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Mammographic density as a marker of susceptibility to breast cancer: a hypothesis

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We propose that radiological features of breast tissue provide an index of cumulative exposure to the current and past hormonal and reproductive events that influence breast cancer incidence. The changes in breast tissue that occur with ageing, and changes in the associated radiological features of the breast, are similar to the concept of "breast tissue ageing" proposed by Pike, and may explain features of the age-specific incidence of breast cancer, both within the population and between populations. These radiological features can be observed and measured, can be related directly to risk of breast cancer, and are likely to be of value in research into the etiology of breast cancer. Identification of the sources of variation in this radiological characteristic of the breast is likely to lead to a better understanding of the factors that cause breast cancer and to new approaches to prevention of the disease.

Introduction

Pike *et al.* (1983) have described a model of breast cancer incidence that incorporates the principal reproductive and endocrine risk factors for the disease. The factors included in the model are age at menarche, age at first pregnancy and age at menopause. The model has since been extended to incorporate the timing of pregnancies (Rosner & Colditz, 1996). The model is based on the concept that the rate of "breast tissue ageing", rather than chronological age, is the relevant measure for describing the incidence of breast cancer. The concept of breast tissue ageing is closely associated with exposure of breast tissue to hormones, and the effects that hormones have on the kinetics of breast cells, and is illustrated in Figure 1(*a*). The rate of breast tissue ageing is most rapid at the time of menarche, slows with each pregnancy, slows further in the perimenopausal period, and is least after the menopause. After fitting suitable numerical values for breast tissue ageing, Pike *et al.* (1983) showed that this model provided a good fit to the actual age-specific incidence curve for breast cancer. Thus, cumulative exposure to breast tissue ageing, given by the area under the curve in Figure 1(*a*), describes the age-incidence curve for breast cancer shown in Figure 1(*b*).

The hypothesis that we propose is that radiological features of breast tissue provide an index of exposure of breast tissue to the current and past hormonal and reproductive events that influence breast cancer incidence, and are a measure of susceptibility to breast cancer related to the concept of breast tissue ageing (Pike *et al.*, 1983) (by susceptibility is meant a state in which risk of disease is altered, but the presence of premalignant changes is not implied). These radiological features can be observed and measured, can be related directly to risk of breast cancer, and are likely to be of value in research into the etiology and prevention of breast cancer.

The radiographic appearance, or mammographic pattern, of the female breast varies between individuals because of differences in the relative amounts and X-ray attenuation characteristics of fat, connective and epithelial tissue (Ingleby & Gerson-Cohen, 1960). Fat is radiologically lucent and appears dark on a mammogram. Connective and epithelial tissues are radiologically dense and appear light, an appearance that we refer to in this paper as mammographic densities. These variations are illustrated in Figure 2.

