



TIINA SALMINEN

Causes and Consequences of Mammographic Parenchymal Patterns

*University of Tampere
Tampere 2000*

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ACADEMIC DISSERTATION

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Cover design by
Juha Siro

Printed dissertation
Acta Universitatis Tamperensis 766
ISBN 951-44-4902-9
ISSN 1455-1616

Electronic dissertation
Acta Electronica Universitatis Tamperensis 57
ISBN 951-44-4903-7
ISSN 1456-954X
<http://acta.uta.fi>

Tampereen yliopistopaino Oy Juvenes Print
Tampere 2000



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ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the auditorium of the
School of Public Health of the University of Tampere,
Medisiinarinkatu 3, Tampere,
on September 15th, 2000, at 12 o'clock.

*University of Tampere
Tampere 2000*

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List of original publications

This dissertation is based on the following original publications, which are referred to by Roman numerals in the text.

- I Salminen TM, Saarenmaa IE, Heikkilä MM and Hakama M (1999): Unfavourable change in mammographic patterns and the breast cancer risk factors. *Breast Cancer Res Treat* 57:165-173.
- II Salminen T, Hakama M, Heikkilä M and Saarenmaa I (1998): Favorable change in mammographic parenchymal patterns and breast cancer risk factors. *Int J Cancer* 78:410-414.
- III Salminen TM, Saarenmaa IE, Heikkilä MM and Hakama M (1998): Risk of breast cancer and changes in mammographic parenchymal patterns over time. *Acta Oncol* 37:547-551.
- IV Salminen TM, Saarenmaa IE, Heikkilä MM and Hakama M (2000): Is dense mammographic parenchymal pattern contraindication to hormonal replacement therapy. *Acta Oncologica*. In press.

Abbreviations

BMI = body mass index

CI = confidence interval

HRT = hormonal replacement therapy

MPP = mammographic parenchymal pattern

MRI = magnetic resonance imaging

OR = odds ratio

RR = relative risk

1 Introduction

Breast cancer is the most common cancer type among Finnish women. Every year over 3000 new breast cancer cases are diagnosed and over 800 will die from it. Besides of sex and age the other risk factors for breast cancer, mainly related to hormones (i.e. oestrogen and progesterone), have only a moderate effect on the risk of breast cancer. Therefore, there are only moderate means for primary prevention of breast cancer, and the attention has been focused on early diagnosis and treatment of breast cancer through screening with mammography, which has been shown to reduce the mortality from breast cancer. The breast pattern can be assessed from the mammography and in other countries it has been shown that these patterns are strongly related to the risk of breast cancer. However, less is known about the causes of these patterns. The purpose of this thesis is to give some insight into the aetiology of mammographic parenchymal patterns and estimate the risk of breast cancer related to the patterns using a cohort of Finnish females who were screened in a pilot screening project for the nationwide screening programme from 1982 to 1990 in Kotka area, southeastern part of Finland.

2 Review of literature

2.1 Mammographic parenchymal patterns

2.1.1 *Anatomy of the breast*

Breast consists of 15 to 20 glandular lobes. The lobes are connected with fibrous connective tissue and in the intervals between the lobes there is adipose tissue. (Romrell and Bland 1991.) Each lobe consists of 30-80 lobules and has its own milk duct ending at the nipple (Barth and Prechtel 1991). Fatty, fibrous and ductal elements form the three main tissue types of the breast (Egan 1988). Breast parenchyma is used as a common term for ducts, lobules and interlobular fibrous tissue, and it is diffusely distributed within the fat tissue (Bartow and Fenoglio-Preiser 1988).

Age, composition of breast tissue and hormonal environment (both past and present) have an effect on breast tissue development (Reid et al. 1996). Genetic, nutritional and conditioning factors have an effect on the ultimate size, density and inherent shape of a mature breast. In normal breast development and management, the effects of reproductive hormones (oestrogen, progesterone and prolactin) are the most important ones. (Keller-Wood and Bland 1991.)

Breasts change throughout a woman's life. Changes are due to cyclic changes of menses, altered physiology and anatomy during pregnancy and lactation, and the progressive factor of ageing. (Egan 1988.) Structural changes during menstrual cycle are due to changes in ovarian hormone levels. Breast tissue is found to be less radiographically dense in the follicular phase than in the luteal phase among premenopausal women. (White et al. 1998.) During pregnancy and lactation there are changes in both the functional activity of breast and in the amount of glandular tissue. Decline of ovarian functions at menopause causes breast involutes. In this process the glandular component of breast is replaced by fat and connective tissue. With ageing the breast volume usually decreases and the breast becomes less firm. (Romrell and Bland 1991.)

2.1.2 Breast imaging

a) Mammography

The most common imaging method of breast is mammography (i.e. plain-film radiography of the breast). Three major types of breast tissue can be seen on breast imaging; fibrous, glandular and adipose. The term fibroglandular has been used to describe the structures of both fibrous and glandular tissues. Fibrous and glandular tissues are anatomically intimately associated and they are of similar density, whereas adipose tissue is more radiolucent providing the contrast on the mammogram. The breast is primarily characterised by the relative amount of fat and fibroglandular tissue which also influences the diagnostic accuracy of mammography. (Egan 1988.) The assessment of radiographic pattern of breast is based on the amount and distribution of radiodense breast parenchyma (composed of fibrous stroma and epithelial, glandular elements) in radiolucent fatty tissue. The total amount of radiodense tissue within the breast is to some extent a reflection of the amount of tissue "at risk" for developing of cancer. (Bartow et al. 1995.)

During pregnancy there is a remarkable change in the size and density of the breasts. The glandular tissue fills all the central portion of the breast and most of the radiolucent adipose tissue disappears. During lactation more radiolucent areas appear, and after lactation the breast begins to return to a more normal appearance. Even if there is some change in the volume of the breast during the menstrual cycle there is no significant change in the density of the breast noticed on the mammogram. (Egan 1988.)

According to Barth and Prechtel (1991), the following developmental stages of the breast can be distinguished on the mammogram: 1) the juvenile breast 2) the breast of a mature woman 3) the breast during pregnancy and lactation 4) the involuted breast.

The appearance of the breasts on mammography is different among women, and also in the same woman at different stages of her life (Egan 1988, Feig 1994). The mammographic differences among women are due to differences in the relative amounts of fat, connective and epithelial tissue, and the different X-ray attenuation characteristics of these tissues are referred to as the parenchymal patterns of the breast (Boyd et al. 1998). These differences also have implications for radiographical evaluation of breasts.

Breasts with an abundant mammary fibrous tissue are more difficult to evaluate by mammography than predominantly fatty breasts because they have less radiographic contrast between tumours and fatty tissue. (Bartow and Fenoglio-Preiser 1988.) Ma et al. (1992) concluded that the extent of radiologic density in the breast is associated with the failure to detect breast cancer by mammography, a result also found by Rosenberg et al. (1998). Substantial decrease in the sensitivity of mammography has been found with the combination of oestrogen replacement therapy use and higher breast density (Rosenberg et al. 1998).

