

***In-utero* and early life exposures in relation to risk of breast cancer**

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Abstract

Objectives: In response to a hypothesis by Trichopoulos that risk of adult breast cancer is related to high estrogen exposure *in utero*, studies have been undertaken using proxy indicators of prenatal estrogens. The epidemiologic studies addressing these early factors will be reviewed, consistency with proposed biologic mechanisms will be addressed and recommendations for future research will be presented.

Methods: All studies identified in the literature addressing these *in utero* and early life factors related to adult breast cancer will be included in the review. The study results will be summarized by risk factor, followed by commentary on the findings.

Results: Review of epidemiologic studies suggests strong risks related to having been born of a twin pregnancy and reduced risks from a preeclamptic or eclamptic pregnancy. Birthweights greater than 4000 grams have been associated with relative risks of 1.5–1.7 for breast cancer compared with normal birthweights (2500–2999 grams). Having been breastfed as an infant has been associated with a 20–35% reduction in risk of premenopausal breast cancer in four of six studies evaluating this factor. Some studies suggest an influence of older maternal age, perhaps only for firstborn offspring, but the data are not consistent. Smoking during the pregnancy does not seem to impart any risk for the daughter, severe nausea for two or three trimesters may be related to increased risk, and results are inconsistent for birth length, placental weight and gestational age.

Conclusion: Although the results from epidemiologic studies assessing prenatal exposures are consistent with the hypothesis concerning estrogen exposure, the specific biologic mechanisms remain largely unknown. Relatively few epidemiologic studies have been published addressing these novel hypotheses; more studies with innovative research methods and analytic approaches are warranted to evaluate these exposures in the distant past.

Introduction

There is wide international variation in rates of breast cancer, and migrant studies provide compelling evidence that environmental and not genetic differences are responsible for the international variation [1]. Risks among the first-generation immigrants from countries of low incidence, particularly Asians, to countries of high incidence show some elevation in rates, and substan-

tially increased rates are observed among the generation born in the adoptive country [2]. These changes in rates and the similarity of rates between the second-generation immigrants and those of the host country have led to hypotheses that environmental exposure early in life may explain the observed variation in rates across populations [1, 3, 4].

Data from animal studies and natural experiments in human populations provide leads to the importance of both *in utero* and childhood exposures. In animal model systems, adult carcinogens administered during a pregnancy result in mammary tumors among the mature offspring, suggesting an influence of the *in utero* environment [5, 6]. It is of interest that the tumors present in adult animals and not in the young animals. In rodent model systems, exposure to a carcinogenic agent *in utero*

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followed by exposure to a tumor promoter postnatally demonstrated that both factors are necessary for tumor manifestation [7]. Diets high in fat during a pregnancy have been related to increased levels of estradiol in the pregnant animals and to increases in mammary tumors in the first-generation female offspring [8]. In another rodent system, exposure to high dietary fat during gestation of one generation resulted in more aggressive mammary tumors in second-generation offspring who had experienced low-fat diets during their gestation [9]. These results are consistent with multigenerational effect of nutrition during gestation on birthweight observed in humans [10]. The evidence from other human studies are limited but suggestive of prenatal or childhood influences on risk of adult disease. The observed excess relative risk (ERR) of breast cancer among atomic bomb survivors who were less than 20 years old (ERR = 2.4, 90% CI = 1.6–3.4) compared with women who were older at the time of the bombing (ERR = 1.3, 90% CI = 0.8–1.9 for 20–39 years of age, and 0.5, 90% CI = 0.0–1.3 for ≥ 40 years of age) provides strong evidence for a vulnerable time period [11]. Among women younger than age 20, risk was nonsignificantly greater for those 0–9 (ERR = 3.2, 90% CI = 1.5–6.1) at the time of the bombing than for those ages 10–19 (ERR = 2.2, 90% CI = 1.4–3.3) [11]. In another example of radiation exposure at young ages, irradiation of the thymus in infancy was associated with significantly increased risk of early-onset breast cancer among young women (RR = 3.6, 95% CI = 1.8–7.3) [12]. Finally, it has been known for over 20 years that DES exposure *in utero* results in vaginal adenocarcinoma in young adulthood for the women exposed [13]. It is still unclear whether DES exposure will result in increased risk of breast cancer among female offspring [14]. Nonetheless, these data suggest an influence of *in utero* and early postnatal environment on adult cancer risk, but the relevance of irradiation or synthetic estrogen to typical later-onset disease is unknown.

A variety of studies have shown associations between early life environment and other chronic diseases of adulthood, particularly cardiovascular disease and its risk factors. More extensive reviews of the literature for cardiovascular disease can be found elsewhere [15, 16], but some highlights relevant to the breast cancer studies will be mentioned. Ecologic data have shown associations between low birthweight and low weight at 1 year with ischemic heart disease mortality (standardized mortality ratios (SMR) = 111 for ≤ 18 pounds at 1 year vs. SMR = 42 for ≥ 27 pounds at 1 year) and with chronic obstructive lung disease (SMRs = 129 and 29, respectively) [17]. Associations were also observed between birthweight or weight at 1 year and risk factors

for ischemic heart disease, such as blood pressure, body mass index, waist/hip ratio, serum lipids, plasma clotting factors, and impaired glucose tolerance (OR = 6.6 for birthweight ≤ 5.5 pounds compared with > 9.5 pounds) [18]. These relationships between early weight and the risk factors persisted after adjustment for potential confounding factors such as social class, smoking and obesity. Findings for blood pressures have received much attention with associations demonstrated for low birthweight as well as for a high ratio of placental weight to birthweight [18]. These data suggest that an adverse environment in early life can predispose individuals to disease later in life, and that prenatal as well as postnatal factors influence risk.

In 1990, Trichopoulos suggested that, given the evidence for an influence of early life events on later risk of disease, efforts should be directed toward investigating *in utero* exposures and breast cancer risk [19]. The basic tenets of his hypothesis were the following: (1) estrogen exposure is thought to be related to risk of adult disease; (2) exposures that act postnatally can also act prenatally; (3) estrogens are 10 times higher during pregnancy than at other times in a woman's life; and (4) pregnancy estrogens vary widely across individuals and may be related to exogenous factors. This hypothesis has sparked a substantial amount of recent work on prenatal and perinatal exposures and breast cancer risk, which will be the focus of this review.

Materials and methods

All epidemiologic studies identified through computer searches of medical databases or from citations within papers were included. There were no papers excluded that were considered of insufficient quality. First, the evidence for each risk factor is summarized, and then the consistency of the observed findings with the proposed mechanisms is considered, followed by recommendations for future efforts.

Results

Preeclampsia/eclampsia

Preeclampsia is a pregnancy condition characterized by hypertension, hyperuricemia and proteinuria; the ensuing condition, eclampsia, also includes one or more convulsions. Preeclampsia usually occurs in the latter half of pregnancy (usually 34 weeks or later) and in some cases labor induction is indicated. Lower than

normal levels of pregnancy estrogens, estriol specifically [20–22], in this condition led to the hypothesis that breast cancer risk in offspring would be reduced.

