Effects of lifestyle on the onset of puberty as determinant for breast cancer

Magda J.A.M. Vandeloo[a], Liesbeth M. Bruckers[b] and Jaak Ph. Janssens[c,d]

Breast cancer is more than ever the leading cause of death in women. In this article, we investigate the influence of lifestyle factors, and in particular nutrition (i.e. soft drinks), on physical development, puberty, breast growth and menarche to understand the potential impact of these environmental and lifestyle factors on the induction of breast cancer susceptibility. A questionnaire was obtained from 1146 girls of 10 schools in Belgian Limburg, attending the second year of secondary school. Their mean age was about 13 years. The analyses of the data were performed with 'survival analysis', in particular with the 'Cox regression' model for menarche. This project was conducted in the school year of 1999–2000. In the univariate and multivariate analysis investigating the most important variables of the period from birth to the age of menarche, there was clear evidence that lifestyle factors, including nutrition, have an effect on breast development and menarche. The following variables were significantly related to breast development and menarche: body mass index, drinking high-carbohydrate drinks, i.e. soft drinks, height of the father and the mother, weight of the mother at the start of pregnancy, history of mononucleosis, origin and education of the parents and physical activity. Lifestyle factors, including nutrition (i.e. soft drinks), affect the age at puberty and menarche. The same factors are known to be related to breast cancer risk. Better control of these variables during puberty might reduce breast cancer risk later in life. ***European Journal of Cancer Prevention*** **16:17–25 © 2007 Lippincott Williams & Wilkins.**

European Journal of Cancer Prevention 2007, **16**:17–25

Keywords: breast cancer prevention, breast development, lifestyle, menarche, nutrition, puberty, soft drinks

[a]Open University of the Netherlands, Heerlen, The Netherlands, [b]Centre for Statistics, [c]Biomedical Institute, Hasselt University and [d]European Cancer Prevention Organization, Campus Diepenbeek, Diepenbeek, Belgium

Correspondence to Mrs Magda J. Vandeloo, Open University of the Netherlands, Valkenburgerweg 177 Postbus 2960, 6401 DL Heerlen, The Netherlands
Tel: +32 11 27 52 21; e-mail: magdavandeloo@scarlet.be

Received 1 November 2005 **Accepted** 1 December 2005

Introduction

Breast cancer causes the highest mortality of cancer in women in developed countries (Janssens, 1999b; Bray *et al.*, 2002). Between 1960 and 2000, breast cancer incidence doubled in most areas and mortality continued to increase slightly despite huge efforts to treat the disease (Coebergh *et al.*, 2001).

Numerous scientific data support the hypothesis that the susceptibility for breast cancer originates during the organogenesis of the breast. Early menarche (the first menstruation), late first full-term pregnancy, increased height and weight, are known to be important determinants for breast cancer (Korenman, 1980; Baanders and de Waard, 1992; Koprowski *et al.*, 1999). This can hardly be surprising as the growth, development and maturation of the breast is maximal at the onset of puberty and remains throughout puberty and adolescence up to the first full-term pregnancy or the age of about 24 (Janssens, 1999a). Earlier menarche in the Western hemisphere is usually associated with earlier onset of hyperinsulinaemia, and numerous case–control studies report that fasting hyperinsulinaemia is also a marker of increased breast cancer risk (Stoll *et al.*, 1994; Stoll, 1998).

Little is known about the sequence of endocrine events early in life. Early puberty, breast development and menarche seem to follow a naturally occurring process determined by a biological clock that, once initiated, turns on a rather independent process of senological (breast) and gynaecological (primary sexual organs) development and maturation (Apter and Sipilä, 1993; Apter, 1996). The age at menarche, however, seems to be affected by nutrition also because ovulation and menstruation need a critical weight. Furthermore, children with an intense physical life, like ballerinas or young athletes, will have a retarded menarche. Thus, the biological clock can be influenced by sociocultural, environmental and nutritional factors altering the timing of the involved neuroendocrine mechanisms (Wheeler, 1991; Apter and Sipilä, 1993; Apter, 1996).

In view of the importance of pubertal development and breast cancer risk and the possible influence of lifestyle factors on pubertal development, a study was initiated to correlate lifestyle risk factors with the onset of puberty, breast development and menarche. In this way, pubertal development could possibly be used as an intermediate biological marker to predict breast cancer risk.

0959-8278 © 2007 Lippincott Williams & Wilkins

Material and methods

Methodology

A questionnaire on lifestyle factors and physical development was given to 1150 girls of Belgian Limburg, attending the second year of secondary school. Their mean age was about 12.8 years. This age was chosen, because about 80% of the girls experienced some degree of breast development at this point and about 50% of the girls reached menarche. All these girls were followed from birth onwards with regular (approximately 2 yearly) physical examinations before the completion of the questionnaire and final physical examination. After exclusion of four questionnaires (incomplete data), 1146 study cases were taken up in the analysis.

Study population

All girls were recruited in 10 geographically well-distributed centres of Medical School Supervision (MSS) in Belgian Limburg. Care was taken also to invite different types of schools to balance socioeconomic characteristics. In each centre, the first 115 children attending the second year of secondary school were selected. The other selection criterion was the absence of obvious disease. Informed consent was given by the children and the parents through written and oral information. The participation was almost 100% and after 1150 questionnaires were collected, the inclusion was terminated. Three questionnaires were not taken into account because of poor quality, probably owing to language problems. Another girl was included but left the province before finishing the study. So the study includes 1146 data sets.