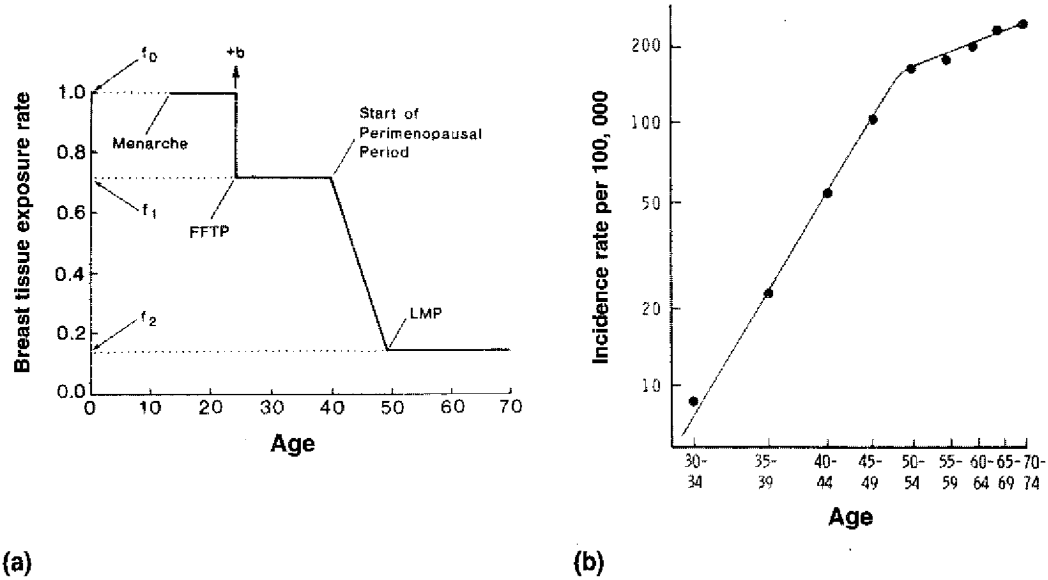

Figure 1. (a) Variation in the rate of "breast tissue ageing" with chronological age

Adapted from Pike *et al.* (1983) and Rosner & Colditz (1996). The rate of breast tissue ageing is greatest after menarche, declines with successive pregnancies and in the peri-menopausal period, and is lowest after the menopause. FFTP, first full-term pregnancy; LMP, last menstrual period

(b) Log–log plot of age-specific breast cancer incidence rates for Canada

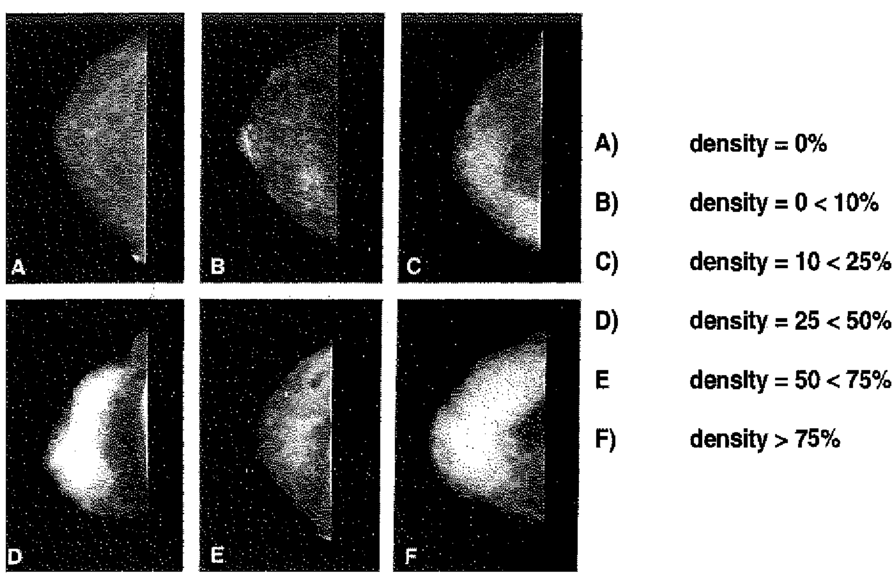

Figure 2. Six categories of mammographic density

Mammographic densities and risk of breast cancer

Wolfe (1976a,b) proposed a classification that related variations in the appearance of the mammogram to risk of breast cancer. While most well designed epidemiological studies have found that Wolfe's classification does identify individuals at different risk of breast cancer (Saftlas & Szklo, 1987; Oza & Boyd, 1993), quantitative classification of mammographic densities has given more consistent results and created larger gradients in risk. Table 1 summarizes the results of all studies published to date that have used quantitative methods to classify mammographic densities. Although definitions of categories of density vary somewhat between studies, in all, women with extensive breast tissue densities in more than 60–75% of the breast area were found to have a 4–6-fold greater risk of breast cancer than women with little or no densities. This gradient in risk is larger than is associated with any other risk factor for the disease, except age and mutations in the *BRCA1* and *BRCA2* genes (Easton *et al.*, 1995; Struewing *et al.*, 1997).

Extensive areas of mammographically dense breast tissue are common among subjects with breast cancer and estimates of attributable risk show that mammographic densities in more than 50% of the breast may account for 28% of breast cancer, a much larger fraction of disease than can be attributed to any other single risk factor (Byrne *et al.*, 1995).