Both the size of the breast and the woman's age may contribute to apparent variation in thickness on the mammograms. Small breasts usually are firmer. (Egan 1988.) Although there is a relationship between the age of the woman and the x-ray appearance of the breast, it is inconsistent (Egan 1988, Feig 1994).

b) Others

There is no scientific evidence on the reduction of mortality from breast cancer by other imaging techniques but mammography.

Ultrasound is widely used in the detection of breast cancer. It has some very attractive features like no ionising radiation, noninvasiveness, high reproducibility and good patient acceptability. According to a consensus statement by the European Group for Breast Cancer Screening, ultrasound is an important adjunct to mammography and physical examination in further assessment of palpable and impalpable breast abnormalities (Teh and Wilson 1998). However, in its present format it has been found to be inadequate of consistently diagnosing small breast cancers (Ennis 1991) and due to its high rates of false positive and negative outcomes, it cannot be used in population screening of asymptomatic women (Teh and Wilson 1998).

Magnetic resonance (MR) imaging is also used in the detection of breast disease (Weinreb and Newstead 1995). There is neither ionising radiation nor known radiobiological hazards related to the use of MRI (Ennis 1991). MRI has been found to be useful in evaluating the integrity of silicone-filled breast implants (Gorczyca et al. 1992), in assessing a multifocal and multicentric tumour in a patient with a known primary carcinoma (Orel et al. 1995, Mumtaz et al. 1997), and in screening high-risk women

based on personal or family history or genetic analysis (Kuhl et al. 2000). However, both an overlap in signal intensity between malignant and benign tissue (increases the number of false positive findings) and the inability to detect microcalcifications (increases the number of false negative findings) reduce the application of MRI in the detection of early breast cancer (Ennis 1991). In addition, there is no single, standardised and generally accepted technique for all breast MR imaging examinations (Weinreb and Newstead 1995).

2.1.3 Mammographic classification of the breast

The idea of the association between mammographic parenchymal pattern and risk of breast cancer was first described by Ingleby and Gershon-Cohen in the 1960's (Oza and Boyd 1993). Subsequently Wolfe (1976a, 1976b) developed the classification of breast and indicated its association with the risk of breast cancer. Wolfe's classification is based on the relative amounts of fat, epithelial and connective tissue densities and prominent ducts observed in the mammogram, and consists of four different classes N1, P1, P2, DY. N1 represents an essentially normal breast (varies somewhat according to the age of the patient), P1 is a breast with a prominent duct pattern to a minimal degree, P2 describes a breast involved with prominent duct pattern of a moderate to severe degree, and DY an extremely dense parenchyma which usually denotes connective tissue hyperplasia. (Wolfe 1976a.) The P2 and DY patterns are characterised by greater density of mammograms (Sala et al. 1998). Wolfe (1976c) also suggested that a fifth class named QDY is needed to categorise the breasts of women younger than 40. The QDY breast is something between N1 and DY and is characteristically rather dense with discrete islets of fat throughout.

Also other classifications of the breast have been developed (e.g., Tabar classification, Gram et al. 1997), some of which are more based on the quantitative assessment of mammographic densities. Those measurements of mammographic parenchymal densities include visual estimation of the proportion of the breast area occupied by densities, measurement of planimetry of the area of density, and the

measurement of densities in digitised images with computer-assisted methods (Boyd et al. 1998). Wolfe et al. (1987) found a good agreement ($k=0.91$) between parenchymal patterns and measurement of planimetry of the area of density. In a doctoral thesis by van Gils (1998), automatic assessment of mammographic breast density based on digitised mammograms was used, and quite a good agreement between classifications by automated methods and radiologists was observed. Also, the possibility to use magnetic resonance imaging (MRI) or digitised film mammograms in the evaluation of breast pattern have been studied with promising results (Poon et al. 1992, Graham et al. 1996, Lee et al. 1997, Byng et al. 1998).

According to Toniolo et al. (1992), differences in interpretation and coding of mammographic parenchymal patterns by different radiologists may have led to limited acceptance of Wolfe's classification in practice. Classifications used so far have been subjective and therefore, to some degree, there is a lack of consistency both between studies and within them. Misclassification can greatly underestimate the risk. (Grove et al. 1985a.) In Wolfe's classification the interobserver variation has ranged from 52 percent to 97 percent for exact agreement and from 69 percent to 87 percent for intraobserver variation (Oza and Boyd 1993). Boyd et al. (1986) found in their study high levels of agreement for the classification of mammographic pattern. Agreement was substantially greater than agreement for any other feature of mammographic interpretation, including diagnosis and recommendation. Reproducibility of mammographic parenchymal patterns can be improved by training (Carlile et al. 1985), by consensus opinion (Toniolo et al. 1992) or by combining low risk (N1 and P1) and high risk patterns (P2 and DY).

2.1.4 Factors associated with mammographic parenchymal patterns

Most of the studies concerning the associations between mammographic parenchymal patterns and breast cancer risk factors are cross-sectional prevalence studies. Only those looking at the effect of hormonal replacement therapy on mammographic patterns have used at least some follow-up period. Such breast cancer risk factors as age, menopausal

status, parity and body size have been found to be the most consistently ones associated with mammographic densities. Some association has been found also with alcohol consumption, nutritional variables, family history of breast cancer and race. (Boyd et al. 1998.)

Age and menopause

Age and menopause have been most consistently found to be associated with mammographic parenchymal patterns (Wolfe 1976c, Bergkvist et al. 1987, Flook et al. 1987, Hart et al. 1989, de Stavola et al. 1990, Bartow et al. 1995, Stomper et al. 1996). According to Wolfe (1976c), only a breast initially classified as DY is likely to change with age. The change usually occurs between the ages of 35 and 50. Also Flook et al. (1987) observed that DY patterns tended to change to P2 or P1 with age. It has been suggested that the association between age and high risk pattern is nonlinear (Bergkvist et al. 1987). In addition, de Stavola et al. (1990) found an opposite effect of age on mammographic parenchymal pattern in pre- compared with postmenopausal women. The probability of high risk patterns (i.e. P2 and DY) increased with increasing age in premenopausal women but decreased in postmenopausal women.

There has been some debate whether it is age or menopausal status that mainly has the effect on parenchymal patterns. According to Boyd et al. (1998), the decline in the prevalence of mammographic density with increasing age means that it is density at a given age rather than density per se, that is a relevant measure regarding the risk of breast cancer.

Reproductive variables (age at first birth, parity)

It has been discovered that dense parenchymal pattern is related to the reproductive period (van Gils et al. 1995). De Waard et al. (1984), Bergkvist et al. (1987) and de Stavola et al. (1990) found high age at first birth to be associated with high risk patterns.

Tabar and Dean (1982), de Stavola et al. (1990) and Kaufman et al. (1991b) found that nulliparity was associated with a significantly higher frequency of P2 and DY patterns. Relationship between low parity and high risk patterns was found by de Waard et al. (1984). According to Grove et al. (1985b), the frequency of a high risk pattern (P2 and DY) decreases with additional pregnancies by 6% per pregnancy on the average.