All the girls had a record with clinical data in MSS and had been followed from birth onwards with physical examinations at regular intervals (mostly every 2 years). Each girl received a questionnaire on lifestyle and nutritional factors that was completed by the help of one of the parents and the school nurse or physician. After completion of the questionnaire, the children had a complete physical examination. Using all these data, we constructed a database with 272 variables.

Validation

To evaluate the representativity of the study group in relation to the general Flemish population, we compared the growth curves of length, weight and body mass index (BMI) with those of the official statistics 'Health Indicators 1998' of the 'Ministry of Health of the Flemish Community in Belgium' (Aelvoet *et al.*, 2000).

Questionnaire

The questionnaire was prepared in cooperation with the MSS, physicians, representatives of the 'European Cancer Prevention Organization' and cooperators of the 'Centre for Statistics of Limburgs Universitair Centrum'. The questionnaire was a compromise between the demands of the investigators and the feasibility of data retrieval from the school. No interventional procedures (e.g. blood withdrawal) and no technical examinations were allowed.

The questionnaire was partially completed by the medical team, that is, nurse or physician in the presence of the child. It was the part where all the medical data from birth until the age at final visit were recorded.

The second part including familial, social and environmental variables was completed by the girls and one of the parents and was supervised by one of the nurses or physician.

The questionnaire was divided into four chapters each corresponding to a period of life: the perinatal period (from birth to 3 years); the period from 3 to 6 years; the period of early puberty from 6 years to menarche and the period after the menarche. Only the girls who had menarche completed the latter chapter of the questionnaire.

Puberty, menarche and early puberty endpoints

In this study, puberty is defined as the period between the first appearance of breast growth or pubic hair (Tanner and Whitehouse, 1976). Usually breast development appears first and at the age of 7–8 years. In our study, early puberty coincides with stage 2 or more of breast development. Early puberty ends with menarche.

Food and drink groups

We stratified groups of excessive intake either towards low-energy food, food with high-fat content and food with high-carbohydrate (sugar) contents. The fourth group had no excess and was considered as mixed. The same was done for drinks. To classify children into one of the groups, the preference of food class or drink was selected at each meal during the day: morning, 11 h, noon, 16 h, supper and late snack. The noon and supper counted for two to balance the quantity of these meals. When the total preference rates (weighed sum of preference of the different meals) more than 6 on a scale of eight in any direction (fat, carbohydrate or low energy), the child was allocated to that group. In the other cases, the meal or drink was considered mixed.

Body mass index for children

As weight growth for children (until 18 years) is disproportionate to length growth, it was not obvious to use the normal Quetelet index or BMI index (BMI = weight/length^2). We can value weight by expressing weight in percent of the 50th percentile (Vervaet *et al.*, 1997; Van Winckel and Braet, 2000) resulting in a weight length index (WLI). This index is also called the 'percentile-BMI'. Weight of the girls was evaluated thus by using the 'body mass index percentile curves' (Aelvoet *et al.*, 2000).

Statistical methods

The endpoints of interest are time to event outcomes, for example, time to start of breast development and time to menarche. The most important covariates of the three different periods of the questionnaire, namely the perinatal period (from childbirth to 3 years), the prepubertal period (3–6 years) and the period of early puberty (6 years to age at menarche), were related to one of the dependent variables of the statistical model, for example, breast development.

We started by investigating the relations between these covariates in a univariate analysis first to the age of the onset of breast development, second to the age at menarche and later to the interval between breast development and age of the first menstruation. In the second phase, all explanatory variables were considered together in a multivariate model.

Results

In the study group, breast development started at the age of 7–8 years, closely followed by the appearance of pubic hair. Axillary hair growth followed later. For the girls who attained menarche during the study, the mean age for menarche was 11.9 ± 0.8 years. For the whole group, statistical analysis projected the mean age for menarche as: 12.3 ± 0.8 years. In this study group of 1146 girls, 535 (46.7%) reached menarche at the time of the final physical examination.

Early puberty

In the univariate analysis with regard to the onset of breast development, the following relations were significant (Table 1):

Nutrition did not attribute any significant relation to the onset of breast development, except for 'high-carbohydrate drinks'. The latter seems to be an important variable, not only for the period 3–6 years ($P = 0.028$) but also for the period of 6 years to menarche ($P = 0.052$). For the period 6 years to menarche, 'mixed drinks' lay a role as well ($P = 0.042$). Girls who had a substantial increased consumption of high-carbohydrate drinks, that is, soft drinks, had an earlier breast development (Table 1).

The variable WLI was divided into four groups: underweight ($\text{WLI} \leq 90$), normal weight ($90 < \text{WLI} \leq 120$), overweight moderate ($120 < \text{WLI} \leq 140$) and explicit overweight ($\text{WLI} > 140$). The association between the BMI of the children and the onset of breast development was very significant ($P < 0.001$). Underweight girls started significantly later in time with breast development. For example, at the age of 11 years about 40% of the underweight girls reached breast development, whereas 60% of the normal weighed and almost 65% of the overweight girls reached breast development. The fate of moderate and explicit overweight girls coincided (Table 1).

