Amory and Amory correctly note that grapefruit juice inhibits CYP3A4. Indeed, the same phenomenon may be seen with intact grapefruit segments.[4] This effect is confined to intestinal rather than hepatic CYP3A4, and significant increases in drug levels are most likely with CYP3A4 substrates that normally undergo a high degree of presystemic metabolism.[5] With the exception of cisapride (which is no longer in widespread use), this is not the case for most of the CYP3A4 substrates implicated in the genesis of torsades de pointes. Nevertheless, a recognition of the potential effects of grapefruit on drug bioavailability is essential, given the multitude of drugs metabolized by CYP3A4.

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Birth Weight and Breast Cancer

TO THE EDITOR: Ahlgren et al. (Oct. 14 issue)[1] report the importance of both birth weight and childhood growth on the risk of breast cancer. Although the authors do not provide information about early growth (from the postnatal period to the age of eight years) or birth length, the size of their study permits additional analyses to enhance our understanding of how growth patterns relate to disease.[2] For example, were there any interactions between birth weight and childhood body size? Underweight babies who are well nourished in early childhood may have a greater risk of chronic disease later in life because of the hormonal changes that accompany rapid catch-up growth.[3-5] If so, persons with a low birth weight and peak height at an early age may have a greater increase in the risk of breast cancer than persons with a higher birth weight whose peak height occurs later. Babies who have "catch-down" growth may also have a different risk profile. Since the effect of menarche on breast cancer was mediated by other growth variables, models showing how measures of growth in infancy and early childhood are associated with markers of intermediate growth, including age at peak height, would provide crucial insight into the underlying pathways.

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TO THE EDITOR: Ahlgren et al. report that birth weight and childhood growth influence the risk of breast cancer. We recently analyzed these relationships in a British cohort followed from birth to the age of 53 years.[1,2] A higher risk of breast cancer at the age of 53 years was associated, in multivariable models, with the gain in height between 4 and 7 years and between 11 and 15 years and with the decrease in the body-mass index between 2 and 4 years. These effects were stronger the earlier the age at menarche, reflecting a similar pattern in the relationship between adult height and the risk of breast cancer (Table 1, top of page 305). Thus, it appears that women who grew faster in early childhood, had an earlier menarche, and continued to grow during the postpubertal period, reaching an adult height that was above av-

Table 1. Relative Risks of Breast Cancer Associated with 1-SD Increases in Anthropometric Measures at Certain Ages, According to the Age at Menarche.*

Age at Menarche	Model with All Childhood Growth Components†			Model with Adult Height‡
	Yearly Change in BMI, 2.1–4.0 yr	Yearly Change in Height, 4.1–7.0 yr	Yearly Change in Height, 11.1–15.0 yr	
	relative risk (95 percent confidence interval)			
<12.5 yr	0.50 (0.33–0.75)	1.95 (1.25–3.04)	1.66 (1.00–2.78)	1.85 (1.20–2.84)
12.5–13.4 yr	0.95 (0.54–1.65)	1.37 (0.82–2.31)	1.89 (1.13–3.15)	0.96 (0.58–1.58)
≥13.5 yr	0.89 (0.55–1.44)	1.07 (0.66–1.77)	0.76 (0.43–1.32)	1.13 (0.72–1.77)
Linear trend§	0.01	0.001	0.01	0.02
Interaction¶	0.02	0.07	0.13	0.04

* Data, which are from the Medical Research Council National Survey of Health and Development, are based on a total of 2187 women and 59 cases of breast cancer.[1] BMI denotes body-mass index.
† Relative risks were estimated with the use of a logistic-regression model that included all growth components (height at 2.0 years of age; yearly changes in height from 2.1 to 4.0 years, 4.1 to 7.0 years, 7.1 to 11.0 years, 11.1 to 15.0 years, and 15.1 years to adulthood; BMI at 2.0 years of age; and yearly changes in BMI from 2.1 to 4.0 years, 4.1 to 7.0 years, 7.1 to 11.0 years, and 11.1 to 15.0 years). Results are shown only for anthropometric measures for which there was evidence that their effect on breast cancer was modified by age at menarche.
‡ Relative risks were estimated with the use of a logistic-regression model that included only adult height, age at menarche, and their interaction.
§ The likelihood-ratio test was used to assess linear trend in the age-at-menarche–specific relative risks.
¶ The Wald test was used to assess the heterogeneity of the age-at-menarche–specific relative risks.

erage for their age at menarche, were at greatest risk. Our findings, although based on a limited number of cancers in relatively young women, may help elucidate the complex relations among childhood growth, the onset of menarche, and the risk of breast cancer that are described — but not explained — in the report by Ahlgren et al.