The earliest investigation of breast cancer risk in the offspring of preeclamptic pregnancies reported an increased risk of breast cancer among women born of preeclamptic pregnancies (Table 1), but these results were based on only four cases [23]. Two Swedish studies [24, 25] that followed the initial report found a highly protective effect of preeclamptic pregnancies. These studies used cancer registry data from 1958 to 1990 to identify cases born between 1874 and 1961 in five hospitals in one region of Sweden. Birth records at the participating hospitals were obtained for these breast cancer cases. Control subjects were the next three consecutive births at the same hospital as the case, who were alive and free of breast cancer at the time of cancer diagnosis in the matched case. A marked reduced risk of breast cancer among babies born to preeclamptic mothers was noted in the first analysis [24] of 458 cases (OR = 0.2, 95% CI = 0.1–0.7) and similar results were obtained with the addition of more cases (1068 cases, OR = 0.4, 95% CI = 0.2–0.8) [25]. Both analyses adjusted for other maternal and pregnancy factors such as maternal age, maternal socioeconomic status, maternal parity, birth weight, and in addition, the second study [25] also controlled for severe prematurity (< 33 weeks or 33+ weeks), twin membership and neonatal jaundice. In studies such as these it is not possible to evaluate confounding or effect modification by adult risk factors of the offspring. Lack of detail in these two reports regarding the severity of the disease (*i.e.* whether eclampsia or preeclampsia was diagnosed, or whether preeclampsia was diagnosed before [severe disease] or after 37 weeks [mild disease]) limits the ability to determine if one syndrome was more strongly related to risk. In the analyses, finer delineation of gestational

age may have impacted the results since preeclamptic/eclamptic pregnancies are often of shorter duration than normal pregnancies but are not severely premature as defined in one of the studies [25]. Further, although the results were statistically significant, the small number of subjects born of preeclamptic/eclamptic pregnancies (eight cases and 45 controls [24]; and 14 cases and 81 controls [25]) warrants caution in interpreting this as a stable finding. A recent case-control study using data from subjects' mothers [26] also suggested a protective effect of preeclamptic pregnancies but was also limited by few cases with this pregnancy condition (20 cases).

Gestational age

Studies of the impact of time *in utero*, or gestational age, on subsequent breast cancer risk have been inconsistent (Table 2). Although one study reported an increased risk of breast cancer (OR = 4.0, 95% CI = 1.5–11) for women who were born at 33 weeks of gestation or earlier [25], none of the other investigations observed an association with having been born before term. LeMarchand *et al.* [23] showed no significant association for being born at 7–8 months compared with 9–10 months (OR = 1.2, 95% CI 0.5–2.7), Michels *et al.* [27] found no associations for having been born 2, 2–4 or 4+ weeks early; Sanderson and co-workers [28] reported no association for having been preterm among pre- or postmenopausal breast cancer cases. Although no association was observed for preterm births in a recent study, there was a suggestion of increased risk for long gestational length (OR = 1.5, 95% CI = 0.8–2.6 for ≥ 43 weeks compared with 37–42 weeks) [26]. Small numbers of subjects who had been pre- or post-term, lack of attention to the combined effects of birthweight and gestational age, or to trends limited these studies by gestational age. Further, few studies specified how gestational age was determined or whether the data were reliable.

Twins

Several epidemiologic studies have reported on risk of breast cancer in twins compared with singletons (Table 3). The rationale for evaluating twins is that pregnancies involving two placentas, that is dizygotic twin pregnancies, would be producing more estrogens and other factors than single-placenta pregnancies (*i.e.* monozygotic twin and singleton pregnancies). Investigators from one of the Swedish studies [25] reported increased risk of breast cancer for dizygotic (OR = 1.7, 95% CI = 0.9–3.2) but not monozygotic twins (OR = 0.4, 95% CI = 0.1–1.7). Two other studies

Table 1. Risk of breast cancer associated with having been born of a preeclamptic pregnancy

Author, year, ref.	Cases	Controls	Total preeclamptic pregnancies	RR (95% CI)*
LeMarchand <i>et al.</i> 1988 [23]	153	461	8	3.5 (0.9–14)
Ekbom <i>et al.</i> 1992 [24]	458	1197	53	0.2 (0.1–0.7)
Ekbom <i>et al.</i> 1997 [25]	1068	2727	95	0.4 (0.2–0.8)
Sanderson <i>et al.</i> 1988 [26]	509	433	41	0.8 (0.4–1.5)

* Reference is "normal pregnancy".

Table 2. Risk of breast cancer associated with gestational age

Author, year, ref.	Cases	Controls	Gestational age comparison	RR (95% CI)	Comments
LeMarchand <i>et al.</i> 1988 [23]	153	457	7-8 months vs. 9-10 months*	1.2 (0.5-2.7) 1.0	Matched analysis, 9 cases, 22 controls were preterm
Michels <i>et al.</i> 1996 [27]	571	1525	> 4 weeks early 2-4 weeks early < 2 weeks early Not premature*	1.0 (0.5-2.4) 0.9 (0.5-1.5) 0.8 (0.4-1.4) 1.0	Adjusted for adult risk factors, mothers' data, 8 cases and 26 controls in > 4 weeks category
Sanderson <i>et al.</i> 1996 [28]	746 401	960 439	Preterm vs. not preterm*	1.1 (0.7-1.7) [†] 1.1 (0.5-2.1) [‡]	Adjusted for subjects' age, menopausal status, maternal smoking
Ekblom <i>et al.</i> 1997 [25]	1068	2727	< 33 weeks ≥ 33 weeks*	4.0 (1.5-11) 1.0	Adjusted for maternal and perinatal factors, 10 case and 9 controls were < 33 weeks
Sanderson <i>et al.</i> 1988 [26]	510	436	< 37 weeks 37-42 weeks* ≥ 43 weeks	0.9 (0.5-1.8) 1.0 1.5 (0.8-2.6)	Early-onset disease, mothers' data, no confounding by adult risk factors

* Reference category.

[†] Risk for women 21-45 years of age.[‡] Risk for women 50-64 years of age.

Table 3. Risk of breast cancer associated with having been born of a twin pregnancy

Author, year, ref.	Cases	Controls	Type of twin comparison	RR (95% CI) (twin vs. singleton)	Comments
Ekblom <i>et al.</i> 1997 [25]	1068	2727	Dizygotic* Monozygotic*	1.7 (0.9-3.2) 0.4 (0.1-0.7)	Adjusted for maternal and perinatal risk factors
Hsieh <i>et al.</i> 1992 [29]	870	2641	Twin brother Twin sister	1.5 (0.6-3.7) 1.3 (0.6-2.9)	Adjusted for maternal and subjects' adult risk factors, 17 case and 33 control twin subjects
Weiss <i>et al.</i> 1997 [30]	2150	1961	Twin brother Twin sister	2.1 (1.0-4.5) 1.4 (0.7-2.6)	Adjusted for subjects' adult risk factors, 51 case and 26 control twin subjects, early-onset disease
Sanderson <i>et al.</i> 1996 [28]	746 401	960 439	Twin birth Twin birth	0.6 (0.3-1.3) [†] 0.9 (0.4-2.2) [‡]	Adjusted for subjects' age, menopausal status, maternal smoking

* Dizygotic twins have two placentas, monozygotic twins have one placenta.

[†] Risk for women 21-45 years of age.[‡] Risk for women 50-64 years of age.

evaluated the risk for having a twin brother, which is a proxy for being dizygotic, or having a twin sister, which represents a mixture of monozygotic and dizygotic twins. These studies [29, 30], which could control for established breast cancer risk factors in the offspring, reported increased risk for having a twin brother (OR = 1.5, 95% CI = 0.6-3.7; OR = 2.1, 95% CI = 1.0-4.5, respectively) and lower risk estimates for having a twin sister (OR = 1.3, 95% CI = 0.6-2.9; OR = 1.4, 95% CI = 0.7-2.6, respectively). The international case-control study [29] observed a stronger effect of having a twin or twin brother among premenopausal women, but the number of subjects was limited.