Table 1 Significant relations with regard to the onset of early puberty

Dependent variable: onset of early puberty (breast development)			
Independent variables			
	Risk ratio (95% CI)	*P*-value	*P*-overall
Univariate analysis			
Weight of mother at the beginning of pregnancy	1.013 [1.006; 1.021]		0.001
Education of father			0.045
1. Lower school	0.953 [0.579; 1.567]	0.848	
2. Lower secondary school	0.910 [0.596; 1.389]	0.661	
3. Higher secondary school	0.891 [0.588; 1.349]	0.586	
4. High school and university	0.728 [0.478; 1.110]	0.140	
5. Others	1.515 [0.724; 3.169]	0.270	
6. No certificate			
Walking age	0.969 [0.939; 1.001]		0.052
Chemicals at home (3–6 years) (ref = chem)	0.819 [0.706; 0.950]		0.008
Chemicals at home (6–menarche) (ref = chem)	0.789 [0.681; 0.913]		0.002
Mononucleosis (3–6 years) (ref = mononuc.)	0.423 [0.253; 0.705]		0.001
High-carbohydrate drinks (3–6 years)	1.041 [1.004; 1.079]		0.028
High-carbohydrate drinks (6 to menarche)	1.033 [1.000; 1.067]		0.052
Mixed drinks (6 to menarche)	0.941 [0.888; 0.998]		0.042
Length of the girl (6 to menarche)			< 0.001
1. Tall	1.725 [1.413; 2.107]	0.000	
2. Normal	1.364 [1.133; 1.643]	0.001	
3. Small			
Weight length index (WLI)			< 0.001
1. Underweight $\text{WLI} \leq 90$	0.498 [0.367; 0.676]	0.000	
2. Normal $90 < \text{WLI} \leq 120$	0.765 [0.581; 1.007]	0.056	
3. Overweight moderate $120 < \text{WLI} \leq 140$	1.019 [0.745; 1.395]	0.904	
4. Overweight explicit $\text{WLI} > 140$			
Skin thickness	1.001 [1.000; 1.002]		0.014
Waist contour	1.025 [1.017; 1.033]		< 0.001
Hip contour	1.026 [1.019; 1.033]		< 0.001
Multivariate analysis			
Hip contour	1.033 [1.022; 1.043]		< 0.001
Mononucleosis (3–6 years) (ref = mononuc.)	0.382 [0.203; 0.717]		0.003

The continuous covariates, 'skin thickness, waist contour and hip contour' turned out also to be very important variables. Collectively, they are a measure of obesity. The higher the values of skin thickness, waist contour and hip contour, the earlier the breast development, with skin thickness ($P = 0.014$), waist contour ($P < 0.001$) and hip contour ($P < 0.001$). In the multivariate analysis 'hip contour' also remained very significant ($P < 0.001$) (Table 1).

Higher weight of the mother at the beginning of pregnancy induced earlier breast development of the daughter ($P = 0.001$). The higher the weight of the mother at the beginning of pregnancy, the earlier the breast development of the daughter started ($R = 1.013$) (Table 1).

The 'education of the father' also seemed to be another important variable. Girls who had a father with higher education started their breast development later in time than the ones for whom the father had no certificate; that is, a negative correlation. Higher education of the father predicted delayed breast development ($P = 0.045$) (Table 1).

Considering the period of development of the child, we found that later age at starting of walking implied later breast development. The P-value for this covariate was 0.052 (Table 1).

To study the variable 'chemicals at home', two categories were formed namely: 'chemicals at home, yes or no', the former being the reference group. With 'chemicals at home' we meant insecticides, weed-killers, pesticides, paint products and glue products. Chemicals at home induced earlier breast development not only for the period 3–6 years ($P = 0.008$) but also for the period 6 years to menarche ($P = 0.002$) (Table 1).

Presence of 'mononucleosis' in the period 3–6 years was described in the survival analysis as a categorical variable; namely having had mononucleosis: yes (reference group) or no. Not only in the univariate ($P = 0.001$) but also in the multivariate analysis ($P = 0.003$), we concluded that mononucleosis in the period 3–6 years induced earlier breast development (Table 1).

To study the variable 'length of the girl', this parameter was recoded into three subgroups namely: tall, normal and small girls. We found that girls who were tall in the period 6 years to menarche had earlier breast development than children who had a normal length or the small girls ($P < 0.001$) (Table 1).

Age at menarche

In the univariate analysis with regard to the age at menarche, the following relations were significant (Table 2).

A statistically significant relationship was found between WLI and age at menarche ($P < 0.001$) (Table 2). The explicit overweight girls (WLI $>$ 140) and the moderate overweight ($120 < \text{WLI} \leq 140$) children had their menarche much earlier than the underweight girls. For example, at the age of 12 years only 10% of the underweight girls had their menarche, whereas 40% of the normal girls and 60% of the moderate and explicit overweight girls experienced their first menstruation. Moderate and explicit overweight girls showed no difference.

For the continuous variables 'skin thickness, waist contour and hip contour', we found a positive relationship with regard to the age at menarche. The higher the values for these covariates were the earlier the girl reached menarche ($P < 0.05$) (Table 2).

