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Reply 1: An assessment of the preconceptional mitochondrial hypothesis

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Sir,

We found Dr van Noord's preconceptional mitochondrial hypothesis interesting particularly in line with a recent report linking polymorphisms of two DNA base excision repair genes (XRCC1 and hOGG1) to breast cancer risk in daughters born to older mothers (Hodgson et al, 2003). Manganese superoxide dismutase (MnSOD) may impair the mitochondria's ability to reduce oxidative stress (Oberley and Oberley, 1997). MnSOD has been linked to breast cancer (Ambrosone et al, 1999), and may be another pathway through which older maternal age may function. Further support for this hypothesis comes from a recent study that found mitochondrial DNA damage in breast cancer tissue (Richard et al, 2000).

To test this hypothesis, we analysed the association of parental age with breast cancer risk using data from the Shanghai Breast Cancer Study (SBCS), and the results are in shown Table 1. After adjustment for established breast cancer risk factors and pregnancy order, we did not find an association between older maternal or paternal age and premenopausal breast cancer in our low-risk population. Additional adjustment for paternal age

resulted in a nonsignificantly elevated risk of breast cancer associated with older maternal age. All perinatal information was based on maternal report.

Although we collected information on whether the mother had a threatened miscarriage with the index pregnancy, too few women reported this adverse event (six case mothers, 13 control mothers) to provide a stable risk estimate. Other studies may have sufficient numbers of mothers to investigate this aspect of Dr van Noord's hypothesis.

Dr van Noord argued that insulin-like growth factor- I (IGF-1) might be unlikely to explain the inconsistent findings on birth weight and breast cancer risk in the literature, since the link between IGF-I and breast cancer risk has been found primarily in premenopausal women, while the high birth weight-breast cancer association has been seen among pre- and postmenopausal women. A previous report from the SBCS showed that elevated levels of IGF-I were associated with an increased risk of breast cancer among all women, but the association was more pronounced among women diagnosed premenopausally and among women with a high body mass index or waist-to-hip ratio (Yu et al, 2001). We found in a large US study that high birth

Table 1 Odds ratios of breast cancer associated with maternal age and paternal age

	Cases (n = 288)	Controls (n = 350)	ORa	(95% CI)	ORb	(95% CI)
Maternal age (years)						
<25	73	98	1.0	(referent)	1.0	(referent)
25 – 29	123	127	1.4	(0.8 – 2.3)	1.6	(0.9 – 2.7)
30 – 34	63	77	1.1	(0.6 – 2.0)	1.5	(0.8 – 2.9)
⩾35	29	47	1.1	(0.5 – 2.2)	1.6	(0.7 – 3.9)
P trend			P = 0.84		P = 0.34	
Paternal age (years)						
<25	34	41	1.0	(referent)	1.0	(referent)
25 – 29	96	94	1.4	(0.7 – 2.8)	1.3	(0.6 – 2.7)
30 – 34	88	103	1.3	(0.7 – 2.7)	1.2	(0.6 – 2.6)
⩾35	70	111	0.9	(0.4 – 1.9)	0.7	(0.3 – 1.8)
P trend			P = 0.13		P = 0.08	

aAdjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, age at first live birth, and pregnancy order. bAdjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, age at first live birth, pregnancy order, and maternal age or paternal age.

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weight was associated with an elevated risk among premenopausal women (OR = 1.7, 95% CI 1.1–2.5), but a nonsignificantly reduced risk among postmenopausal women (OR = 0.6, 95% CI 0.3–1.1) (Sanderson *et al*, 1996). Therefore, IGF-I as a potential explanation for the birth weight-breast cancer relationship cannot be ruled out.

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Reply 2: Birth weight as a predictor of breast cancer: a case–control study in Norway

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Sir,

We welcome the comments of van Noord concerning the different results for birth weight and breast cancer risk reported by ourselves (Vatten *et al*, 2002) and Sanderson *et al* (2002). He suggests that women's breast cancer risk is influenced by the preconception viability of their mothers' oocytes, particularly the quality of their mitochondria, since mitochondrial quality declines with age. Therefore, van Noord proposes that maternal age at birth is positively associated with breast cancer risk, suggesting that we reanalyse our data to test this hypothesis.

Reliable information on maternal age at birth was available in the Trondheim data, and hence this analysis is based on 186 breast cancer cases and 662 age-matched controls. We used conditional logistic regression to explore the association between the risk of breast cancer and maternal age at birth, and the estimated odds ratios are adjusted for age at first birth and parity. As shown in Table 1, we found no association with breast cancer risk over the four categories of maternal age at birth.

Although van Noord has proposed an interesting hypothesis, we found no evidence to support that maternal age at birth is positively associated with breast cancer risk. In light of our original findings, that both birth weight and birth length are positively associated with breast cancer risk, important mechanisms linking birth characteristics to breast cancer may be related to

Table 1 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer associated with maternal age at birth

Variable	Case patients	Control subjects	OR[ab]	95% CI
Maternal age at birth				
<25	56	196	1.0	Reference
25–29	60	212	1.0	0.7–1.5
30–34	41	155	1.0	0.6–1.5
≥35	29	99	1.0	1.6–1.6
			P trend = 0.97	

[a]ORs are computed using conditional logistic regression with cases and controls matched on year of birth. [b]ORs are adjusted for age at first birth and parity in the regression model.

foetal growth. Recent research has shown that both birth weight and maternal pre-eclampsia are associated with adolescent growth and maturation (Vatten *et al*, 2003), and therefore, the intrauterine environment may initiate a tracking pattern of growth that ranges throughout childhood and adolescence. Ultimately, this may play a critical role in the development of breast cancer.

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