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Comment on: 'Hypertensive diseases in pregnancy and breast cancer risk'

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Sir,

In 2012, Opdahl *et al* published their findings in this journal (Opdahl *et al*, 2012) showing a link between hypertensive diseases in pregnancy and subsequent breast cancer risk in a Norwegian cohort of 919 712 women. They found reduced risk for hypertensive disease in any pregnancy which was enhanced for term and post-term pregnancies. In the Child Health and Development Studies (CHDS), we also observe a reduced risk of breast cancer ($N = 1221$ incident cases through 2011) for hypertensive disease in pregnancy among our 15 528 mothers, recruited from the Kaiser Foundation Health Plan, Oakland, California facility from 1959 to 1966. This protection was significant and more robust for live-born, term pregnancies (hazard ratio (HR) 0.31, 95% confidence interval (CI) 0.11, 0.82), similar to findings in the Norwegian cohort, where the strongest protective associations were observed for women with hypertension in pregnancy who delivered at term/post-term (HR 0.81, 95% CI 0.75, 0.88) or had a child of average birth weight (HR 0.77, 95% CI 0.69, 0.85).

In 2001, we reported that blood pressure increase between the second and third trimesters of pregnancy, and certain placental insufficiencies including small placental diameter and maternal floor infarction of the placenta protected against breast cancer incidence in a subset of CHDS mothers (Cohn *et al*, 2001). Specifically, blood pressure increase and maternal floor infarction were significantly associated with a reduced breast cancer risk of 50 and 60% respectively. Smaller placental diameter was also significantly associated with reduced risk of breast cancer, and protection was stronger for women with older age at first pregnancy.

Earlier findings were based on 146 cases of invasive breast cancer diagnosed through 1997, prospectively identified in white CHDS mothers with available placental exams. Currently, 295 cases of invasive breast cancer cases diagnosed through 2011 have been identified in this same subset, doubling the number of previous cases. Previously and now, we find that blood pressure increase between the second and third trimesters exhibits an inverse linear relationship with breast cancer incidence, and in particular, the highest blood pressure increase (fourth quartile) is associated with a 40–50% reduction in breast cancer risk (Table 1). Smaller placental diameter is also associated with a significant reduction in breast cancer risk—previously we found this association interacted with age at first pregnancy, but currently we find an overall significant protection for this placental marker that is not dependent on age at first pregnancy. And as before, we find that maternal floor infarction remains a significant marker of reduced breast cancer risk (Table 1).

It is notable that these pregnancy characteristics have endured in our long-term cohort as stable markers of breast cancer protection with an additional accumulation of 10 years of diagnoses. This accumulation has expanded the range of age at diagnosis towards older ages among CHDS mothers who are in their mid- to late-70s. This would suggest that these markers relate not only to early breast cancer but also to cancers through and beyond menopause. Does this evidence favour one mechanism over another, given the stability of these associations across periods of highly different levels of endogenous oestrogen? Indeed, Opdahl *et al* suggested that the stronger association they observed for term pregnancies may signal a prominent role for maternal metabolic factors. The persistent and apparent independent breast cancer protection conferred by gestational blood pressure increase and placental dysfunction seem to support the possibility of multiple pathways. Certainly the longevity of these associations would seem to diminish the role of pregnancy or its immediate aftermath as the primary antecedent, but rather may suggest that pregnancy mobilises some host factor(s) that explains the protective effect. Searching for mechanisms that align with blood pressure regulation and placental dysfunction during pregnancy may hold

Table 1. Associations of pregnancy and placental factors with invasive breast cancer: Comparison of previous (diagnoses through 1997) *vs* current (diagnoses through 2011) findings

	2001 Findings[a] N = 146 cases			2015 Findings[b] N = 295 cases		
		95% CI			95% CI	
	HR	Lower	Upper	HR	Lower	Upper
Pregnancy characteristic						
Systolic blood pressure increase[c]						
First quartile	— (Reference)			— (Reference)		
Second quartile	0.92	0.60	1.40	1.07	0.79	1.46
Third quartile	0.64	0.40	1.02	0.88	0.66	1.18
Fourth quartile	0.49	0.30	0.80	0.58	0.41	0.82
p for trend	*<0.01*			*<0.01*		
Maternal floor infarction (present *vs* absent)	0.40	0.18	0.88	0.56	0.34	0.92
Low placental weight (<400 g)	0.74	0.46	1.17	1.15	0.86	1.54
Small placental diameter (<21 cm)[d]				0.66	0.52	0.84
Age 19 year at first pregnancy	1.19	0.70	2.04	—	—	—
Age 30 years at first pregnancy	0.44	0.27	0.71	—	—	—
p for interaction	*0.01*			0.19		

Abbreviations: CI = confidence interval; HR = hazards ratio. The italics values are statistically significant at $P<0.05$.

[a]Adjusted for all factors presented in this table plus age, parity, maternal weight gain between the second and third trimesters; age at first pregnancy and birth year. Results are based on invasive diagnoses through 1997.

[b]Adjusted for all factors presented in this table along with age, parity and weight gain between the second and third trimesters. Age at first pregnancy and birth year were not included because they were not independently significant and did not influence results reported here. Results are based on invasive diagnoses through 2011.

[c]Rate of systolic blood pressure increase between the second and third trimesters.

[d]The association for small placental diameter was not different by age at first pregnancy for the contemporary analysis.

promise for identifying the factors that are responsible for protecting against breast cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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