Daughters of tall fathers and mothers had later menarche. We found a significant P-value for these covariates namely: length father ($P = 0.010$) and length mother ($P = 0.044$) (Table 2).

Higher weight of the mother at the beginning of pregnancy predicted earlier menarche ($P = 0.002$). In Table 2, we observed a risk ratio-value more than 1 ($R = 1.015$), which means that there was more risk to reach the age at menarche earlier.

Girls of parents who had only an education of lower school and lower secondary school had their menarche much earlier than girls from parents with an education of higher secondary school, high school or university ($P = 0.005$). For example, at the age of 12 years only 30% of the girls of mothers of higher education had their menarche in contrast to, approximately 50% of the girls of mothers with lower education. For the parents with higher education or university, we observed a significant P-value for the variable 'education of the father' ($P = 0.003$) and for the variable 'education of the mother' ($P = 0.017$) (Table 2).

We found a trend that girls of parents who lived in the city or village in the period from birth to 3 years ($P = 0.084$) and in the period from 6 years to menarche ($P = 0.090$) had an earlier menarche. The P-values for these variables were, however, borderline (Table 2).

Girls whose parents were born outside of Europe or in the rest of Europe had their menarche much earlier than girls whose parents were locally born (in Belgium or the Netherlands) ($P < 0.001$). We observed that at the age of 12 years not even 40% of the girls from local parents in contrast to approximately 60% of the children of parents were born outside Europe (Table 2).

In the present study we also found that tall girls at birth had a trend to later menarche ($R = 0.974$). The P-value for this variable was, however, borderline ($P = 0.086$) (Table 2). Girls who had breast feeding had a trend to later menarche. The P-value for this covariate was borderline ($P = 0.107$) (Table 2). The fact that mother cooked fresh vegetables instead of using industrial preparations seemed to have also an influence on the age at menarche. We found that girls that ate industrial prepared vegetable meals had an earlier menarche ($R = 1.743$). The P-value for this relation was significant ($P = 0.041$) (Table 2).

Considering the results of present study with regard to nutrition in the period 6 years to menarche, we found an

Table 2 **Significant relations with regard to the age at menarche**

Dependent variable: menarche			
Independent variables			
	Risk ratio (95% CI)	*P*-value	*P*-overall
Univariate analysis			
Length of father	0.981 [0.967; 0.995]		0.010
Length of mother	0.983 [0.967; 0.999]		0.044
Weight of mother at the beginning of pregnancy	1.015 [1.006; 1.025]		0.002
Education of father			0.005
1. Lower school	0.816 [0.470; 1.418]	0.470	
2. Lower secondary school	0.727 [0.454; 1.164]	0.184	
3. Higher secondary school	0.610 [0.384; 0.969]	0.036	
4. High school and university	0.486 [0.301; 0.783]	0.003	
5. Others	0.493 [0.168; 1.442]	0.196	
6. No certificate			
Education of mother			0.005
1. Lower school	0.986 [0.579; 1.678]	0.959	
2. Lower secondary school	0.874 [0.550; 1.387]	0.567	
3. Higher secondary school	0.748 [0.475; 1.178]	0.210	
4. High school and university	0.568 [0.357; 0.903]	0.017	
5. Others	0.770 [0.264; 2.245]	0.633	
6. No certificate			
Living area of father and mother (0–3 years)			0.084
1. City or village	1.064 [0.847; 1.338]	0.592	
2. Country	0.849 [0.668; 1.079]	0.181	
3. Between 1 and 2			
Living area of father and mother (6 to menarche)			0.090
1. City or village	1.140 [0.808; 1.608]	0.454	
2. Country	0.784 [0.538; 1.143]	0.206	
3. Between 1 and 2			
Country of birth of father			<0.001
1. Belgium	0.495 [0.325; 0.753]	0.001	
2. The Netherlands	0.683 [0.390; 1.198]	0.184	
3. Rest of Europe	0.810 [0.496; 1.325]	0.402	
4. Outside Europe			
Country of birth of mother			<0.001
1. Belgium	0.433 [0.282; 0.665]	0.000	
2. The Netherlands	0.455 [0.250; 0.828]	0.010	
3. Rest of Europe	0.651 [0.392; 1.083]	0.098	
4. Outside Europe			
Length at birth	0.974 [0.945; 1.004]		0.086
Breast feeding (ref = breast feeding)	1.152 [0.970; 1.369]		0.107
Breast growth (3–6 years) (ref = breast growth)	0.514 [0.317; 0.834]		0.007
Vegetables self-made (0–3 years) (ref = self m)	1.743 [1.023; 2.970]		0.041
High-carbohydrate food (6 to menarche)	0.942 [0.877; 1.012]		0.102
Low-energy food (6 to menarche)	1.091 [0.994; 1.197]		0.068
Sport (6 to menarche) (ref = sport)	1.288 [1.054; 1.573]		0.013
Length of the girl (6 to menarche)			<0.001
1. Tall	3.666 [2.620; 5.128]	0.000	
2. Normal	2.480 [1.783; 3.449]	0.000	
3. Small			
Weight length index (WLI)			<0.001
1. Underweight $WLI \leq 90$	0.130 [0.085; 0.200]	0.000	
2. Normal $90 < WLI \leq 120$	0.523 [0.390; 0.701]	0.000	
3. Overweight moderate $120 < WLI \leq 140$	0.949 [0.683; 1.319]	0.755	
4. Overweight explicit $WLI > 140$			
Skin thickness	1.001 [1.000; 1.003]		0.043
Waist contour	1.048 [1.039; 1.057]		<0.001
Hip contour	1.055 [1.047; 1.064]		<0.001
Multivariate analysis			
Forward stepwise			<0.001
Length of father	0.979 [0.957; 1.001]		0.060
Length of mother	0.970 [0.943; 0.997]		0.028
Hip contour	1.032 [1.004; 1.061]		0.025
Country of birth of father			0.036
1. Belgium	0.559 [0.292; 1.069]	0.079	
2. The Netherlands	0.583 [0.239; 1.423]	0.236	
3. Rest of Europe	1.199 [0.534; 2.692]	0.659	
Breast feeding (ref = breast feeding)	1.435 [1.068; 1.928]		0.017
Length of the girl (6 to menarche)			<0.001
1. Tall	3.280 [1.853; 5.807]	<0.001	
2. Normal	1.970 [1.183; 3.282]	0.009	