Exogenous hormones

De Stavola et al. (1990) found an association between mammographic parenchymal pattern and the use of oral contraceptive. However, the effect of the use was different for pre- and postmenopausal women, whereas Leinster and Whitehouse (1986) observed both in pre- and postmenopausal women an increase of N1 patterns and decrease of P2 patterns among women exposed to an oral contraceptive. In a review by Saftlas and Szklo (1987) it was concluded that there is an increased proportion of low risk patterns (N1,P1) among ever users of contraceptive pills.

Hormonal replacement therapy (HRT) has been found to be associated with changes in mammographic parenchymal patterns (Cyrllak and Wong 1993, McNicholas et al. 1994, Laya et al. 1995, Stomper et al. 1996, Leung et al. 1997, Persson et al. 1997). Those changes include symmetric and asymmetric increase in breast density, increase in the size of fibroadenomas, and development or increase in the size of cysts (Cyrllak and Wong 1993) and also, focal, multifocal or diffuse mammographic increase in density (McNicholas et al. 1994). The increase was also associated with breast pain (McNicholas et al. 1994). It has been suggested that HRT inhibits involutinal processes within the breast and therefore the women under HRT have higher risk parenchymal patterns for a longer period of time and, subsequently, may have a higher risk of developing breast cancer (Kaufman et al. 1991a).

Persson et al. (1997) concluded that HRT may increase the breast parenchymal density on mammographic image, and that the increase is mostly dependent on the type of regimen and the age of patient. Three major therapeutic principles (i.e. oestrogen alone, oestrogen in cyclic combination with progestogen, and oestrogen in continuous

combination with progestogen) are used for hormonal replacement. These different methods have different effects for example on the endometrium and may also differ as to their effects on the normal breast which was actually shown by Lundström et al. (1999). Greatest increase in mammographic density was observed for women receiving combination hormone replacement therapy. Also Persson et al. (1997) observed that increase in breast density was associated with combined oestrogen-progestin HRT especially in women older than 50 years of age.

According to Boyd et al. (1998), mammographic parenchymal patterns can be altered by hormonal interventions. Spicer et al. (1994) concluded that reduced oestrogen and progestogen exposures to the breast that were achieved by the hormonal contraceptive regimen (gonadotropin-releasing hormone agonist GnRHA) resulted in substantial reductions in follow-up mammographic densities at 1 year compared with the baseline. Atkinson et al. (1999) found that tamoxifen among postmenopausal women decrease the mammographic breast density.

Height, weight and breast size

Some studies have found an increase in the proportion of high risk patterns (P2,DY) according to increasing tallness (Saftlas and Szklo 1987). Weight as such (Brisson et al. 1984, Brisson et al. 1988) as well as body mass index (BMI) have been found to be negatively associated with high risk patterns (de Stavola et al. 1990, Bartow et al. 1995). Also the waist/hip ratio as an indicator of body fat topography has been found to be negatively associated with mammographic parenchymal patterns (i.e., women with predominant fat accumulation in the abdominal region were statistically significantly less likely to have a high risk (P2,DY) mammographic parenchymal pattern) (Beijerinck et al. 1991). Also the size of the breast has a relationship with mammographic parenchymal patterns: small breast size is associated with increased parenchymal density in mammograms (Bartow et al. 1995, Stomper et al. 1996).

Nutrition and exercise

Knight et al. (1999) who conducted a randomised trial of dietary intervention in women with extensive areas of radiologically dense breast tissue in mammography noticed that low-fat, high-carbohydrate diet is associated with a significant reduction in area of density among women going through menopause. Also Boyd et al. (1997) found that a two-year low-fat, high-carbohydrate diet reduced the area of mammographic density significantly, and in 1998, Boyd et al. concluded that through dietary interventions the mammographic parenchymal patterns can be altered.

Gram et al. (1999) found only weak and statistically non-significant association between physical activity and mammographic densities. Information on physical activity both at work and leisure was obtained through questionnaires.

Race

Hart et al. (1989) found some difference in breast density between ethnic groups (Anglos, Hispanics and American Indians) as well as Bartow et al. (1995) (Anglo, Hispanic, Native American), whereas Grove et al. (1985b) found no differences (Caucasian, Japanese and Chinese).

Breast biopsy and histologic features

Bergkvist et al. (1987) found that a history of breast biopsy increased the likelihood of having a high risk pattern (OR=1.57).

Arthur et al. (1990) did not find any correlation between Wolfe's patterns and histologic evidence of epithelial hyperplasia, atypia or in situ carcinoma. It seemed that the differences in Wolfe's patterns were related to the distribution of fibrous and adipose tissue in the breast interlobular stroma but they had no association with epithelial parenchymal content. However, Boyd et al. (1992) found that the risk of detecting

atypia/carcinoma in situ differed substantially according to the extent of mammographic density.

Family background

Kaufman et al. (1991b) and de Stavola et al. (1990) did not find any correlation between family history of breast cancer and mammographic parenchymal patterns. However, Kaprio et al. (1987) observed similarity in parenchymal patterns of twins, which could suggest a familial, possibly genetic influence on the parenchymal pattern. After estimating the familial correlations in breast density and performing a genetic segregation analysis Pankow et al. (1997) concluded that the mammographic parenchymal pattern may in fact be genetically influenced.

Independent risk factors

In a multivariate analysis de Stavola et al. (1990) found out that age, parity and adiposity were significantly related to Wolfe's grade pattern. Bartow et al. (1995) found race/ethnicity, BMI, age, and breast size to be significantly associated with breast patterns. Beijerinck et al. (1991) found a significant association of age, parity, BMI and waist/hip ratio with Wolfe's pattern. The risk of an unfavourable breast pattern (P2,DY) was associated with age, nulliparity, age at first birth, and prior breast biopsy in a study by Bergkvist et al. (1987). Leinster et al. (1988) found the association between breast cancer risk factors and the mammographic parenchymal pattern to be somewhat different for pre- and postmenopausal women. In a multivariate analysis for premenopausal women parenchymal patterns were associated with breast size, weight, age at first pregnancy, history of biopsy and history of cyclical breast pain, whereas for postmenopausal women the association with breast size, weight, weight change, age at first pregnancy, a history of biopsy and a history of breast feeding was observed.

2.2 Breast cancer in Finland

Breast cancer has been the most common cancer type among Finnish females since the 1960's. In 1997, 3324 new breast cancer cases were diagnosed in Finland, and the figure is increasing all the time. The increase is due to the increasing number of elderly women in the population, improvements in diagnostic methods, and the strengthening effect of breast cancer risk factors on the Finnish female population (Hakulinen et al. 1989). The age-adjusted incidence of breast cancer has increased from 27 in 1956 to 79 per 100 000 woman years in 1997 (Finnish Cancer Registry 2000) (Figure 1). However, at the same time, a 5-year relative survival rate for breast cancer has improved and it is nowadays 80% (Dickman et al. 1999). Therefore, the increase is only modest concerning mortality from the breast cancer (Hristova and Hakama 1997).

