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Comments and Critique

Prenatal Factors may Influence Predisposition to Breast Cancer

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PRENATAL ENVIRONMENTAL factors may contribute to carcinogenesis by direct exposure of embryonic fetal somatic cells to a carcinogenic agent, or by prezygotic exposure of the germ cells.

Many chemicals of very different structures cause prenatal carcinogenesis in several animal species [1, 2] and there is strong evidence for carcinogenic effects *in utero* in humans: intrauterine exposure to ionising radiation causes leukaemia and other tumours in children [3, 4]. People exposed *in utero* to more than 0.30 Gy during the atomic bombing of Hiroshima and Nagasaki had a cumulative incidence of cancer four times higher than that of unexposed individuals [5]. Intrauterine exposure to diethylstilboestrol (DES) causes vaginal adenocarcinoma in young girls [6] and the cumulative incidence of vaginal and cervical intraepithelial neoplasia was twice as high in women exposed to DES as in those not exposed to this synthetic oestrogen [7]. Whether the effects of DES are mediated through its oestrogenic activity or through its ability to interact directly with DNA is not known. There is also evidence that intrauterine exposure to high levels of endogenous oestrogens may increase the risk of gonadal germ cell tumours [8, 9].

There is compelling evidence to suggest that the *in utero* environment may predispose to some breast cancers. Oestrogens are well-known component factors in breast carcinogenesis [10]. Factors which increase the risk of cancer when they act postnatally may also increase the risk of cancer when they act *in utero* [2]. Oestrogen concentrations are at least 10 times higher during pregnancy than during other periods of adult life, and oestrogen concentrations and secretion rates vary widely between individuals in pregnancy [11]. Based on these, Trichopoulos [12] proposed that raised concentrations of maternal hormones in pregnancy might increase the probability of daughters having breast cancer, by creating so-called "fertile soil" for subsequent cancer initiation. Some epidemiological data appear to support this hypothesis. Urinary levels of follicular oestrogens (especially oestradiol and oestrone) are substantially higher in North Americans, as is the incidence of breast cancer, compared with Japanese women [13]. Moreover, Petridou *et al.* [14] have shown that total blood concentrations of oestrogens in pregnancy are significantly lower in younger women (<20 years) than in older women (20–29 years). Several workers have shown that the risk of breast cancer in daughters increases with increasing maternal age at birth [15].

If an altered intrauterine hormonal environment does predispose to breast cancer, one might expect to see anomalous development in other structures that are influenced by the same intrauterine factors, such as the central nervous system. The human brain has a consistent pattern of structural asymmetries [16–18]. The left occipital pole is frequently wider and extends further posteriorly than does the right, whereas the right frontal area is often wider and protrudes further anteriorly than does the left. Such asymmetry can be related to gender, race and right handedness [18,19]. Geschwind and Galaburda [20] have proposed that variations in intrauterine hormone concentrations can result in atypical cerebral asymmetry. Sandson *et al.* [21] investigated computed tomographic scans of 79 right handed, white patients with breast cancer and 97 controls to assess the pattern of cerebral asymmetry. Women with breast cancer had a reversed pattern of cerebral asymmetry significantly more often than did controls ($P<0.0001$) for both frontal and occipital width. These findings supported the view of Trichopoulas [12], and suggested that an intrauterine or early life factor, probably hormonal, could predispose to breast cancer in adulthood.

An indirect approach to substantiate the effect of oestrogen would be to identify indicators of high levels of pregnancy oestrogens, and to investigate the associations of these indicators with breast cancer risk or with breast cancer epidemiological studies. Severe nausea during pregnancy and maternal obesity are considered as indicators of high levels of pregnancy oestrogens [8, 9, 14]. Petridou *et al.* [14] have shown that pregnancy oestrogens are important determinants of birth weight. More recently, Ekbom *et al.* [22] studied 458 breast cancer cases and 1197 matched controls. These authors have assessed the relationship between breast cancer risk and indicators of pregnancy oestrogen concentrations. Pre-eclampsia/eclampsia (characterised by low oestrogen level) was negatively associated with breast cancer risk. Linear trends for breast cancer incidence with increasing birth weight, birth length and placental weight (which indicates high oestrogen level) showed a positive trend, but were not significant.

All the above reports implicate an altered intrauterine hormonal environment, particularly oestrogen, as an important factor in increasing the breast cancer risk in adult life.

Although factors other than oestrogens may be responsible for these observations, it is an interesting hypothesis and worth further consideration. If this is true, one might expect to find some supportive evidence by studying development of the fetal

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breast, as this is a primary end-organ for the action of these hormones. We have published a detailed microanatomical and histological study of the human infant breast [23]. Specimens from newborn babies and infants showed striking variations in the structural development of the breast. Some had a well developed ductal system with numerous branching ducts and terminal lobules; others had a less developed ductal system without lobular development. This morphological variation in the newborn breast might result from differences in the hormonal environment *in utero*. In addition, there appears to be a positive correlation between the birth weight, length and mammary gland development [24]. These data provide indirect evidence that variations in mammary gland development of the newborn might be the result of variations in the oestrogen concentrations during pregnancy.