Table 2 ***(Continued)***

Dependent variable: menarche			
Independent variables			
	Risk ratio (95% CI)	*P*-value	*P*-overall
Weight length index			<0.001
1. Under weight WLI ≤ 90	0.793 [0.259; 2.426]	0.685	
2. Normal 90<WLI ≤ 120	1.758 [0.731; 4.228]	0.208	
3. Overweight moderate 120<WLI ≤ 140	3.076 [1.376; 6.879]	0.006	
Backward stepwise			<0.001
Length of father	0.978 [0.957; 1.000]		0.054
Length of mother	0.971 [0.944; 0.998]		0.034
Hip contour	1.033 [1.005; 1.062]		0.020
Living area of father and mother (0–3 years)			0.067
1. City or village	0.889 [0.604; 1.309]	0.550	
2. Country	0.660 [0.449; 0.970]	0.034	
3. Between 1 and 2			
Country of birth father			0.052
1. Belgium	0.576 [0.301; 1.101]	0.095	
2. The Netherlands	0.565 [0.229; 1.398]	0.217	
3. Rest of Europe	1.183 [0.525; 2.664]	0.686	
4. Outside Europe			
Breast feeding (ref=breast feeding)	1.482 [1.101; 1.994]		0.009
Length of the girl (6 to menarche)			<0.001
1. Tall	3.377 [1.905; 5.987]	<0.001	
2. Normal	1.984 [1.191; 3.304]	0.008	
3. Small			
Weight length index			<0.001
1. Under weight WLI ≤ 90	0.838 [0.273; 2.571]	0.757	
2. Normal 90<WLI ≤ 120	1.853 [0.766; 4.486]	0.171	
3. Overweight moderate 120<WLI ≤ 140	3.260 [1.446; 7.349]	0.004	

association between the 'high-carbohydrate food' group and the 'low-energy food' and the age at menarche. Girls who ate more of high-carbohydrate food in the period from 6 years to menarche had a trend to later menarche ($P = 0.102$). In contrary, girls who ate more of low-energy food seemed to have a trend to earlier age at menarche ($P = 0.068$). These correlations were, however, borderline (Table 2).

Physical activity delayed the age at menarche. Girls who did some sport in the period from 6 years to menarche had their first menstruation later in time than girls who did not ($P = 0.013$) (Table 2).

Looking at the development of the child, we found that girls who had breast growth in the period 3–6 years experienced earlier menarche ($R = 0.514$). The *P*-value for this significant association was 0.007 (Table 2). With regard to the age at menarche, the length of the girl was also a key variable. Small girls developed their first menstruation much later in time than the tall girls of the same age. For example, at the age 12 years about 50% of the tall girls reached menarche whereas only 40% of the normal ones and not even 20% of the small girls. We observed a reverse relationship; the taller the girl, the earlier the age at menarche. The correlation was significant ($P < 0.001$) (Table 2).

After the forward stepwise procedure in multivariate analysis, we concluded that the taller the father and mother, the later the age at menarche of the girl ($R < 1$). For the continuous variable 'hip contour', we observed a reverse relationship, that means the higher the value for hip contour, the earlier the age at menarche ($R = 1.032$). For the variable 'country of birth of the father', we found that girls whose father was born local had their first menstruation later in time than girls whose father was born outside Europe. Girls who had 'breast feeding' early in life, however, experienced later menarche in the multivariate analysis. The variable was more highlighted in the multivariate model than in the univariate model ($P = 0.017$). For the variable 'length of the girl' in the period from 6 years to menarche, we concluded that tall and normal girls have an earlier age at menarche than the small girls. We observed in Table 2 a risk ratio more than 1 namely: for the tall girls ($R = 3.280$) and the normal girls ($R = 1.970$), that means that they had more risk to reach menarche than the small girls who were the reference group. In this final model, we also found that underweight girls had a later menarche than normal and overweight girls. As noted in Table 2, the relations for all these covariates in this final model were very significant ($P < 0.001$). In the backward procedure of this multivariate analysis, we observed the same relations as described in the forward procedure.