The two main histological types of breast cancer are ductal and lobular according to their site of origin. Both invasive and non-invasive types of ductal and lobular carcinoma exist. The rest of very rare carcinomas derive their names from the combination of histologic patterns and cytologic characteristics (tubular, papillary, mudullary, mucinous, adenoid cystic, secretory, apocrine, Paget's disease). (Bartow and Fenoglio-Preiser 1988.)

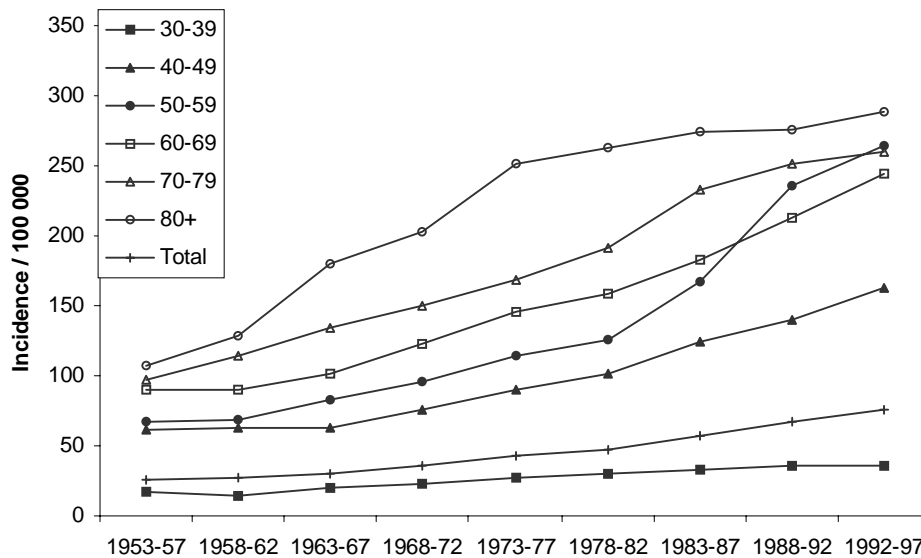


Figure 1. Incidence of breast cancer per 100 000 women in Finland.

The most common invasive breast cancer type is the invasive ductal carcinoma which accounts for 75-80% of breast cancers. The proportion of invasive lobular carcinomas is 10-15 %. The proportion of in situ carcinomas depends on the diagnostic patterns, especially on the coverage of screening in the population at issue.

2.2.1 Factors associated with breast cancer

The most important risk factor of breast cancer is sex; being a woman increases the risk by over a 100 times. Another important demographic risk factor is increasing age. Breast cancer is quite rare before the age of 30 but a rapid increase takes place at the age of 40. The risk of breast cancer is also affected by the social class. Women in high social classes have the highest risk of breast cancer (Pukkala 1995, Pukkala and Weiderpass 1999). Also factors such as being single compared to being married, and living in an urban rather than in a rural area increase the risk of breast cancer (Tomatis et al. 1990).

Hormones have a major role in the aetiology of breast cancer. In physiological amounts, oestrogen and to a lesser extent, progesterone are mitogenic to breast tissue. Most of the known risk factors for breast cancer can be understood as measures of the cumulative exposure of the breast to oestrogen, and perhaps to progesterone. Those affect the rate of cell division which is an essential element in the genesis of human cancer. (Henderson et al. 1996.) There is clinical data which suggests a link between a woman's exposure to oestrogen and progesterone and the development of breast cancer (Reid et al. 1996).

Early menarche increases the risk of breast cancer (Cole 1980, Kelsey et al. 1993). Women with early menarche (age 12 or younger) and rapid establishment of regular cycles are at increased risk of breast cancer compared to women with late menarche (age 13 or older) and long duration of irregular cycles (Hendersson et al. 1996). Also late age at the first full-term pregnancy and nulliparity are associated with modest elevations in the risk of breast cancer (Cole 1980, Kelsey et al. 1993), whereas breast feeding has been found to have some protective effect on the breast cancer risk (Kelsey et al. 1993, Henderson et al. 1996), which is due to a substantial delay in re-establishing

ovulation following a completed pregnancy (Henderson et al. 1996).

At menopause the hormonal milieu changes dramatically when ovaries stop producing oestrogen (Tomatis et al. 1990) This change also has an effect on the risk of breast cancer. Early menopause (Kelsey et al. 1993), also an artificial one (through either bilateral oophorectomy or pelvic irradiation), reduces the risk of breast cancer (Henderson et al. 1996).

A long term use of oral contraceptive pills seems to increase the risk of breast cancer (Kelsey and Bernstein 1996) but there is no elevated risk after 10 years of cessation of the use (Collaborative Group on Hormonal Factors in Breast Cancer 1996).

Strenuous physical activity may delay menarche and moderate physical activity during adolescence can lead to anovular cycles, therefore, physical activity may decrease the risk of breast cancer (Henderson et al. 1996). Both leisure time and work-related physical activity has been assessed by using self-reported questionnaires. Results have been somewhat contradictory probably because of different measures of physical activity and different levels of adjustment (Frisch et al. 1987, Paffenbarger et al. 1992, Vihko et al. 1992, Dorgan et al. 1994, Thune et al. 1997).

Some elevation of risk of breast cancer has been observed according to tallness (Kelsey and Bernstein 1996). The effect of weight on breast cancer risk is critically dependent on age (Henderson et al. 1996). The increase in the risk of breast cancer by obesity is mainly noticed among postmenopausal women (Cole 1980). This association can be partly explained by the fact that adipose tissue is the major source of oestrogen among postmenopausal women (Tomatis et al. 1990). In a case-control study carried out in Finland, it was found out that the waist to hip ratio was a better marker for breast cancer risk than body mass index. Among both pre- and postmenopausal women those in the highest quintile for the waist-hip ratio had the highest risk of breast cancer (Männistö 1999).

The risk of breast cancer is increased if a woman has a sister or/and a mother who has been diagnosed with breast cancer especially if it was diagnosed at an early stage or had bilateral disease (Henderson et al. 1996). About 5% of breast cancers may have a genetic component in the aetiology (Moss 1996).

Some increase (9 to 11% per one daily alcohol drink) in the risk of breast cancer among women who drink alcohol has been observed (Rosenberg et al. 1993, Longnecker 1994, Smith-Warner et al. 1998), whereas in the case of smoking, the association is somewhat unclear; both protective and risk increasing hypothesis have been presented (Palmer and Rosenberg 1993). Such components of diet as fat intake, antioxidant vitamins and phytoestrogens have been suggested to be associated with breast cancer (Kelsey and Bernstein 1996). In a meta-analysis by Gandini and co-workers (2000), the authors concluded that high consumption of vegetables decreased moderately the risk of breast cancer whereas the effect of fruits was more unclear.

