), data preparation, and maintain research data (including software code, where it is necessary to interpret the data itself) for initial use and later reuse. Formal analysis: C.F.: application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data. Funding acquisition: M.G., G.S., R.G.: acquisition of the financial support for the project leading to this publication. Investigation: S.P.G., M.P.: conducting a research and investigation process, specifically performing the experiments, or data/evidence collection. Methodology: S.P.G., M.P., G.R., R.G., C.F.: development or design of methodology; creation of models. Project administration: S.P.G., M.P., G.R., M.G., R.G.: management and coordination responsibility for the research activity planning and execution. Resources: S.P.G., M.P., G.R., B.M., S.G.-R., G.S., V.S., F.F., R.E., Y.D., M.B., H.S., C.S., T.B., C.S., G.P., M.S., R.H., D.H., H.R., W.K., U.W., M.G.: provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools. Supervision: R.G., S.P.G., M.P.: oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. Validation: S.P.G., M.P., C.F., G.R., B.M., S.G.-R., G.S., V.S., F.F., R.E., Y.D., M.B., H.S., C.S., T.B., C.S., G.P., M.S., R.H., D.H., H.R., W.K., U.W., M.G.: verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs. Visualization: C.F.: preparation, creation, and/or presentation of the published work, specifically visualization/data presentation. Writing – original draft preparation: S.P.G., M.P., G.R.: creation and/or presentation of the published work, specifically writing the initial draft (including substantial translation). Writing – review and editing: C.F., B.M., S.G.-R., G.S., V.S., F.F., R.E., Y.D., M.B., H.S., C.S., T.B., C.S., G.P., M.S., R.H., D.H., H.R., W.K., U.W., M.G.: preparation, creation, and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.

## Availability of Data and Material

The datasets analyzed during the current study are not publicly available due to confidentiality obligation but are available from the corresponding author on reasonable request.



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