Discussion

The familial predisposition is an important risk factor for breast cancer (Kuschel *et al.*, 2002). Nevertheless, breast cancer is largely caused by nongenetic factors that act primarily at young ages (Lichtenstein *et al.*, 2002). In previous decennia, there has been an intensive research with regard to lifestyle factors. Recent cohort and case–control studies, however, are less convincing probably because in these epidemiological studies only adults were included. No attention was focused on children up to now. This is remarkable because most recognized determinants for breast cancer risk seem to act early in life; at the time of breast development and maturation and before breast involution (Apter, 1996; Janssens, 1999b).

The results of present study showed that the BMI of the children was one of the important variables with regard to the onset of puberty. Overweight girls had earlier onset of puberty and menarche. It is known that the age at menarche is influenced by nutrition because ovulation and menstruation need a critical weight. The sooner this weight is acquired, the earlier a regular bleeding pattern starts (Janssens, 1999a). Early menarche, increased height and weight are recognized as important determinants for breast cancer (Hsieh *et al.*, 1990; Petridou *et al.*, 1996). Both earlier menarche and adult tallness are markers of increased risk to breast cancer (Baanders and de Waard, 1992). The age of puberty appeared more to be related to body weight than to chronological age (Baker, 1985). The higher the weight of the children, the earlier the onset of early puberty and menarche.

In our study investigating the lifestyle of children, there seemed to be no association between the different food groups to the onset of breast development and menarche. This finding is in line with the results of a recent study of Trichopoulou *et al.* (1995); which concluded that major categories of macronutrients did not show significant associations with breast cancer risk. Vegetables and fruits were inversely significantly and strongly associated with the risk. Evidence also exists that olive oil consumption might reduce the risk of breast cancer (Trichopoulou *et al.*, 1995, 2000). In the present study, we found an association for the 'high-carbohydrate food' group and the 'low-energy food' group for the period 6 years to menarche with regard to the age at menarche. These correlations were borderline.

Investigating the lifestyle and nutrition habits of children, we found that the more the soft drinks were consumed, the earlier the onset of breast development occurred. No relationship was found with the age at menarche. The results might be meaningful considering the high intake of carbohydrate drinks in youngsters (Ludwig *et al.*, 2001; French *et al.*, 2003). Besides, carbohydrates in food tend to have a slower digestion and metabolization than the high glycaemic sugars in drinks. The data confirm earlier studies of soft drinks in children (Janssens *et al.*, 1999c).

During the growth of the human breast in childhood, the breast is extremely vulnerable for toxic influences such as radiation, unbalanced hormones and nutrition (Baanders and de Waard, 1992). Insulin is important in the development of the breasts and interacts with both oestrogen and progesterone. Therefore, insulin is one of the key factors in a normal development of the human breast and inappropriate secretion of insulin might induce lesions in the breast cells leading to breast cancer later in life. Although the association of regular soft drinks and breast cancer is far from established, care should be taken to the biological role of soft drinks in the origin of breast cancer and other chronic diseases later in life (Janssens *et al.*, 1999c; Ten and Maclaren, 2004).

The rising prevalence of obesity in children, that has been linked in part to the consumption of sugar-sweetened drinks, was extensively studied by others (Ludwig *et al.*, 2001; Giammattei *et al.*, 2003; Gillis and Bar-Or, 2003; St-Onge *et al.*, 2003). Ethnically diverse schoolchildren ($n = 548$, age 11.7 years, SD 0.8) from public schools in four Massachusetts communities were prospectively studied for 19 months from October 1995 to May 1997. The association between baseline and change in consumption of sugar-sweetened drinks and difference in measures of obesity was examined. The investigators concluded that for each additional serving of sugar-sweetened drink consumed, both BMI and frequency of obesity increases after adjustment for anthropometric, demographic, dietary and lifestyle variables. Consumption of sugar-sweetened drinks was associated with obesity in children (Ludwig *et al.*, 2001). In a recent longitudinal study of children aged 6–13 years Mrdjenovic and Levitsky (2003) also noted that excessive sweetened drink consumption was associated with higher daily energy intake and greater weight gain (Mrdjenovic and Levitsky, 2003). In addition, consumption of fast food among children in the United States and, increasingly, throughout the world seemed to have an adverse effect on dietary quality in ways that plausibly could increase risk for obesity (Bowman *et al.*, 2004).

The percentage of children who are overweight or at-risk of overweight has increased over the past 20 years. Policies that revitalize physical activity and physical education programmes for all children and educational efforts that encourage sedentary behaviour will be more successful in combating overweight than an undue focus on beverage consumption (Forshee *et al.*, 2004).

Physical activity delays the age at menarche. It appears that an alteration of energy balance in early life through increased physical activity could delay age at menarche and reduce the risk for breast cancer in later life (Petridou *et al.*, 1996). In relation to the onset of breast development there seems no correlation, probably because the onset of puberty is determined already much earlier in life. The data are in line with earlier work (Baker, 1985; Moisan *et al.*, 1991; Sharma and Shukla, 1992; Giammattei *et al.*, 2003).