High doses of ionising radiation exposure to chest before the age of 40 increases the risk of breast cancer (John and Kelsey 1993, Kelsey 1993, Kelsey and Bernstein 1996). Estimates of the relative risk of breast cancer have ranged from 1.4 to 2.2 per Gray (John and Kelsey 1993).

Also benign breast diseases such as benign proliferative diseases, ductal carcinoma in situ and lobular carcinoma in situ have been found to be associated with increased risk (Kelsey and Bernstein 1996).

However, less than 25 per cent of women with breast cancer can be found to have any of the known risk factors including family history of breast cancer, late menopause, nulliparity, a first full term pregnancy after the age of 35, increasing age and mammographic parenchymal patterns P2 or DY (McDermott 1991).

Mammographic parenchymal patterns

Boyd et al. (1998) proposed that the risk of breast cancer associated with the mammographically dense breast tissue is due to the combined effects of two processes: cell proliferation (mitogenesis) and damage to the DNA of dividing cells (mutagenesis). The mammographically dense breast tissue reflects proliferation of the breast epithelium and stroma, in response to growth factors induced by circulating levels of sex hormones (mitogenesis). Spicer et al. (1994) believed that decreased mammographic densities reflect the reduction in mitotic activity.

In the first two studies Wolfe found 37 and 21 times higher incidence of breast cancer among women with a DY pattern compared with women with an N1 pattern (Wolfe 1976b). No adjustment for confounders was done. The first study included women who were at least 30 years old and had had a xeromammography made at Hutzel Hospital during a period from January 1967 to January 1972 (N=5284). The second study was based on the information from period January 1972 to January 1973 (N=1930). Both materials were based on clinical patients. The information on breast cancer diagnosis was based in the first study to registry information, whereas in the second study, it was based on a questionnaire filled in by the women themselves.

A year later, a study by Egan and Mosteller (1977) was published where they concluded that dense fibroglandular tissue delays detection of breast cancer by mammography, and the increase in breast cancer risk in dense breasts is due to this delay. Therefore, a long-term (at least 3 years) follow-up is needed in assessing the history of breast cancer by mammography. Later on, this hypothesis was named to a masking hypothesis. According to the hypothesis there, is a difference in cancer detection associated with different patterns of breast parenchyma. More cancers will be missed in mammography among women with a dense pattern than in women with a fatty pattern and later on when missed cancers surface themselves clinically, it will be concluded that the risk of breast cancer is higher among women with dense breasts than in women with lucent breasts. (Saftlas and Szklo 1987, Oza and Boyd 1993.) This may cause apparent differences in the lead time of diagnosis of breast cancer in women with different mammographic appearances, and therefore give a rise to a bias in prevalence studies (Oza and Boyd 1993). This implies that the breast cancer risk estimates related to dense breasts in prevalence studies are less than one whereas in follow-up studies the risk estimates are over one given true independency.

To study the masking effect, Whitehead et al. (1985) followed up 40 000 women and conducted a nested case-control study including 221 prevalent and 706 incident breast cancer cases and two controls for each case individually matched on the clinic, 5-year age range and the date of the initial mammogram. Their study showed that women with dense breasts are disadvantaged by an increased breast cancer risk compared to women with fatty breasts and also, tumours are more difficult to detect in dense breasts.

They concluded that the masking effect does exist but it operates in addition to a difference in the risk of breast cancer within the four Wolfe classes. Similar results from different kind of studies do not support the hypothesis that masking would be responsible for the estimates of the increased risk of breast cancer associated with mammographic densities (Boyd et al. 1998). It has also been suggested that the mammographic parenchymal pattern merely represents radiographic reflection of one or a combination of commonly recognised risk factors in breast cancer, and that the patterns themselves may have little significance (Buchanan et al. 1981).

Since then, plenty of studies have been conducted giving somewhat contradictory results. The results of association between mammographic parenchymal pattern and breast cancer have varied according to whether the mammograms were taken before, at the time of or after the diagnosis of breast cancer. It is important to find out whether the association exists already before the disease. (Saftlas and Szklo 1987) Heterogeneity in the risk estimate is partly due to substantial methodological differences among the studies and variations in the quality of studies (Boyd et al. 1984). The contradictory results are largely explained by methodological differences between studies in their design, execution or analysis. Variation can be caused also by selection of control subjects, the age of subjects studied and classification used. (Warner et al. 1992.) According to Byrne (1997), the use of lower contrasts filmscreen images, not blinding the radiologist reading the mammograms to case status, use of diagnostic images for assessment and inadequate training of radiologists may have caused biases in the studies.

Warner et al. (1992) made a meta-analysis about the risk of breast cancer associated with mammographic parenchymal patterns. They found that the risk estimates using Wolfe's classification based on cohort studies, case-control studies and prevalence studies were 5.19 (95 % CI 3.6-7.48), 1.8 (95 % CI 1.5-2.13) and 0.54 (95 % CI 0.4-0.7) respectively. The studies using quantitative estimates of breast densities resulted in higher odds ratios than those using Wolfe's method. Boyd et al. (1998) concluded that the estimates of the RR of breast cancer associated with mammographic density are substantial and stronger than those associated with any other nongenetic risk factor in breast cancer except age. Boyd et al. (1995b) found out that the increased breast cancer risk associated with dense breast pattern lasted at least five years.

According to Boyd et al. (1995a), a group of women with extensive breast parenchymal densities have an approximately 4-5 times greater risk of breast cancer than that of the general population of the same age. Kato et al. (1995) found the association of Wolfe's mammographic patterns and the risk of breast cancer to be stronger among pre- than postmenopausal women.

Even if the association of mammographical parenchymal patterns and the risk of breast cancer fulfils most of the Bradford Hill criteria, areas like biological plausibility, reasoning by analogy and experimental evidence need further investigation (Goodwin and Boyd 1988).

Hormonal replacement therapy

It is known that endogenous hormones directly affect the risk of breast cancer. The effect of exogenous hormones given for therapeutic purposes (contraceptive pill, HRT) on breast cancer risk has been matter of debate over the years. Postmenopausal oestrogen replacement therapy is used to help women to cope with menopausal symptoms (i.e. hot flushes, vaginal dryness, and mood swings). A negative effect of oestrogen replacement is an increased risk of breast cancer. Progesterone is usually added to oestrogen replacement to reduce the risk of endometrial cancer in women receiving unopposed oestrogen therapy. However, it is not known how these added hormones affect the risk of breast cancer. (Josefson 2000.)