Although there is a large body of evidence to implicate oestrogen acting prenatally to increase the susceptibility of the individual to breast cancer risk, the precise mechanism involved in unknown. Three possible ways by which oestrogen can predispose to breast cancer susceptibility are discussed below.

Albanes and Winick [25] have postulated that cancer risk is proportional both to the number of cells and to the rate of cell division. Mammary gland size is also suspected to be a risk factor for breast cancer [26]. The breasts of newborn babies that show a greater degree of development might be "primed" to respond to hormonal stimulation during puberty and the cyclic changes seen within the menstrual cycle. This could result in a greater number of epithelial cells being targets for carcinogens. Breasts of these individuals might, therefore, have an increased cancer risk in adult life. Most known risk factors for breast cancer can be related either directly or indirectly to the effects of steroid hormones. It is, therefore, reasonable to consider the possibility that variations in breast development may be important contributory risk factors. In this respect, it could be predicted that the inherited predisposition seen in some families will relate to genes that disturb hormonal balance during development, through abnormalities in the hormones themselves, their synthetic pathways or their receptor transduction mechanisms. The resulting hormonal imbalances, which may be very subtle, might alter overall epithelial cell numbers and proliferation sufficiently to increase the risk from, as yet, unidentified aetiological factors [27].

An alternative possibility is that epithelial proliferation in the fetal breast, induced by oestrogen, could contribute to the risk of breast cancer by increasing the number of potential *in utero* mutations [28].

A third possibility by which oestrogen can cause increased susceptibility to breast cancer is by an imprinting mechanism. Imprinting or organisational effects have been described as developmental modifications to nerve endings in specific areas of the brain, as a consequence of exposure to steroids during a limited critical period of development [29]. Biochemical imprinting effects are permanent and sex differentiated. Imprinting mechanisms appear to play a prominent role in the complex interplay hormonal expression and regulation of activation/detoxication enzymology [30, 31]. The expression of this type of hormonal effect may not occur until the onset of sexual maturation, long after the original effector has been metabolised and excreted. The critical period of brain development in laboratory rats is during the last few days of pregnancy through to the first week after birth, while in humans the critical period is primarily during the last trimester of pregnancy [32].

In relation to hormones, altered imprinting has permanent effects on the hypothalamic–pituitary axis, and can influence both metabolism and potential for toxicity. This could have serious implications for the formation and disposition of toxic electrophilic metabolites. Exposure of neonatal rats to xenobiotics, such as DES, phenobarbital and 7,12-dimethylbenzanthracene, has been shown to produce long-term changes in hepatic enzymes not seen in adult animals exposed to the same compounds [33–35]. It is possible that oestrogen acting prenatally might induce an altered response of breast epithelial cells to normal adult hormonal levels of carcinogens.

In conclusion, there is accumulating evidence that the prenatal environment may be an important contributory factor to mammary carcinogenesis. We have no direct evidence that oestrogens are responsible for the correlations observed or that this is the hormone that mediates breast development *in utero*. We present these observations as a conceptual framework for future epidemiological studies.

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Predicting the Future Health Care Expenses of Cancer

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IN RECENT years, the scarcity of health care resources has become more obvious in the industrialised world. On the one hand, health care needs are increasing at a fast pace, due to changes such as technological advances in medical equipment and the development of new drugs. On the other hand, the amount of resources a society can afford to spend on health care is not unlimited. A growing reluctance among government officials to increase public health care spending can be observed, for example, due to huge government deficits.

This growing scarcity increases the need for thorough economic evaluations in order to achieve an efficient allocation of health care resources: the total available amount of resources should be used in such a way as to improve the health status of the population as much as possible, or put differently, a nation should try to achieve a target health status for its population with as few resources as possible.

A prerequisite for the efficient allocation of health care resources, now and in the future, is the availability of reliable data on the costs and effects of different health care interventions. Future health care provisions can only be planned, and future health care policies designed, in an accurate way if reliable information on the expected future expenses for different population groups, pathologies, etc. is available. The article by Koopmanschap and his colleagues contributes to this need by proposing a methodology to predict the future health care expenses on cancer in the Netherlands.

Its main contribution lies in the methodology it proposes to predict future costs. The authors calculated an average cost of cancer per patient, for different 'types' of patients, depending on the tumour site, sex, age and disease stage (i.e. first year after incidence, intermediate, or last year of life) for the year 1988. By calculating how many patients of each type there will be in 2005 and 2020, under different scenarios concerning the future age structure of the population, the incidence of cancer and the survival rate, the future costs of cancer in the Netherlands can be calculated.

This research clearly illustrates the need for multidisciplinary research in the field of health economics, or health services research: medical input is necessary to provide data on effects, such as survival rates; the economist is responsible for correct calculation of the costs and their allocation across patient groups, pathologies, years; epidemiologists can propose reasonable future scenarios on demography, incidence, etc. Each of these and other disciplines are clearly complementary, compared with independent efforts, for good research.

GENERALISATION OF THE RESULTS

The methodology proposed by the authors can obviously be applied to other diseases, or to cancer expenses in other countries. As the paper stands, however, the direct applicability of the cost predictions to other countries is limited, since the authors do not provide enough information on (i) which cost items they included and (ii) how each cost component was calculated. With some methodological, or even presentational

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