Epidemiological clues from screening

In 1976 the American radiologist Wolfe published his finding with xeroradiography that certain mammographic patterns seemed to be associated with breast cancer—the so called DY and P2 patterns.[1] This led to a number of studies that concluded that the association was too weak to be used for decision-making in screening. However, these patterns were risk factors of a degree comparable with other risk factors, such as nulliparity, late age at first birth, increased weight and height, or family history of breast cancer.

In our screening programme at Utrecht we discovered a striking relation between Wolfe's breast parenchymal patterns DY and P2 and the reproductive variables—low parity and late age at first birth.[2] This finding was confirmed by Bergkvist *et al* using data from the Swedish two counties project in Sweden.[3]

These findings opened up interesting new lines of thought. Here one encountered morphological changes in the breast as seen on *x* ray pictures associated with personal histories of low reproduction. Might it be that the association was causal? In other words, might pregnancies prevent the occurrence of the morphological changes, and which histological changes were to be found in DY and P2 types of breast?

Studies by Boyd and coworkers[4] in Canada provided an important clue—especially in DY breasts there is an increase in the number of hyperplastic lobules with atypia. Now the experimental work by Russo and Russo[5] proved to offer a key to causal reasoning as these authors had shown in the rat that pregnancy prevented the occurrence of breast cancer by bringing about differentiation of breast lobules, a response which prepares the breast for its task—lactation.

Suddenly the chain of events became clear; the breasts of mammals including humans need pregnancies in order to promote cells to differentiate, and differentiation is known to prevent carcinogenesis.

The lifestyle in the Western World seems to disregard this important notion. In contrast with women in the Third World, there is a strong tendency for Western women to postpone pregnancies and to limit their number. This will lead to years of proliferation of lobular cells without proper differentiation.

Moreover, nutritional affluence in Western women leads to earlier ovarian maturation with earlier menarche and higher postmenarcheal oestrogen levels[6] which, by implication, means stronger proliferative stimuli. This will increase the number of replication errors and the occurrence of hyperplastic breast lobules with and without atypia, leading to a greater probability of breast cancer.

Thus Wolfe's findings in mammography seem to have provided a new insight into the causation of breast cancer. Does this open horizons for primary prevention? From now on the focus should be on the need for cellular differentiation in the adolescent breast. As it is unlikely that modern women in the Western World will revert to Third World reproductive lifestyles, research in the 21st century may become oriented towards developing hormonal substitution as a special form of chemoprevention.

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