HRT has been found to be a factor which makes mammographic parenchymal patterns more dense (Stomper et al. 1990, Kaufman et al. 1991a, McNicholas et al. 1994, Laya et al. 1995). HRT itself has been found to be a risk factor for breast cancer increasing the risk by 10 to 40% depending on the regimen and length of exposure (Colditz et al. 1990, Colditz et al. 1995, Collaborative Group on Hormonal Factors in Breast Cancer 1997, Schairer et al. 2000). There is also a biologically plausible mechanism for the association between HRT and breast cancer (LaCroix and Burke 1997, Colditz 1998). Oestrogen and combined treatment by oestrogen and progestogen increase the cell division rate of breast, and there is some evidence that cell proliferation is the

underlying process by which DNA damage accumulates and the risk of breast cancer increases (Colditz 1998). HRT can also make the detection of breast cancer more difficult by reducing the sensitivity of mammography to detect small tumours, and by reducing the quality of mammography by increasing breast tenderness and making the adequate compression of the breast difficult (Laya et al. 1996, Persson et al. 1997, Rosenberg et al. 1998, Litherland et al. 1999, Kavanagh et al. 2000). It has also been found that the recall rate for incident screening is likely to be higher in women on HRT (Litherland et al. 1997, Persson et al. 1997). That leads to greater costs and causes anxiety among screenees (Litherland et al. 1997). The HRT can also reduce the specificity through increased mammographic density, which makes radiologists uncertain of the interpretation of the mammogram and increases the number of false positive findings. This may increase the cost of screening programme and decrease its benefits. (Laya et al. 1996.)

Holli et al. (1998) concluded that breast cancers diagnosed among women using HRT are biologically less aggressive (measured as size, histologic differentiation and proliferation rate) than cancers among women without previous HRT, whereas Stallard et al. (2000) did not find difference in type, size, or grade of tumour in users compared with non-users. Neither did Roubidoux et al. (1998) find any significant differences in the stage of the disease between women using HRT and women not using HRT.

In Finland the use of HRT started to increase in the mid 1970's and in 1989 the use of HRT was more common than in several other countries with prevalence of 22% (among women aged 45-64) (Topo 1997). However, women mainly used hormones for a short period around menopause (Topo et al. 1993). Based on the sales information of hormones, until the mid-1980's, oestrogens and their combinations were sold more than the combination of oestrogens and progestins. By 1987 an equal amount of both types of hormones were sold. (Topo et al. 1991.)

2.2.2 Selective screening for breast cancer

The primary prevention of breast cancer has only limited potential because many of the etiological factors are probably unknown, and the known ones cannot be affected. Some suggestions through a diet and hormonal treatment (tamoxifen, luteinizing-hormone-releasing hormone) have been made (Kelsey and Bernstein 1996), but their effect will probably be quite small due to the small population etiological fraction. Therefore, secondary prevention through mammography screening has been the focus of attention, with the object to detect the breast cancer at a preclinical stage. Because mammography screening is costly and besides its benefits it also has its disadvantages (false positive results, anxiety etc), the possibility to use selective screening based on known breast cancer risk factors has been studied.

The information on a woman's reproductive characteristics, family history of breast cancer and use of hormones have been studied as criteria for selective screening. In those studies these variables defined a high-risk population with a size from 37 to 65% of the total population, and the proportion of cancers estimated to be detected in such a high risk subgroup varied from 63 to 84% which was regarded to imply poor validity, if applied for selective screening (Farewell 1977, Soini and Hakama 1978, Brisson et al. 1989). So far, not even a combination of these risk factors is recommended to be used as a criterion for selective screening.

Wolfe (1976b) in his first study suggested that his classification could be used to select women to screening. However, the use of mammographic parenchymal patterns for the selection of women for breast cancer screening has been criticised because breast cancer is also diagnosed among large numbers of women who do not have mammographic marks indicating an increased risk (Tabar and Dean 1982, Ciatto et al. 1990, Oza and Boyd 1993), i.e. the sensitivity of mammographic pattern as a screening test is low. Also, the patterns are not practical because of high prevalence of high risk patterns (Kato et al. 1995), i.e. also the specificity is poor. The suggestion to use the mammographic parenchymal pattern to determine the interval between screenings has been more acceptable (Whitehead et al. 1985, Oza and Boyd 1993, Boyd et al. 1995b, van Gils et al. 1995, Boyd et al. 1998).

It may be possible to use mammographic parenchymal patterns for moderate prevention of breast cancer since those patterns can be changed through hormonal and dietary intervention. So far, no combination of risk factors, not even mammographic parenchymal patterns included, has been shown to be an adequate means of selective screening. According to McDermott (1991), the risk factors which included a high risk mammographic parenchymal pattern (P2,DY) were prevalent only in 25% of breast cancer patients.

3 Aims of the study

The purpose of this study is to find out causes of mammographic parenchymal patterns and to compare them to the risk factors for breast cancer. This was done by finding out the factors that account for the change of a favourable pattern to an unfavourable one and vice versa. This level of specificity assumed a cohort design with a follow-up. Next step was to evaluate the role of mammographic parenchymal pattern in the aetiology of breast cancer, and especially the joint effect of mammographic parenchymal pattern and hormonal replacement therapy on the risk of breast cancer considering other breast cancer risk factors as confounders.

The articles included here were conducted with the specific purpose to estimate

- 1) the change from favourable to unfavourable mammographic parenchymal patterns in relation to risk factors for breast cancer (I)
- 2) the change from unfavourable to favourable mammographic parenchymal patterns in relation to risk factors for breast cancer (II)
- 3) the effect of mammographic parenchymal patterns on breast cancer in relation to other risk indicators of breast cancer (III)
- 4) the joint effect of mammographic parenchymal patterns and hormonal replacement therapy on the risk of breast cancer (IV).

4 Material and methods

4.1 Finnish Cancer Registry and Mass Screening Registry

The Finnish Cancer Registry was founded in 1952 and it works under the supervision of the National Research and Development Centre for Welfare and Health and is technically run by the Cancer Society of Finland. The registration of cancer cases started in 1953. The coverage and accuracy of the registry are of high quality. (Hakulinen et al. 1989.) In 1968 the Cancer Society of Finland established Mass Screening Registry for evaluation of screening. The Mass Screening Registry takes care of identification, invitation and follow-up of cohorts to be screened and evaluates the effectiveness of screening programmes through linkage of the cohorts to the national registry of deaths and cancer registrations. The Mass Screening registry operates within the Finnish Cancer Registry. (Hakama et al. 1991.)

4.2 Basic population of the study

The Cancer Society of Finland initiated a mammography-based pilot screening programme in southeastern Finland in 1982 (Hakama et al. 1995). The primary aim of the study was to gain experience for a nationwide population-based organised programme, and to predict the potential effectiveness of a public health policy. Women residing in the city of Kotka and in 12 municipalities around it, and born in 1936, 1938, 1940 or 1942 were identified (N=4163) by the national population registry and invited to attend the screening by a letter announcing the place and time. The invitation was repeated every other year. Those born in 1935, 1937, 1939, 1941 and 1943 remained as controls who were not invited to the screening and have not been included in the present study. In 1990 this pilot programme was merged with the national public health policy which gradually began in 1987. Compliance with screening in the study period was 86 per cent and 4122

women attended at least one screening. Details on the original material have been reported elsewhere (Hakama et al. 1995).