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DR. AHLGREN REPLIES: Inspired by Dr. Terry's comments and those of Dr. De Stavola and colleagues, we conducted a further analysis (Table 1, below);

Table 1. Association between Growth Variables and Breast Cancer, According to Birth Weight.*

Growth Variable	Birth Weight			P Value for Effect Modification
	Quintile 1	Quintiles 2, 3, and 4	Quintile 5	
	*relative risk (95 percent confidence interval)**			
Age at peak growth	0.88 (0.80–0.97)	0.91 (0.86–0.97)	0.88 (0.79–0.98)	0.79
Height at age 8	1.11 (1.01–1.23)	1.13 (1.06–1.20)	1.08 (0.97–1.21)	0.80
Height increase, age 8 to age 14	1.14 (0.96–1.37)	1.15 (1.03–1.29)	1.07 (0.87–1.30)	0.80
BMI at age 14	0.91 (0.68–0.95)	0.95 (0.92–0.98)	0.94 (0.89–1.00)	0.27

* The relative risk is for each one-year increase in age at peak growth, each 5-cm increase in height, and each 1-unit increase in the body-mass index (BMI).

we investigated whether birth weight modified the main results. As shown in Table 1, we found no significant effect modification.

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Autoimmune Lymphoproliferative Syndrome and Perforin

TO THE EDITOR: Clementi et al. (Sept. 30 issue)[1] describe the occurrence of autoimmune lymphoproliferative syndrome (ALPS) and lymphoma in a patient carrying both a heterozygous *Fas* mutation and a heterozygous mutation in the perforin gene (*Prf1*). It is likely that, in addition to *Fas* mutations, associated genetic defects could contribute to the ALPS phenotype.[2] However, the possibility that the described *Prf1* variant, which resulted in the replacement of asparagine with serine at position 252 of the perforin protein (N252S), would be such an associated factor is questionable. Although this variant was identified in a patient with hemophagocytic lymphohistiocytosis,[3] two additional *Prf1* mutations (resulting in the replacement of glycine with arginine at position 45 [G45R] and the replacement of glycine with serine at position 149 [G149S]) were later found in this patient (our unpublished data), casting doubt about the pathogenicity of the N252S variant.[4] In addition, this *Prf1* variant is found in 18 percent of healthy controls and 10 percent of patients with ALPS type I (our unpublished data). We have also found a heterozygous *Fas* mutation (resulting in the replacement of glycine with serine at position 237 of Fas), together with the N252S *Prf1* polymorphism, in a patient with ALPS and his healthy father (Fig. 1). The absence of any disease in the father strongly suggests that the heterozygous *Prf1* N252S mutation in the patient described by Clementi et al. was not pathogenetic.

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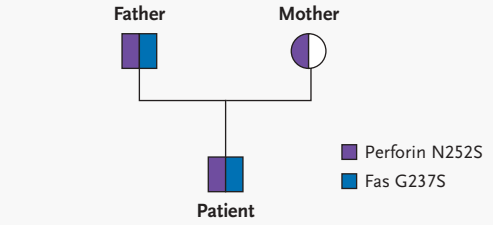

Family Member	Fas	Fas-Mediated Apoptosis (%)	Perforin	Clinical Status
Father	G237S	25	N252S	Healthy
Mother	Wild type	90	N252S	Healthy
Patient	G237S	23	N252S	ALPS

Figure 1. Pedigree of the Patient.
The *Fas* mutation was inherited from the patient's healthy father, whereas the *Prf1* N252S variant was found in all members of this family.

THE AUTHORS REPLY: Rieux-Laucat et al. question the role of the N252S perforin mutation in ALPS. We argue that it can contribute to ALPS for the following reasons. First, the frequency of N252S cited by Rieux-Laucat et al. is much higher than the published data.[1] Moreover, Rieux-Laucat et al. do not mention the ethnic origins and actual numbers of subjects. To date, we have found this variant in 1 of 330 Italian controls (0.3 percent).

Second, we recently found the N252S variant in a second patient with ALPS type III who had a remarkable defect in natural-killer-cell activity. The frequency of N252S in patients with ALPS (2 of 25) and in controls (1 of 330) suggests its associa-