In our study, we found clear evidence that the 'education of the parents' has an important role in relation to the onset of breast development and also to the age at menarche. That means that girls of fathers or mothers with higher education reached their onset of breast development or the age at menarche later in time than girls of parents with lower education or no certificate. Rogers *et al.* (2003) found that children of nonsmokers and more highly educated mothers consumed a diet that conformed more closely to current guidelines on healthy eating. It was also noted that children of smokers were more likely to drink sugar-sweetened soft drinks (Rogers *et al.*, 2003). In our study, the smoking status of the mother during pregnancy was also inquired but no relationship was found with the onset of puberty. In a recent study, Grimm *et al.* (2004) identified factors associated with nonalcoholic carbonated beverage (soft drink) consumption in children and suggested that several factors might be associated with soft drink intake in school-aged children, most notably taste preferences, soft drink consumption habits of parents and friends, soft drink availability in the home and school, and television viewing (Grimm *et al.*, 2004). The home environment remained the largest source of children's soft drink access, an increasing share was obtained from restaurants and fast food establishments, vending machines and other sources. Away-from-home sources of soft drink are an important factor for dieticians to consider when evaluating the dietary intake and nutritional status of youth (French *et al.*, 2003).

Vereecken *et al.* (2004) suggested that differences in children's food consumption by mother's educational level were completely explained by mother's consumption and other food parenting practices for fruit and vegetables but not for soft drinks. They also noted in another recent study a considerable variation between secondary schools in the consumption of soft drinks, sweets and crisps (but not fruit). The results indicated that school food policy can have an impact on children's food habits (Vereecken *et al.*, 2005). A targeted, school-based education programme produced a modest reduction in the number of carbonated drinks consumed, which was associated with a reduction in the number of overweight and obese children (James *et al.*, 2004).

The cause of overweight in children, as well as its prevention, may lie in the hands of the caregiver (Mrdjenovic and Levitsky, 2005). Nutrition education messages targeted to children and/or their parents should encourage limited consumption of soft drinks. Policies that limit children's access to soft drinks at day-care centres and schools should be promoted (Harnack *et al.*, 1999; American Academy of Pediatrics Committee on School Health, 2004).

In conclusion, the present study supports the hypothesis that lifestyle factors, including nutrition (i.e. soft drinks) affect the age at puberty and menarche. The same factors are known to be related to breast cancer risk. Better control of these variables during puberty may reduce breast cancer risk later in life. This observation can have major implications in breast cancer prevention.

Acknowledgements
This study was the emanation of the work of so many people whom we like to gratitude with our deepest respect, for the accumulation of the data, the scientific guidance throughout the statistics and the interpretation of the data.

The authors thank the supervisor of the Open University of the Netherlands; Dr Ir. Elisabeth W. Fredrix, for her advice, patience and flexibility in busy times. We thank also Mrs Ann Onkelinx, chief adviser of the Open University Diepenbeek Belgium who was always prepared to give advice and support in good and difficult times.

We gratefully acknowledge Dr Irma H. Russo, Dr Jose Russo and Dr Joanne F. Dorgan of the Fox Chase Cancer Center in Philadelphia, United States of America for giving advise and support during this project.

Our thoughts go especially to all the girls and their parents, who gave permission to use their medical records and were prepared to respond to the extensive questionnaires. These 'cases' became our most important partners. We also would like to acknowledge the physicians and representatives of the Medical School Supervision who were exceptionally effective in the guidance of the children and have our deepest admiration.

References
Aelvoet W, Cloots H, Fortuin M, Hooft P, Vanoverloop J (2000). Gezondheidsindicatoren 1998. Ministerie van de Vlaamse Gemeenschap Brussel (Health Indicators 1998. Ministry of Health of the Flemish Community in Belgium). Claes Printing. p. 227.
American Academy of Pediatrics Committee on School Health (2004). Soft drinks in school. *Pediatrics* **113**:152–154.
Apter D (1996). Hormonal events during female puberty in relation to breast cancer risk. *Eur J Cancer Prev* **5**:476–482.
Apter D, Sipilä I (1993). Development of children and adolescents: physiological, pathophysiological, and therapeutic aspects. *Curr Opin Obstet Gynaecol* **5**:764–773.
Baanders AN, de Waard F (1992). Breast cancer in Europe. The importance of factors operating at an early age. *Eur J Cancer Prev* **1**:285–291.
Baker E (1985). Body weight and the initiation of puberty. *Clin Obstet Gynaecol* **28**:573–579.
Bowman SA, Gortmaker SL, Ebbeling CB, Pereira MA, Ludwig DS (2004). Effects of fast food consumption on energy intake and diet quality among children in a national household survey. *Pediatrics* **113**:112–118.