Being a twin was not associated with increased risk of either pre- or postmenopausal breast cancer in a case-control study in Washington State [28], however. Although small numbers of twins limited some of these analyses, there is some consistency to the finding of increased breast cancer risk for dizygotic twins, possibly only at young ages.

Another type of study uses twin registries to follow a cohort of twins and compare their rates of disease to the rates expected in the general population. In a study based on the Danish Twin Registry, Holm [31] reported a higher risk of breast cancer in twins of both zygosity compared with the general population. In contrast, in a

study based only on same-sex twins in the Finnish Twin Registry, breast cancer rates were lower in twins compared with the general population (RR = 0.7) [32]. A study from the Swedish Twin Registry showed no overall increased risk for mono- or dizygotic twins, but showed an increased risk for a subset of dizygotic twins with cancer diagnosed between age 20 and 29 [33]. Monozygotic and dizygotic twins of other age groups showed no elevation in rates of breast cancer.

Other studies that compare breast cancer risk among twins have been inconsistent and generally do not report risk for twins compared with singleton births. Swerdlow *et al.* [34] showed no elevation in risk of early-onset breast cancer in women whose co-twin was male compared with female (OR = 1.1, 95% CI = 0.8–1.6) in a population-based study of twins. However, in a recent report based on the Swedish Twin Registry, risk of breast cancer was greater in monozygotic than dizygotic twins among the same-sex twins, suggesting a genetic component to the disease, particularly among younger cases [35]. These twin registry studies do not indicate higher risk for dizygotic twins, whereas the other epidemiologic studies [25, 29, 30] are more consistent with this hypothesis. Other physiological differences between singleton and twin, or male co-twin pregnancies may reveal etiologic leads. Unfortunately, complex methodologic issues, such as representativeness of the twin population, and loss to follow-up of both twins possibly resulting in a healthy participant or otherwise biased sample limit twin studies based on twin registries.

In summary, the analytic epidemiologic studies suggest an increased risk for dizygotic twins, and the twin registry studies are inconsistent regarding risk compared with the general population or by type of twin. However, some consistency was observed across studies regarding an influence of twinning on early-onset as opposed to postmenopausal breast cancer.

Birthweight

There are several studies that addressed the issue of whether larger babies are at increased risk of breast cancer (Table 4). In 1988 LeMarchand and colleagues [23] reported no association of high birthweight in women who later developed breast cancer. Adjustment for other risk factors did not influence the finding. A slight increase in risk was observed for low (<2500 g) and high birthweights (>3500 g) in the first Swedish study [24], although the findings were not statistically significant. In the follow-up study in Sweden [25], no association between birthweight and breast cancer was observed. A J-shaped relation was also observed in premenopausal women in the United States [28], however. Compared with the reference group (2500–2999 g), low birthweight (<2500 g) and high birthweight (4000 g+) were associated with increased risk (OR = 1.3 and 1.7, respectively). In contrast to the finding for premenopausal women, evaluation of postmenopausal women showed a nonsignificant decreased risk for high birthweight (4000 g+) [28]. A later study of early-onset disease [26] using information from

Table 4. Risk of breast cancer associated with birthweight

Birthweight (g)	Author, year, ref.					
	Ekbom <i>et al.</i> 1992 [24]	Ekbom <i>et al.</i> 1997 [25]	Sanderson <i>et al.</i> 1996 [28]		Michels <i>et al.</i> 1996 [27] [‡]	Sanderson <i>et al.</i> 1998 [26] [†]
			Premenopausal	Postmenopausal		
<2500	1.2	0.8	1.3	0.9	0.55 [§] (0.8)	1.2
2500–2999	1.0*	1.0*	1.0*	1.0*	0.66 [§] (1.0)* [†]	1.0*
3000–3499	1.3	1.0	1.3 [§]	1.1	0.68 [§] (1.0)	1.0
3500–3999	1.5	1.0	1.2	0.8	0.86 (1.3)	1.0
4000+	1.2	1.0	1.7 [§]	0.6	1.00* (1.5)	1.3
Birthweight (g)	LeMarchand <i>et al.</i> 1988 [23]					
1162–2948	1.00*					
2949–3340	0.65					
3341–4451	0.76					

* Reference group.

[†] Reference group changed for comparison with other studies using this reference category.

[‡] Data provided by mothers of subjects.

[§] Confidence interval excludes 1.0.

mothers from two case-control studies showed no significant associations but slight elevations in the very low and high birthweight categories. Finally, compared with a birthweight of 4000 g or greater (8 lb 12.8 oz), a linear trend of decreasing risk (OR = 0.86, 0.68, 0.66, 0.55 for birthweights 3500-3999 g, 3000-3499 g, 2500-2999 g, and <2500 g, respectively) was observed in a case-control study nested in the Nurses' Health Study cohort [27]. This association was stronger for premenopausal breast cancer but limited numbers of postmenopausal women restricted analysis of this group. The birthweight data were provided from mothers of subjects and agreed well with results from the subjects whose mothers were included in the study. Analyses were adjusted for adult risk factors [27, 28] or maternal pregnancy characteristics [24, 25, 27, 28] but not necessarily measures of socioeconomic status [27, 28], which may have confounded the findings. Nonetheless, there is evidence that high-birthweight babies may be at an increased risk of adult breast cancer, perhaps only premenopausal breast cancer, compared with lower-birthweight babies. No consistency emerges regarding the risk for babies born in the lowest birthweight category (<2500 g), however.

Maternal age and birth order

Modestly increased risks have been observed for daughters born to older mothers [23, 36-40], but other studies have failed to observe an association [24, 25, 28, 30, 41-43]. In one study the increased risk was restricted to daughters who were parous in their adulthood [40], though this interaction was not reproduced in a later study [43]. Results among studies may be inconsistent because investigators did not evaluate pre- and postmenopausal disease separately, even though in two studies effects appeared to vary by menopausal status [43, 44]. Alternatively, lack of adjustment for breast cancer risk factors among the daughters may be responsible for positive findings since adjustment attenuated the maternal age effect in at least one study [43].

The effect of maternal age may be modified by birth order as evidenced by Hsieh *et al.* [44] and Janerich [45]. Being second born was associated with a reduced risk compared with being first born (0.7, 95% CI = 0.5-0.9) and this risk estimate was attenuated with adjustment for maternal age [44]. In the other study [45] no association was observed for birth order in the crude analysis, but being first born was associated with an odds ratio of 1.4 (1.0-2.0) for 10-year increments in maternal age. Joint effects of older maternal age and being first born have not always been observed, however [37]. Several studies that evaluated birth order

as a main effect have shown no association [23, 28, 36, 37, 39].