Factors that influence mammographic density

Reproductive variables

Parity has been found in several studies to be related to mammographic density (Bergvist *et al.*, 1987; Brisson *et al.*, 1982b; de Waard *et al.*, 1984;

Table 1. Quantitative studies of breast density and cancer risk

Author	Design	Age	Odds ratio	95% CI	Trend
Boyd *et al.* (1982)	Case–control	40–65	a) 6.0[a,d]	2.5–14.1	Yes
			b) 2.8[a,d]	1.4–5.6	No
			c) 3.7[a,d]	1.7–4.1	Yes
Brisson *et al.* (1982a)	Case–control	20–69	a) 5.4[b]	2.5–11.4	Yes
			b) 3.8[c]	1.6–8.7	Yes
Brisson *et al.* (1984)	Case–control	–	4.4[d]	2.5–7.9	Yes
Brisson *et al.* (1989)	Case–control	40–67	a) 4.6[b]	2.4–8.5	Yes
			b) 3.2[c]	1.6–6.5	
			c) 5.5[d]	2.3–13.2	
Wolfe *et al.* (1987)	Case–control	30–85	4.3[d]	1.8–10.4	No
Saftlas *et al.* (1991)	Nested case–control	35–74	4.3[d]	2.1–8.8	Yes
Boyd *et al.* (1995)	Nested case–control	40–59	a) 6.0[d,e]	2.8–13.0	Yes
			b) 4.0[d,f]	2.1–7.7	Yes
Byrne *et al.* (1995)	Nested case–control	–	4.3[d]	3.1–6.1	Yes

[a] Odds ratios shown for each of three radiologists who estimated density
[b] Odds ratio for homogeneous density
[c] Odds ratio for nodular density
[d] Odds ratio for total density
[e] Odds ratio for estimation of area of density by radiologist
[f] Odds ratio for computer assisted measurement of area of density

Ernster *et al.*, 1980; Grove *et al.*, 1979, 1985; Kaufman *et al.*, 1991a; Whitehead *et al.*, 1985). Nulliparous women, at higher risk for breast cancer than parous women (Kelsey *et al.*, 1993), have denser breast tissue. Density decreases further with increasing number of children (de Waard *et al.*, 1984). Among parous women, density decreases further with earlier age at first birth and increasing number of pregnancies, both variables that decrease risk of breast cancer (de Waard *et al.*, 1984; Whitehead *et al.*, 1985). The effect of mammographic density on risk of breast cancer, however, remains strong after adjustment for the effect of reproductive variables.

Evidence of hormonal responsiveness

Hormone replacement therapy may increase breast densities (Bergkvist *et al.*, 1989; Berkowitz *et al.*, 1990; Cyrlack & Wong, 1993; Doyle & McLean, 1994; Kaufman *et al.*, 1991b; Laya *et al.*, 1995; Stomper *et al.*, 1990), and Spicer *et al.* (1994) have shown that the administration for one year of a hormonal contraceptive regimen that minimizes exposure of the breast epithelium to estrogen and progesterone reduces mammographic densities.

Age and the menopause

The prevalence of mammographically dense breast tissue in the population declines with increasing age (Grove *et al.*, 1979, 1985) and dense breast tissue is more common before than after the menopause (Grove *et al.*, 1979; Wolfe, 1976c). Menopausal status appears to be a stronger determinant of breast density than age. Direct evidence of a striking reduction in the proportion of the breast occupied by mammographic densities at the menopause has now been observed in a cohort of women examined by mammography before and after the cessation of menstrual activity (Boyd *et al.*, 1997).

Variations in change with age

The epidemiological data on risk presented in Table 1 show that over the range of the ages of the subjects included in the studies (between about 20 and 70 years), the mean tissue density in the mammogram of subjects who developed breast cancer was greater than in controls of the same age. Thus, the factors associated with variations in density over this range of ages may have an important influence on cancer risk. The potential sources of variation, that might give rise to differences in breast density between individuals, include differences in the quantity of breast epithelium and stroma at telarche, differences in the age at which the events of menarche, pregnancy and menopause occur, differences in the number and spacing of pregnancies, or differences in the magnitude of the reduction in mammographic density associated with pregnancy or the menopause. Diet, for example, appears to modify the magnitude of the reduction in mammographic density that occurs at the menopause (Boyd *et al.*, 1997).