The breast cancer cases not detected by screening were found by linkage to the Finnish Cancer Registry. The follow-up of this cohort was extended to the end of the year 1993. Cases diagnosed before or at the first screening or within six months after the first screening were excluded (N=38). Three women had incomplete information on the status of their breasts and were excluded. 4081 women were thus eligible for participation in the study. Those 4081 attended from 1 to 5 screening rounds which resulted in 16322 screening visits altogether. For 133 screens the information on mammographic parenchymal patterns was missing.

The information on background factors and other variables was recorded by radiologists and nurses in personal interviews. The mammograms were taken with Mamex DC (Soredex, Helsinki, Finland) using first Sakura and later on, Konica film (Instrumentarium, Helsinki, Finland). The developer was delivered by 3M (Helsinki, Finland). A single (oblique) view was taken from each woman. The mammographic patterns were defined by one and the same radiologist throughout the study and recorded at every screening round. The radiologist had an access to the earlier mammograms and other information recorded at previous screening rounds. The definition of mammographic patterns was done according to Wolfe's classification (Wolfe 1976b). The mammographic pattern of both breasts was taken into account by taking the average of right and left breast and rounding it to the less favourable alternative if necessary. For most of the analysis, N1 and P1 as well as P2 and DY patterns were combined. Other information was also recorded for every screening round and it included demographic factors (age, marital status, education), hormonal factors (use of HRT and/or contraceptive pill), breast cancer history among family members (mother and sister), reproductive history (age at menarche, age at first pregnancy, number of pregnancies, miscarriages, menopausal status) and gynaecological operations. The breast size was measured as a brassiere cup size. Body mass index (BMI) was calculated using the formula $\text{weight}(\text{kg})/\text{height}^2(\text{m})$. The use of HRT was recorded systematically at each screening only since 1984.

4.3 Estimation of change of the mammographic parenchymal pattern

For the estimation of the incidence of a P2,DY pattern only those women were included whose breast pattern at the first screening round was either N1 or P1 and who had participated in the screening at least twice. Also, if they were diagnosed with breast cancer, the mammographic pattern had been assessed at least six months prior to the diagnosis.

For the estimation of incidence of N1,P1 only those women whose breast pattern at the first screening round was either P2 or DY and who had participated in the screening at least twice and the assessment of the parenchymal pattern was made at least six months before a possible breast cancer diagnosis, were included. Each screening visit constituted one unit of observation.

The outcome was the possible change in the mammographic pattern between two successive screening visits. The person time for each screening interval was the time between two consecutive screenings. The follow-up started from the first screening and ended either at a screening round with a diagnosis of change in the mammographic pattern or for women with a permanent pattern at the last screening visit. The exposure data on breast cancer risk factors was defined as that recorded at the visit under observation, and the outcome as the pattern at the subsequent visit. The change in mammographic parenchymal patterns between subsequent screenings were compared to prior changes in risk factors. The aim was to estimate the possible effect of a change in risk factors.

A change in the BMI and HRT between any screening rounds was related to the change in the mammographic pattern between the same screening rounds. No lag was allowed because HRT was recorded only from 1984 onwards.

4.4 Estimation of breast cancer risk and the joint effect of mammographic parenchymal patterns and HRT on breast cancer risk

Each screening visit formed one observational unit. The person years for each screening visit were calculated respectively being the time between two screening visits or the time between a screening visit and diagnosis of breast cancer or a screening visit and the end of the follow-up (31.12.1993).

The association between mammographic parenchymal patterns and occurrence of breast cancer was assessed using the information from the first visit and from the visits preceding cancer separately. The effect of a change in the mammographic parenchymal pattern on the occurrence of breast cancer was also assessed. The analysis included women who had been screened at least twice more than 6 months before the breast cancer diagnosis (N=3840). The follow-up started at the second screening (i.e. at the time of first potential change) round and ended either with the first diagnosis of breast cancer or with the end of the follow-up, whichever came first.

4.5 Statistical analysis

The basic incidence rates of mammographic parenchymal patterns were estimated by assuming the N1,P1 or P2,DY event to occur at midpoint of the two successive screening visits. The associations between breast cancer risk factors and unfavourable change (incidence of P2,DY) in mammographic patterns were estimated in terms of odds ratios and the univariate and multivariate analysis of the data were carried out using logistic regression model (Hosmer and Lemeshow 1989). (I)

The associations between breast cancer risk factors and favourable change (i.e. incidence of N1,P1 pattern) in mammographic parenchymal patterns were estimated in terms of relative risks of incidence rates of the N1,P1 pattern. The univariate and multivariate analysis of the data were carried out using Cox proportional hazard model (Cox and Oakes 1984) (II).

The relationship between mammographic parenchymal patterns and breast cancer

was analysed with the Cox proportional hazard model (Cox and Oakes 1984) (III).

The Poisson regression model (Breslow and Day 1987) was used to estimate the possible joint effect of mammographic parenchymal patterns and hormonal replacement therapy on the risk of breast cancer. Confounding effects of breast cancer risk factors which were found to be related to mammographic parenchymal patterns in our previous studies (I, II) were controlled for (IV).

5 Results

At the beginning of the study there were 3840 women with information on at least 2 screening rounds available. Three of them were further excluded because the information on their mammographic parenchymal pattern was missing at the initial screening round. Ultimately, there were 1890 women with favourable i.e. N1 or P1 mammographic parenchymal patterns and 1947 women with unfavourable i.e. P2 or DY mammographic parenchymal patterns. During the study period (from 1982/83 to 1990/91), 1460 changes in patterns took place. 200 of them were transitions to unfavourable and 1260 were transitions to favourable mammographic parenchymal patterns. The incidence of favourable patterns was over 7 times higher than that of unfavourable. (Table 1)

At the first screening round, the prevalence of the N1 pattern was 13% and that of the DY pattern about 4%. Between the first and last screening round there was a drift from unfavourable P2,DY patterns to the favourable N1,P1 patterns. At the last screening round the prevalences of N1 and DY were 46% and 1%, respectively. (Figure 2)

Table 1. Number of women, screening visits, woman years, changes and incidence rates with 95% confidence intervals (CIs) in a study population divided into 2 groups according to the mammographic pattern at the initial screening.

	Initial mammographic pattern	
	N1,P1	P2,DY
Women	1890	1947
Screening visits	5317	4854
Woman years	10546	8714
Number of changes	200	1260
Incidence rate (per 100 woman years)	1.9	14.5
95 % CI	1.6–2.2	13.7–15.3

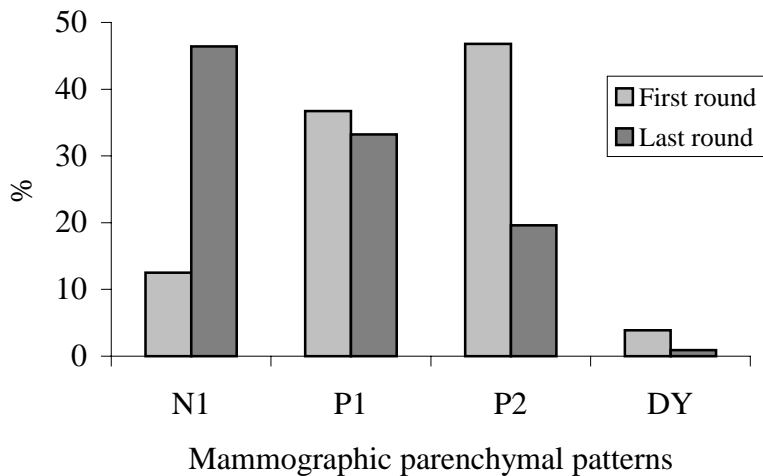


Figure 2. Prevalence of mammographic parenchymal patterns at first and last round.