Breastfed

Four case-control studies have reported a protective effect of having been breastfed [30,46,47,49] (Table 5). All of the studies simply asked a "yes/no" question regarding having been breastfed as an infant. Reporting of past breastfeeding by daughters has been shown to be consistent with reports by their mothers [48]. Nonetheless, for studies showing associations, it is reassuring that the magnitude of the risk estimate and confidence intervals were similar when the information was obtained from the mothers of subjects [30] or from the subjects themselves [46, 47]. Three other analyses, however, have not found an association. In a large case-control study of women age 50 years or more, postmenopausal subjects who reported having been breastfed were not at reduced risk of breast cancer [49]. Interestingly, in this study a protective effect was observed for premenopausal breast cancer (OR = 0.6, 95% CI 0.4-1.0) but the sample size in this group limited the interpretation. A preliminary report from mothers of subjects in a nested case-control study of breast cancer suggested no association for ever having been breastfed and increased risk was associated with having been breastfed for more than 9 months [50]. Results from another study using data from mothers [26] also indicated no association, and this study was restricted to cancers diagnosed in women less than age 45. Using data from the early Swedish [24], the investigators showed no association between having been breastfed at discharge from the hospital and risk of breast cancer [51]. However, there was no variability in the exposure of interest as almost 98% of subjects were breastfed in this population. Thus, four of the six analytic studies suggest reduced risk particularly for early-onset disease [30, 46, 47, 49], whereas results for postmenopausal women are inconsistent [47, 49]. Given the methodologic strengths of the large case-control study [49] and the other negative studies [50, 51], it is likely that breastmilk exposure is not important for postmenopausal disease.

Risk related to exposure to breastmilk had been evaluated in earlier studies of breast cancer etiology. These studies, which were launched to evaluate possible transmission of a viral agent through breastmilk, found little association of having been breastfed with the risk of breast cancer [38, 52, 53]. Many of these studies were limited in a number of ways, including focusing only on subjects with a family history of breast cancer or in populations with no variability in the prevalence of breastfeeding. Fraumeni and Miller [54] detailed the

Table 5. Risk of breast cancer associated with having been breastfed as an infant

Author, year, ref.	Number		Estimated* birth years of subjects	Prevalence of breastfeeding among controls	OR (95% CI) (ever/never)	Comments
	Cases	Controls				
<i>Data from subjects</i>						
Brinton <i>et al.</i> 1983 [46]	1362	1250	1903-1937 (majority)	74%	0.86 (0.7-1.1)	Mostly early-onset disease, adjusted for age at diagnosis
Freudenheim <i>et al.</i> 1994 [47]	528	602	1901-1951	86% postmenopausal 59% premenopausal	0.76 (0.5-1.1)	Consistent by menopausal status, adjusted for menopausal status
Titus-Ernstoff <i>et al.</i> 1998 [49]	3803 205	4071 220	1911-1945	55.6% postmenopausal 48.1% premenopausal	0.95 (0.85-1.1) 0.65 (0.41-1.0)	Adjusted for adult risk factors, no influence of adjustment maternal age, birthweight, birth order
<i>Data from mothers</i>						
Weiss <i>et al.</i> 1997 [30]	534	497	1946-1972	50%	0.74 (0.6-1.0)	Early-onset disease, adjusted for adult risk factors
Michels <i>et al.</i> 1997 [50]	572	1531	(Not available)	64%	1.1 (0.9-1.4) [†]	Adjusted for birthweight, adult risk factors and year of birth
Sanderson <i>et al.</i> 1998 [26]	506	433	1944-1972	45%	1.0 (0.8-1.3) [‡]	Early-onset disease, no confounding by adult risk factors

* Estimated from age ranges at time of interview provided in paper, or from estimated age ranges based on age information provided.

[†] OR = 1.57 (1.1-2.3) for breastfed 9+ months versus never.

[‡] OR = 1.0, 1.1, 1.0 for 1-2.9 months, 3-5.9 months, 6+ months, respectively.

lack of international and national trend data to support the hypothesis of a transmissible agent for breast cancer in breast milk. Further, one focus of the recent large case-control study [49] was evaluation of risk related to a transmissible agent in breastmilk. Risk was not increased in breastfed daughters whose mother later developed breast cancer, which does not support the hypothesis of an infectious etiology for the disease.

Other factors

A number of other pregnancy and neonatal-related factors have been evaluated in several studies, including maternal smoking, pregnancy weight gain, birth length and placental weight. An effect of maternal smoking might be mediated through changes in circulating estrogens or in birthweight. However, there is little evidence that smoking during pregnancy is related to increased or decreased risk of breast cancer in the offspring [26, 28, 30, 55]. Although there was no effect in the overall analysis of women less than age 45 years of age [28], among women less than age 30 breast cancer was associated with maternal smoking during the pregnancy (OR = 1.9, 95% CI = 1.0-3.4). Such an association requires replication in another larger study of young women even though there were *a priori* hypotheses

for evaluating risk in this younger subgroup of 64 cases. Only one study evaluated postnatal passive smoking [26] and suggested slightly increased risks associated with this exposure (OR = 1.3, 95% CI = 0.9-1.7).

A study focusing on mothers' data about her pregnancy with the case or control in relation to risk of early-onset breast cancer [26] found increased risk for a pregnancy weight gain of 25-34 pounds (OR = 1.5, 95% CI = 1.2-2.0) but no increased risk for higher weight gains. Increased risks were observed for use of antiemetic drugs during the pregnancy (OR = 2.9, 95% CI = 1.1-8.1), and suggestive evidence of increased risks for any severe nausea and vomiting for two or more trimesters, with (OR = 1.6, 95% CI = 0.5-5.5) or without (OR = 1.5, 95% CI = 0.8-2.6) use of medication. No associations were observed for prepregnancy body mass index, hypertension, alcohol consumption, oral contraceptive or hormone use, but nonsignificantly elevated risks were noted for anemia and coffee consumption. DES was associated with increased risk (OR = 2.3, 95% CI = 0.8-6.4), but the 13 cases and five controls with this exposure limits interpretation.

In the record linkage study in Sweden [25], an increased risk was noted for infants who experienced jaundice in the hospital, possibly related to an endocrine mechanism. Evaluation of birth length has shown a

slight elevation in risk for longer babies but no trends were observed [24, 25]. In the smaller Swedish study that demonstrated a slightly increased risk for higher birthweight babies, a slightly increased risk for higher placental weights was also observed [24]. However, in the larger Swedish study in which no relation of birthweight and risk of breast cancer was observed, placental weight also was unrelated to risk [25]. It is likely that birth length and placental weight were measured with substantial error unless the staff was specifically trained and standardized procedures were in place for the study. Thus, both of these exposure variables require further analysis in more controlled settings of data collection.

Discussion

Assessment of the evidence

Review of the current literature shows that some associations of prenatal and early life exposures with breast cancer risk are consistent and promising. Daughters born of preeclamptic or eclamptic pregnancies, and those who were breastfed as infants, appear to be at reduced risk of breast cancer. High birthweights and being a twin have been associated with increased risk. The associations for having been breastfed and being a twin may be restricted to early-onset disease. Findings from studies of maternal age and birth order have been inconsistent and conclusions cannot be drawn without further analyses of current data or additional studies.

Many years of epidemiologic research have revealed strong risk factors that operate at other critical time periods [56–58]. For example, age at first birth, age at menopause and recent alcohol intake all suggest that adult experiences have significant impact on risk of disease. It is likely that the early life exposures interact or modify the risks associated with these established risk factors and perhaps should be evaluated in that manner.

Commentary

The observed epidemiologic results lend some support to the proposed biologic mechanisms. The epidemiologic findings related to preeclampsia, twinning, birth order and birthweight are consistent with the principal mechanism that has been proposed, namely early life exposure to high levels of pregnancy estrogens [19]. Although the original hypothesis involved estrogen exposure only, hormone profiles involving other hormones, growth factors and estrogen and progesterone receptor activities could also be consistent with the

observed results. Newer studies may incorporate some of these more complex endocrinologic mechanisms as the field of research evolves.