Bray F, Sankila R, Ferlay J, Parkin DM (2002). Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* **38**:99–166.
Coebergh JW, Janssen ML, Louwman WJ, Voogd AC (2001). Cancer, incidence, care and survival in the South of the Netherlands 1955–1999. A report from the Eindhoven Cancer Registry (IKZ) with cross-border implications. Eindhoven.
Forshee RA, Anderson PA, Storey ML (2004). The role of beverage consumption, physical activity, sedentary behaviour, and demographics on body mass index of adolescents. *Int J Food Sci Nutr* **55**:463–478.
French SA, Lin BH, Guthrie JF (2003). National trends in soft drink consumption among children and adolescents age 6 to 17 years: prevalence, amounts, and sources, 1977/1978 to 1994/1998. *Am Diet Assoc* **103**:1326–1331.
Giammattei J, Blix G, Marshak HH, Wollitzer AO, Pettitt DG (2003). Television watching and soft drink consumption: associations with obesity in 11- to 13-year-old schoolchildren. *Arch Pediatr Adolesc Med* **157**:882–886.
Gillis LJ, Bar-Or O (2003). Food away from home, sugar-sweetened drink consumption and juvenile obesity. *J Am Coll Nutr* **22**:539–545.
Grimm GC, Harnack L, Story M (2004). Factors associated with soft drink consumption in school-aged children. *J Am Diet Assoc* **104**:1244–1249.
Harnack L, Stang J, Story M (1999). Soft drink consumption among US children and adolescents: nutritional consequences. *J Am Diet Assoc* **99**:436–441.
Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S (1990). Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case–control study. *Int J Cancer* **46**:796–800.
James J, Thomas P, Cavan D, Kerr D (2004). Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial. *BMJ* **328**:1237.
Janssens JPh (1999a). Nutrition early in life and breast cancer. *Nutr Today* **34**:197–209.
Janssens JPh (1999b). Organogenese van de borst (Organogenesis of the breast). Project MSS, Limburgs Universitair Centrum en European Cancer Prevention Organization.
Janssens JPh, Shapira N, Debeuf P, Michiels L, Putman R, Bruckers L, *et al.* (1999c). Effects of soft drink and table beer consumption on insulin response in normal teenagers and carbohydrate drink in youngsters. *Eur J Cancer Prev* **8**:289–295.
Koprowski C, Ross RK, Mack WJ, Henderson BE, Bernstein L (1999). Diet, body size and menarche in a multiethnic cohort. *Br J Cancer* **79**:1907–1911.
Korenman SG (1980). The endocrinology of breast cancer. *Cancer* **46**: 874–878.
Kuschel B, Betz B, Niederacher D, Beckmann MW (2002). Hereditary breast cancer: molecular and chemical differences from sporadic breast cancer. *J Women Cancer* **2**:93–100.
Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al.* (2002). Environmental and heritable factors in the causation of cancer. *N Engl J Med* **343**:78–85.
Ludwig DS, Peterson KE, Gortmaker SL (2001). Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* **357**:505–508.
Moisan J, Meyer F, Gingras S (1991). Leisure physical activity and age at menarche. *Med Sci Sports Exerc* **23**:1170–1175.
Mrdjenovic G, Levitsky DA (2003). Nutritional and energetic consequences of sweetened drink consumption in 6- to 13-year-old children. *J Pediatr* **142**: 604–610.
Mrdjenovic G, Levitsky DA (2005). Children eat what they are served: the imprecise regulation of energy intake. *Appetite* **44**:273–282.
Petridou E, Syrigou E, Toupadaki N, Zavitsanos X, Willett W, Trichopoulos D (1996). Determinants of age at menarche as early life predictors of breast cancer risk. *Int J Cancer* **68**:193–198.
Rogers I, Emmett P; ALSPAC Study Team (2003). The effect of maternal smoking status, educational level and age on food and nutrient intakes in preschool children: results from the Avon Longitudinal Study of Parents and Children. *Eur J Clin Nutr* **57**:854–864.
Sharma SS, Shukla NB (1992). Menarcheal age among Indian sportswomen. *Br J Sports Med* **26**:129–131.
Stoll BA (1998). Western diet, early puberty, and breast cancer risk. *Breast Cancer Res Treat* **49**:187–193.
Stoll BA, Vatten LJ, Kvinnsland S (1994). Does early physical maturity influence breast cancer risk? *Acta Oncol* **33**:171–176.
St-Onge MP, Keller KL, Heymsfield SB (2003). Changes in childhood food consumption patterns: a cause for concern in light of increasing body weights. *Am J Clin Nutr* **78**:1068–1073.
Tanner JM, Whitehouse RH (1976). Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child* **51**:170–179.
Ten S, Maclaren N (2004). Insulin resistance syndrome in children. *J Clin Endocrinol Metab* **89**:2526–2539.
Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E, Trichopoulos D (1995). Consumption of olive oil and specific food groups in relation to breast cancer. *J Natl Cancer Inst* **87**:110–116.
Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D (2000). Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev* **9**:869–873.
Van Winckel M, Braet C (2000). Overgewicht bij kinderen; een behandelingsprogramma (Overweight in children, programme for treatment). *Tijdschr Geneesk* **56**:443–446.
Vereecken CA, Keukelier E, Maes L (2004). Influence of mother's educational level on food parenting practices and food habits of young children. *Appetite* **43**:93–103.
Vereecken CA, Bobelijn K, Maes L (2005). School food policy at primary and secondary schools in Belgium-Flanders: does it influence young people's food habits? *Eur J Clin Nutr* **59**:271–277.
Vervaet M, Bogaert M, Van Gaal M, Van Winckel M, Borms J (1997). Gezond vermageren. Een richtlijn voor het behandelen van overgewicht (Healthy weight loss. A guideline for treatment of overweight). *Tijdschr Geneesk* **53**:1269–1281.
Wheeler MD (1991). Physical changes of puberty. *Endocrinol Metab Clin North Am* **20**:1–14.