Average exposure to mammographically dense breast tissue over time resembles the concept of breast tissue ageing proposed by Pike *et al.* (1983). Cumulative exposure to mammographic densities may thus also be represented by the area under the curve of Figure 1(*a*), reflecting cumulative exposure to hormonal stimuli to breast cell division, and be an important determinant of breast cancer incidence. We expect, therefore, that events that increase or decrease cumulative exposure to factors that influence the extent of mammographic densities will have corresponding effects on the incidence of the disease. Thus, late menarche, early first pregnancy, multiple pregnancies and early menopause, which are all known to decrease risk of breast cancer, also decrease cumulative exposure to mammographic densities. Conversely, early menarche, late age at first pregnancy, nulliparity, and late menopause increase cumulative exposure to dense tissue. By considering cumulative exposure to mammographically dense tissue in the population, given by the area under the curve of age-specific average densities, we may be able to account for key features of the age-specific incidence curve for breast cancer. Thus, the steeper pre-menopausal component of the age-incidence curve is associated with a higher prevalence of mammographic densities, the less steep post-menopausal component with a lower prevalence of densities. A reduction in mammographic densities at the time of the inflection in the age-specific incidence curve associated with the menopause has now been observed (Boyd *et al.*, 1997).

Biological plausibility of the hypothesis

The X-ray attenuation characteristics of epithelial and stromal tissues in the breast are responsible for mammographically dense breast tissue (Ingleby & Gerson-Cohen, 1960). Variations between individuals in the extent of mammographically dense breast tissue are thus likely to indicate variations in the number of epithelial and stromal cells in the breast, arising because of differences in stimulation by hormones and growth factors. Sex hormones in the blood, particularly estrogen, progesterone and prolactin, are likely to play a role in the etiology of mammographic densities. Blood levels of prolactin, for example, are reduced by pregnancy and the menopause (Reyes *et al.*, 1977; Wang *et al.*, 1988) and increased by hormone replacement therapy (Andersen *et al.*, 1980), all variables with effects on mammographic densities as described above.

Differences in risk of breast cancer associated with mammographic densities of different extent may thus arise, at least in part, because of differences in the number of cells in the breast that are susceptible to mutagens. Risk factors for breast cancer, such as parity, that are associated with a reduction in the extent of mammographic densities, may influence risk by reducing the size of the population of cells that are potential targets for events that give rise to mutations.

Predictions arising from the hypothesis

The testable predictions that arise from this hypothesis include the following:

(1) Age-specific estimates of the prevalence of radiologically dense breast tissue in the population will allow reconstruction of age-specific rates of breast cancer. As noted above, the principal features of the age-specific incidence curve for breast cancer are in general consistent with what is already known about the distribution of mammographic densities in the population. Little information is available about the radiological characteristics of breast tissue at earlier ages, particularly at the time of menarche, or the factors associated with them. Such information would be have to be acquired using methods of imaging the breast that do not involve exposure to radiation, such as ultrasound and magnetic resonance (Graham *et al.*, 1996; Kaizer *et al.*, 1988). The variations in the radiological appearance of the breast that are seen in middle life may in part be the result of differences that occur at the time of breast development, but events later in life, such as pregnancy and menopause, appear to be influential as well.

(2) Differences in the distribution of mammographic densities over age may be found in populations with different age-specific incidence rates of breast cancer. Studies that have compared Asians and Caucasians, Japanese and English, and North American Indians with Caucasian and Hispanic women, using Wolfe's (1976a) classification of mammographic patterns, have all shown that the population with the lower risk of breast cancer has a lower prevalence of dense patterns (Gravelle *et al.*, 1991; Hart *et al.*, 1989; Turnbull *et al.*, 1993).

(3) Age-related changes in the factors that control mammographic densities, such as hormones and growth factors, will account for the reduction in mammographic densities that occurs with increasing age.

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