Two other hypotheses have been proposed. These hypotheses are only relevant to studies evaluating parental age and birth order, however. One hypothesis related to parental age suggested that germline mutations among older individuals could increase risk of disease [59]. In the other hypothesis, Janerich [60] proposed that fetal antigens related to the paternal contribution to the fetus, produced in first pregnancies, could protect subsequent fetuses through immune mechanisms directed toward breast tissue. This would explain some of the birth order findings and perhaps the maternal age effects, given that older individuals have more limited immune responses. Most of the risk estimates for birth order and maternal age are weak or nonsignificant, however, and there is a lack of consistency across studies.

Most of the research conducted to date focused on proxy variables for the estrogen environment. Therefore, the following discussion will focus on the consistency of the data with this hypothesis and presentation of relevant biologic mechanisms. Additional comments on analytic issues for each potential risk factor will also be addressed.

Preeclampsia/eclampsia. The biologic rationale most often cited for the association between risk of breast cancer and preeclampsia/eclampsia is one related to estrogens. Many women with mild preeclampsia may have urinary estriol concentrations within the normal range but somewhat below the mean value of normal pregnancies [22, 61]. The majority of women with severe preeclampsia will have clinically low estriol concentrations, although some may have normal values [22, 61, 62]. Estriol is a useful clinical diagnostic tool since its concentration normally rises at the end of pregnancy and therefore can help identify women with preeclampsia. Although most investigators document differences in estriol among preeclamptics, one report noted lower estradiol but not estriol concentrations in preeclamptics compared with normal pregnancies [63]. In addition, it remains unclear at what point during the pregnancy lower estrogen levels become apparent. In other words, it is not known whether estrogen concentrations are lower than "normal" throughout the pregnancy or are lower only for a short time during development of the preeclamptic symptoms.

Many factors besides estrogen metabolism are altered in preeclamptic pregnancies, thus the nature of the protective effect on breast cancer risk is uncertain. It may be that the protective effect is related to the timing

of exposure to lower estrogens during gestation, or aspects of a compromised placenta producing less of certain constituents or being permeable to factors that otherwise would not cross to the fetus. Given that there are only two major reports on this risk factor, albeit with compelling risk estimates, other epidemiologic investigations need to verify the association while further elaboration of possible mechanisms is pursued.

Gestational age. It is of interest that there is no reduction in the daughter's breast cancer risk associated with less than a full-term pregnancy, and thus a shorter exposure to high estrogen levels. One might hypothesize that shorter gestation would coincide with lower cumulative estrogen exposure. The lack of associations could indicate a threshold effect, inadequate assessment of gestational age or critical, vulnerable time periods for the exposure. If timing of exposure is important, then proxies for estrogen or other hormonal exposures during different stages of pregnancy need to be assessed. It has been suggested that pregnancy nausea, which occurs predominantly in the first trimester, and severe nausea throughout pregnancy may be related to high estrogen concentrations. One study [26] did document increased risk associated with use of antiemetic drugs and severe nausea for two or three trimesters, which may be indicative of a high estrogen environment but also may be related to high levels of human chorionic gonadotropin and possibly other factors [64]. Thus, evaluation of nausea and timing of the nausea in relation to risk of breast cancer may be pursued but the mechanism for an association would be unclear.

Twinning. Compared with singletons, most studies show higher maternal serum or urinary estriol levels in twin pregnancies [65-67], which have been hypothesized to increase risk in the female offspring [68]. Although it has been theorized that dizygotic twins, in particular, may be exposed to even higher estrogen levels because of the metabolic capacity of two placentas (*i.e.* estrogen production from each placenta), such a difference in urinary estrogens between monozygotic and dizygotic pregnancies has not been shown [69].

Birthweight. It has been hypothesized that larger babies may be exposed to higher estrogen concentrations *in utero*, but the data supporting this association are weak [70] and require verification. Clearly there are other correlates of high birthweights that may be relevant to later disease, such as exposure to high concentrations of insulin or other factors [71-74].

There are several inconsistencies in the epidemiologic findings worth noting. Although the first Swedish study

reported risk associated with high birthweight, the expanded study did not find this association. It appears that age at diagnosis of breast cancer may be an important consideration for analyses of birthweight effects [28]; however, the disparity in the Swedish studies cannot be explained by this factor as the proportions of younger and older cases were similar in the two studies [24, 25]. The other null study [23] had a predominance of young cases (women born after 1945), which contradicts the associations noted only for premenopausal breast cancer [27, 28]. Two studies [26, 27] relied on recalled birthweight from mothers, which has been shown to be highly correlated with birth records ($r = 0.85$) [48]. These studies had inconsistent findings in that one study showed strong a linear relation with birthweight [27], and the other [26] was null or only suggestive of a J-shaped relation. As with all studies attempting to obtain information from mothers of cases and controls, only a small subset of mothers (usually < 50%) are available and willing to participate in the study. Thus, consistency across studies using mothers' data, and with daughters' data, is particularly desirable since the problems of selection among mothers and recall among daughters may be problematic. Although the consistency of the risk estimates for mothers' and daughters' birthweight data was somewhat reassuring in one study [27], there remains concern about the representativeness of this subsample of daughters whose mothers responded to the study. Another study that relied on information from the daughter resulted in a substantial number of women with missing data (10-27%), particularly among postmenopausal women [28]. These methodologic issues may have resulted in attenuated or biased relationships. Nevertheless, there is suggestive evidence for an association of increased risk for high birthweights (> 4000 g) particularly for premenopausal breast cancer. Most of these analyses, however, did not adjust for gestational age and other important determinants of birthweight [75-77], which may be indicators of the *in utero* environment.

Maternal age and birth order. It has been hypothesized that older mothers may impart an increased risk to female offspring through higher circulating levels of endogenous estrogens during the pregnancy or through an increased prevalence of gonadal germ cell mutations. The studies often cited to support the estrogen hypothesis for the maternal age effect are weak and are not consistent with the epidemiologic finding of increased risk for maternal age of 30 years of age or older. Epidemiologic studies that report a positive association between maternal age and daughter's risk show elevated risks for mothers aged 30-34 or older compared with

those less than age 20, and generally not in a dose-dependent gradient with age. Studies of pregnant women show lowest estrogen concentrations for those less than age 20 while highest levels are noted for those aged 20–29, but not for the older mothers [78].

There are few relevant hormonal studies related to birth order for evaluation of a main effect of birth order in epidemiologic studies. Consistent with some findings for higher risk among first-born offspring, maternal free E2 (*i.e.* the estradiol not bound to binding proteins) was 9% higher and percent free E2 was 17% higher in first compared with second pregnancies among the same women measured at approximately week 12 of two pregnancies [79]. These were young women (mean age and standard deviation for first and second pregnancies, 22.6 ± 3.1 and 24.0 ± 3.2 , respectively), however. Only one study [78] evaluated estrogen levels for primigravida women over age 30, where the risk for higher maternal age has been observed. Total estrogen and estradiol but not estriol or placental lactogen were noted to be higher in first compared with second pregnancies among young women (<age 20), but no such tendencies were noted among women age 30–34 or 35–39. In a reanalysis of first and second pregnancies, Bernstein and co-workers [80] showed that estrogen concentrations track within women (*i.e.* are highly correlated, $r = 0.7$ estradiol). Evaluation of these published data indicates that the variability between women is 5–6 times greater than the variability within women in successive pregnancies (data not presented). Therefore, birth order may not have as much impact as other correlates of pregnancy estrogens. The epidemiologic studies that have evaluated birth order either have not addressed maternal age in the analysis or suggest that the combination of older maternal age and being first born confers increased risk [45]. In general, however, the epidemiology and biologic evidence is not consistent with an association of birth order and maternal age with risk of breast cancer through a mechanism of increased estrogen exposure.

Breastfed. The evidence suggests that exposure to breastmilk may be related to reduced risk of premenopausal breast cancer. The mechanism for the association is unknown but, in the aggregate, would be related through protective factors in the breastmilk itself or from detrimental factors in formula preparations in the comparison group. The majority of epidemiologic studies only asked a crude ever/never question regarding breastfeeding, so women who were breastfed for limited periods of time are treated the same as those who were breastfed for long durations. Thus, it is likely that many would have been exposed to artificial feedings for

considerable periods of time, suggesting either nothing detrimental with formula preparations, or protective effects from the initial breastmilk. The main studies to date interviewed women of different cohorts with years of birth ranging from 1901 to 1972 (Table 5). These subjects would have been exposed to different formula preparations, suggesting something protective in the early breastmilk or lacking in all artificial feedings. Some markers of immune response suggest that the colostrum or early breastmilk is critical for the greater immune response among breastfed children to immunizations [81]. It is unclear whether there are long-term influences of having been breastfed on immune responses, however. Another serum parameter, serum cholesterol levels, has been noted to be higher among adult women who were bottle-fed compared with those who were breastfed [82], but this association has not been firmly established. More research is needed to verify the epidemiologic finding of breastmilk consumption and breast cancer risk, and then to evaluate potential mechanisms.

Animal models

Information from animal models suggest an influence of the prenatal as well as the early postnatal environments. Extensive reviews of classic prenatal and perinatal carcinogenesis in animals are available [6, 83, 84], including the most complete and authoritative compilation of reviews by the International Agency for Research on Cancer [6]. Only selected relevant concepts and examples will be discussed in this review. Insights from animal models systems include the critical relevance of timing to exposures. Early in pregnancy, agents are usually teratogenic but not carcinogenic, whereas exposures after organ development are related to tumors in adult offspring [83]. Interestingly, the tumors from exposures after organ development or during the postnatal period do not appear until adulthood. Early postnatal life is also a sensitive time, when organs are developing and systems are vulnerable to programming by environmental factors [18]. For example, early administration of enzyme inducers has shown long-term effects in responses of inducible enzymes to exogenous factors [85, 86]. Without knowledge of the early exposures one might surmise that the adult responses were of a genetic origin. Clearly the assessment of xenobiotic and nutritional influences early in the life of human populations would require more rigorous study designs than those presently available. Although little work was performed in nonhuman primates, and results from rodents and other animal species may not be directly relevant to the human experience, the data suggest that

programming of metabolic pathways, cellular receptors, and other physiologic functions is influenced by exposures during the perinatal period. Effect modification of adult factors (e.g. P450 expression) by early life exposures (e.g. having been breastfed) may seem unlikely, but warrants some consideration. Timing of exposures may be critical and, to the extent possible, should be considered in future epidemiologic studies.

Future directions

Given the daunting task of evaluating early life exposures, especially *in utero* conditions, new approaches and searches for relevant data are needed. Many studies were not originally designed to address early life exposures or exposures with low prevalence, and thus are limited by small numbers of exposed individuals. The inconsistencies observed across studies also indicate, to some extent, the lack of rigor with which some of the analyses have been approached. For example, evaluating birthweight without regard for gestational age, or maternal age without regard for birth order, could produce contradictory results. Investigators with expertise in maternal and child health, such as those who evaluate the determinants of birthweight, or preeclampsia, could help direct the analyses and may contribute insights into the relevant mechanisms. Further, other areas have made progress on evaluating risk related to early exposures and their experience may be useful. For example, the associations of infant feeding and juvenile diabetes or intrauterine growth retardation and adult hypertension seem particularly relevant [16, 87-90]. Many of the cardiovascular disease studies have been criticized because of significant loss to follow-up among the cohort and influential confounding by socioeconomic status [91]. Similar problems may exist in the nested case control studies of breast cancer from Sweden [24, 25]. Careful evaluation of methodologic issues in the breast cancer studies is warranted and integration of experience from other disciplines into future studies should be advantageous.

If the prenatal environment is important to later disease risk, then further investigation into a variety of maternal and pregnancy characteristics should be pursued. Only one study attempted to evaluate a variety of pregnancy characteristics [26] and further studies are needed. Maternal characteristics that could impact or reflect the *in utero* environment include prepregnancy weight and body fat distribution, pregnancy weight gain, gestational diabetes or other pregnancy complications, dietary patterns, maternal nausea, duration of nausea, maternal hormone use, and pregnancy anemia. Fetal and birth characteristics, in addition to birth-

weight for gestational age, might include sonogram information (e.g. estimates of intrauterine growth), birth length, head circumference, ratio of placental weight to birthweight, galactorrhea and development of breasts in infants at birth. Other variables from the first years of life may be influential. Risk related to body weights over the first or second year indicating growth rate, as well as serious illnesses and medications used during these years, may be informative.

A variety of risk factors have been identified in epidemiologic studies with some compelling risk estimates. Strongest evidence was observed for having been born of a preeclamptic or twin pregnancy, having had a high birthweight and having been breastfed, with results potentially restricted to premenopausal breast cancer for some factors. Although some findings are strong and some consistency exists across studies, substantially more research is needed to evaluate these potential breast cancer risk factors. Studies of the correlates of the risk factors are not difficult to accomplish by evaluating populations of pregnant women. Further work is necessary to evaluate the entire profile of risk factors to see consistency and inconsistency with the hypothesized estrogenic mechanism or to determine if another explanation better fits the empirical evidence. The most pressing issues, however, are the requirement for more epidemiologic studies that are launched explicitly to evaluate these new hypotheses and the ascertainment of improved data sources.

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References

1. Buell P (1973) Changing incidence of breast cancer in Japanese-American women. *J Natl Cancer Inst* **51**: 1479-1483.
2. Ziegler RG, Hoover RN, Pike MC, *et al.* (1993) Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst* **85**: 1819-1827.
3. Miler AB, Bulbrook RD (1980) The epidemiology and etiology of breast cancer. *N Engl J Med* **303**: 1246-1248.
4. Willett WC, MacMahon B (1984) Diet and cancer - an overview. *N Engl J Med* **310**: 633-638, 697-703.
5. Napalkov NP (1986) Prenatal and childhood exposure to carcinogenic factors. *Cancer Detect Prev* **9**: 1-7.
6. Tomatis L (1989) Overview of perinatal and multigeneration carcinogenesis. In: Napalkov NP, Rice JM, Tomatis L, Yamasaki

- H, eds. *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96). Lyon: International Agency for Research on Cancer, pp. 1-15.
7. Diwan BA, Ohshima M, Rice JM (1989) Effects of postnatal administration of tumor-promoting barbiturates on the development of tumors initiated by prenatal exposure of fetal rats and mice to *N*-alkylnitrosoureas. In: Napalkov NP, Rice JM, Tomatis L, Yamasaki H, eds. *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96). Lyon: International Agency for Research on Cancer, pp. 75-80.
 8. Hilakivi-Clarke L, Clarke R, Lippman ME (1994) Perinatal factors increase breast cancer risk. *Breast Cancer Res Treat* 31: 273-284.
 9. Walker BE, Kurth LA (1997) Multigenerational effects of dietary fat carcinogenesis in mice. *Cancer Res* 57: 4162-4163.
 10. Lumcy LH (1992) Decreased birth weights in infants after maternal *in utero* exposure to the Dutch Famine of 1944-1945. *Paediatr Perinat Epidemiol* 6: 240-253.
 11. Tokunaga M, Land C, Tokuoka S, Nishimori I, Soda M, Akiba S (1994) Incidence of female breast cancer among atomic bomb survivors, 1950-1985. *Radiat Res* 138: 209-223.
 12. Hildroth NG, Shore RE, Dvoretzky PM (1989) The risk of breast cancer after irradiation on the thymus in infancy. *N Engl J Med* 321: 1281-1284.
 13. Herbst AL, Ulfelder J, Poskanzer DC (1971) Adenocarcinoma of the vagina. Association of maternal stilbesterol therapy with tumor appearance in young women. *N Engl J Med* 284: 878-881.
 14. Hatch EE, Palmer JR, Titus-Ernstoff L, et al. (1998) Cancer risk in women exposed to diethylstilbesterol *in utero*. *JAMA* 280: 630-634.
 15. Barker DJP (1996) Growth *in utero* and coronary heart disease. *Nutr Rev* 54: S1-S7.
 16. Langley-Evans S, Jackson A (1996) Intrauterine programming of hypertension: nutrient-hormone interactions. *Nutr Rev* 54: 163-169.
 17. Barker DJP, Winter P, Osmond C, Margetts B, Simmonds S (1989) Weight in infancy and death from ischaemic heart disease. *Lancet* 2: 577-580.
 18. Fall C (1992) Nutrition early in life and later outcome. *Eur J Clin Nutr* 46: S57-S63.
 19. Trichopoulos D (1990) Does breast cancer originate *in utero*? *Lancet* 335: 939-940.
 20. Kloppner A, Jandial V, Wilson G (1975) Plasma steroid assay in assessment of foetoplacental function. *J Steroid Biochem* 6: 651-656.
 21. Goldkrand JW (1978) Unconjugated estriol and cortisol in maternal and cord serum and amniotic fluid in normal and abnormal pregnancy. *Obstet Gynecol* 52: 264-271.
 22. Goeblsmann U (1979) The uses of oestriol as a monitoring tool. *Clin Obstet Gynaecol* 6: 223-244.
 23. Le Marchand L, Kolonel LN, Myers BC, Mi M-P (1988) Birth characteristics of premenopausal women with breast cancer. *Br J Cancer* 57: 437-439.
 24. Ekblom A, Trichopoulos D, Adami H-O, Hsieh C-C, Lan S-J (1992) Evidence of prenatal influences on breast cancer risk. *Lancet* 340: 1015-1018.
 25. Ekblom A, Hsieh C-C, Lipworth L, Adami H-O, Trichopoulos D (1997) Intrauterine environment and breast cancer risk in women: a population-based study. *J Natl Cancer Inst* 89: 71-76.
 26. Sanderson M, Williams MA, Daling JR, et al. (1998) Maternal factors and breast cancer risk among young women on breast cancer risk in the offspring of preeclamptic pregnancies *Paediatr Perinat Epidemiol* 12: 397-407.
 27. Michels KB, Trichopoulos D, Robins JM, et al. (1996) Birthweight as a risk factor for breast cancer. *Lancet* 348: 1542-1546.
 28. Sanderson M, Williams MA, Malone KE, et al. (1996) Perinatal factors and risk of breast cancer. *Epidemiology* 7: 34-37.
 29. Hsieh C-C, Lan S-J, Ekblom A, Petridou E, Adami H-O, Trichopoulos D (1992) Twin membership and breast cancer risk. *Am J Epidemiol* 136: 1321-1326.
 30. Weiss HA, Potischman NA, Brinton LA, et al. (1997) Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 8: 181-187.
 31. Holm NV (1981) Studies of cancer etiology in the Danish Twin Population. I. Breast cancer. In: L. Gedda, P. Parisi, W.E. Nance, eds. *Twin Research 3: Epidemiological and Clinical Studies*. New York: Alan R. Liss, pp. 211-216.
 32. Kaprio J, Teppo L, Koskenvuo, Pukkalo E (1981) Cancer in the adult same-sex twins: a historical cohort study. In: L. Gedda, P. Parisi, W.E. Nance, eds. *Twin Research 3: Epidemiological and Clinical Studies*. New York: Alan R. Liss, pp. 217-223.
 33. Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN (1995) Effect of twinship on incidence of cancer of the testis, breast, and other sites (Sweden). *Cancer Causes Control* 6: 519-524.
 34. Swerdlow AJ, De Stavola B, Maconochie N, Siskind V (1996) A population-based study of cancer risk in twins: relationships to birth order and sexes of the twin pair. *Int J Cancer* 67: 472-478.
 35. Ahlbom A, Lichtenstein P, Malmstrom H, Feychting M, Hemminki K, Pedersen NL (1997) Cancer in twins: genetic and nongenetic familial risk factors. *J Natl Cancer Inst* 89: 287-293.
 36. Standfast S (1967) Birth characteristics of women dying from breast cancer. *J Natl Cancer Inst* 39: 33-42.
 37. Rothman KJ, MacMahon B, Lin TM, et al. (1980) Maternal age and birth rank of women with breast cancer. *J Natl Cancer Inst* 65: 719-722.
 38. Henderson BE, Powell D, Rosario I, et al. (1974) An epidemiologic study of breast cancer. *J Natl Cancer Inst* 53: 609-614.
 39. Janerich DT, Hayden CL, Thompson WD, Selenskas SL, Mettlin C (1989) Epidemiologic evidence of perinatal influence in the etiology of adult cancers. *J Clin Epidemiol* 42: 151-157.
 40. Thompson WD, Janerich DT (1990) Maternal age at birth and risk of breast cancer in daughters. *Epidemiology* 1: 101-106.
 41. Henderson BE, Bogdanoff E, Gerkins VR, SooHoo J, Arthur M (1974) Evaluation of cancer risk factors in a retirement community. *Cancer Res* 34: 1045-1048.
 42. Baron JA, Vessey M, McPherson K, Yeates D (1984) Maternal age and breast cancer risk. *J Natl Cancer Inst* 72: 1307-1309.
 43. Colditz GA, Willett WC, Stampfer MJ, Hennekens CH, Rosner B, Speizer FE (1991) Parental age at birth and risk of breast cancer in daughters: a prospective study among US women. *Cancer Causes Control* 2: 31-36.
 44. Hsieh C-C, Tzonou A, Trichopoulos D (1991) Birth order and breast cancer risk. *Cancer Causes Control* 2: 95-98.
 45. Janerich DT, Thompson WD, Mineau GP (1994) Maternal pattern of reproduction and risk of breast cancer in daughters: results from the Utah population database. *J Natl Cancer Inst* 86: 1634-1639.
 46. Brinton LA, Hoover R, Fraumeni JF Jr (1983) Reproductive factors in the aetiology of breast cancer. *Br J Cancer* 47: 757-762.
 47. Freudenheim JL, Marshall JR, Graham S, et al. (1994) Exposure to breastmilk in infancy and the risk of breast cancer. *Epidemiology* 5: 324-331.
 48. Troy LM, Michels KB, Hunter DJ, et al. (1996) Self-reported birthweight and history of having been breastfed among younger women: an assessment of validity. *Int J Epidemiol* 25: 122-127.
 49. Titus-Ernstoff L, Egan KM, Newcomb PA, et al. (1998) Exposure to breastmilk in infancy and adult breast cancer risk. *J Natl Cancer Inst* 90: 921-924.

50. Michels KB, Trichopoulos D, Robins JM, *et al.* (1997) Future risk of breast cancer among breast-fed infants. *Am J Epidemiol* **145**: S52.
51. Ekblom A, Hsieh C-C, Trichopoulos D, Yen Y-Y, Petridou E, Adami H-O (1993) Breast-feeding and breast cancer in the offspring. *Br J Cancer* **67**: 842-845.
52. Bucalossi P, Veronesi U (1957) Some observations on cancer of the breast in mothers and daughters. *Br J Cancer* **11**: 337-347.
53. Tokuhata GK (1969) Morbidity and mortality among offspring of breast cancer mothers. *Am J Epidemiol* **89**: 139-153.
54. Fraumeni JF, Miller RW (1971) Breast cancer from breast-feeding. *Lancet* **2**: 1196-1197.
55. Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health* **75**: 487-492.
56. Kelsy JL, Gammon MD, John EM (1993) Reproductive factors and breast cancer. *Epidemiol Rev* **15**: 36-47.
57. Brinton LA, Devesa SS (1996) Etiology and pathogenesis of breast cancer. Epidemiologic factors. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds. *Diseases of the Breast*. Philadelphia: Lippincott-Raven, pp. 159-168.
58. Longnecker MP (1995) Alcohol consumption and risk of cancer in humans: an overview. *Alcohol* **12**: 87-96.
59. Woodall AA, Ames BN (1997) Nutritional prevention of DNA damage to sperm and consequent risk reduction in birth defects and cancer in offspring. In: Bendich A, Deckelbaum RJ, eds. *Preventive Nutrition: The Comprehensive Guide for Health Professionals*. Totowa, NJ: Humana Press, pp. 373-385.
60. Janerich DT (1994) The fetal antigen hypothesis for breast cancer, revisited. *Med Hypoth* **43**: 105-110.
61. Gargoff L, Seppala M (1976) Toxemia of pregnancy: assessment of fetal distress by urinary estriol and circulating human placental lactogen and alpha-fetoprotein levels. *Am J Obstet Gynecol* **126**: 1027-1033.
62. Long PA, Abell DA, Beicher NA (1979) Fetal growth and placental function assessed by urinary estriol excretion before the onset of pre-eclampsia. *Am J Obstet Gynecol* **135**: 344-347.
63. Ranta T, Stenman U-H, Unerus H-A, Rossi J, Seppala M (1980) Maternal plasma prolactin levels in preeclampsia. *Obstet Gynecol* **55**: 428-430.
64. Mori M, Nobuyuki A, Tamaki H, Miyai K, Tanizawa O (1988) Morning sickness and thyroid function in normal pregnancy. *Obstet Gynecol* **72**: 355-359.
65. Duff GB, Brown JB (1974) Urinary oestriol excretion in twin pregnancies. *J Obstet Gynaecol* **81**: 695-700.
66. Trapp M, Kato K, Bohnet H-G, Gerhard I, Weise HC, Leidenberger F (1986) Human placental lactogen and unconjugated estriol concentrations in twin pregnancies: monitoring of fetal development in intrauterine growth retardation and single intrauterine fetal death. *Am J Obstet Gynecol* **155**: 1027-1033.
67. TambyRaja RL, Ratman SS (1981) Plasma steroid changes in twin pregnancies. In: L. Gedda, P. Parisi, W.E. Nance, eds. *Twin Research 3: Twin Biology and Multiple Pregnancy*. New York: Alan R. Liss, pp. 189-96.
68. Murphy M (1990) Does breast cancer originate in utero? *Lancet* **330**: 1604.
69. Kappel B, Hansen K, Moller J, Faaborg-Andersen J (1985) Human Placental lactogen and dU-estrogen levels in normal twin pregnancies. *Acta Genet Med Gemellol (Roma)* **34**: 59-65.
70. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D (1990) Tobacco smoking, pregnancy estrogens and birth weight. *Epidemiology* **1**: 247-250.
71. Dunger DB, Ong KK, Huxtable SJ, *et al.* (1998) Association of the INS VNTR with size at birth. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Nat Genet* **19**: 209-210.
72. Giampietro O, Matteucci E (1997) Gestational diabetes mellitus (GDM) and macrosomia: a controversial story. *Ann Ist Super Sanita* **33**: 399-402.
73. Adams KM, Li H, Nelson RL, Ogburn PL, Jr, Danilenko-Dixon DR (1998) Sequelae of unrecognized gestational diabetes. *Am J Obstet Gynecol* **178**: 1321-1332.
74. Gold AE, Reilly R, Little J, Walker JD (1998) The effect of glycemic control in the preconception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* **21**: 535-538.
75. Brown JE, Berdan KW, Splett P, Robinson M, Harris LJ (1986) Prenatal weight gains relate to the birth of healthy-sized infants to low-income women. *J Am Diet Assoc* **86**: 1679-1683.
76. Goldenberg RL, Davis RO, Cliver SP, *et al.* (1993) Maternal risk factors and their influence on fetal anthropometric measurements. *Am J Obstet Gynecol* **168**: 1197-1205.
77. Brown JE, Potter JD, Jacobs DR, *et al.* (1996) Maternal waist-to-hip ratio as a predictor of newborn size: results of the Diana Project. *Epidemiology* **7**: 62-66.
78. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D (1990) Maternal age, parity, and pregnancy estrogens. *Cancer Causes Control* **1**: 119-124.
79. Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE (1986) Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. *J Natl Cancer Inst* **76**: 1035-1039.
80. Bernstein L, Lipworth L, Ross RK, Trichopoulos D (1995) Correlation of estrogen levels between successive pregnancies. *Am J Epidemiol* **142**: 625-628.
81. Hanson LA, Hahn-Zoric M, Wiedermann U, *et al.* (1996) Early dietary influence on later immunocompetence. *Nutr Rev* **54**: S23-S30.
82. Marmot MG, Page CM, Atkins E, Douglas JWB (1980) Effect of breastfeeding on plasma cholesterol and weight in young adults. *J Epidemiol Community Health* **34**: 164-167.
83. Boland RP (1994) Prenatal carcinogenesis: an appraisal. *Cancer* **74**: 1674-1679.
84. Napalkov NP, Rice JM, Tomasis L, Yamaski H, eds. (1989) *Perinatal and Multigenerational Carcinogenesis* (IARC Scientific Publications, No. 96). Lyon: International Agency for Research on Cancer.
85. Salganik RI, Gryaznova IM, Markel AL, Manankova NM, Solovyeva NA (1980) Enzymatic 'imprinting' as the result of early postnatal administration of enzyme inducers to animals. *Experientia* **36**: 43-45.
86. Faris RA, Campbell TC (1981) Exposure of newborn rats to pharmacologically active compounds may permanently alter carcinogen metabolism. *Science* **211**: 719-721.
87. Kostraba JL (1994) What can epidemiology tell us about the role of infant diet in the etiology of IDDM? (Commentary). *Diabetes Care* **17**: 87-91.
88. Gerstein HC (1994) Cow's milk exposure and type I diabetes mellitus: a critical overview of the clinical literature. *Diabetes Care* **17**: 13-19.
89. Edwards CR, Benediktsson R, Lindsay RS, Seckl JR (1993) Dysfunction of placental glucocorticoid barrier: link between fetal environment and adult hypertension? *Lancet* **341**: 355-357.
90. Leon DA, Koupirova I, Lithell JA, *et al.* (1996) Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* **312**: 401-406.
91. Joseph KS, Kramer MS (1996) Review of the evidence on fetal and early childhood antecedents of adult chronic disease. *Epidemiol Rev* **18**: 158-174.