5.1 Risk of an unfavourable change in mammographic parenchymal pattern

Age, menopausal status, HRT, BMI and breast size were related to the risk of an unfavourable change in mammographic parenchymal patterns. After adjustment to each other, only BMI remained statistically significant, the risk of an unfavourable change being 80% lower (OR=0.2, 95% CI 0.1-0.6) for women with a BMI 25 or more compared to women with a BMI less than 20. (Figure 3) A continued use of HRT increased the risk of an unfavourable change (OR=2.5, 95% CI 1.2-5.1) after adjustment to age.

5.2 Risk of a favourable change in mammographic parenchymal pattern

The incidence of a favourable pattern was positively related to age, number of pregnancies, BMI and breast size. In the multivariate analysis, the risk estimates remained similar except for the breast size which was no more statistically significant probably due to its high correlation with the BMI. (Figure 4) The increase in the BMI between screening rounds was also associated with incidence of a favourable pattern in the screening round preceding the change (RR=1.2, 95% CI 1.0-1.5). However, the association was smaller than for BMI as such (RR=2.3, 95% CI 1.8-3.0).

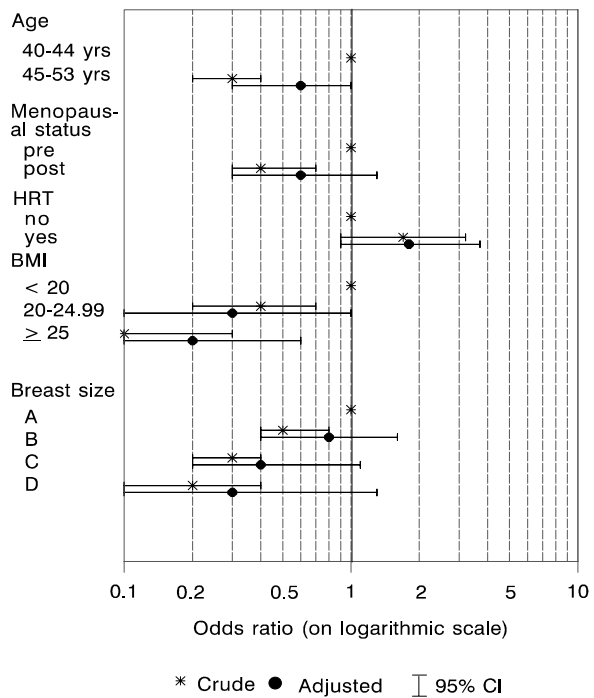


Figure 3. Crude and adjusted odds ratios of an unfavourable mammographic parenchymal pattern (i.e. P2,DY).

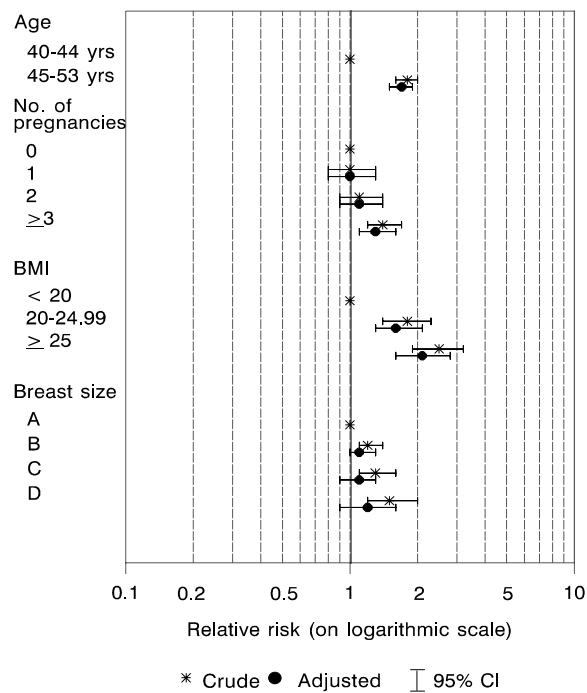


Figure 4. Crude and adjusted relative risk of a favourable mammographic parenchymal pattern (i.e. N1,P1).

5.3 Risk of breast cancer

The study included 68 new and invasive breast cancers from which 85% (58) were ductal carcinomas and 7% (5) lobular carcinomas and the rest five were classified either as unspecified or other histological types. No in situ carcinomas were included. There was no statistically significant risk of breast cancer related to mammographic parenchymal patterns measured at the first screening round whereas taking information on the previous screening from all the screening rounds into consideration, a linear increased breast cancer risk was found according to the mammographic parenchymal patterns (Figure 5). After combining N1,P1 and P2,DY respectively and adjusting for age, the risk of breast cancer was 2.5 times higher for women with P2,DY patterns compared to women with N1,P1 patterns (95% CI 1.5-4.0). Further adjustment for BMI, number of pregnancies and breast size strengthened the association (RR=2.8, 95% CI 1.7-4.9). The risk of breast cancer was highest among women whose breast pattern both at first and last screening round was P2,DY compared to women whose breast pattern was N1,P1. Sensitivity and specificity of mammographic parenchymal patterns used as a screening test was 49% and 65%.

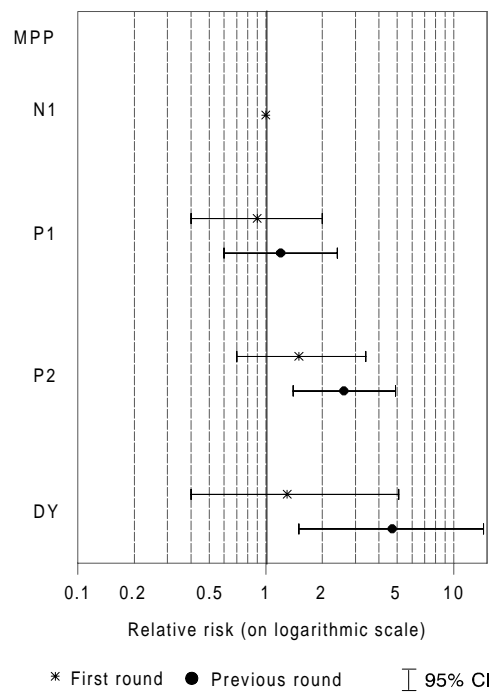


Figure 5. The relative risks of breast cancer related to age-adjusted mammographic parenchymal patterns (MPP) of the initial screening round and all screening rounds.

5.4 Risk of breast cancer related to the joint effect of mammographic parenchymal patterns and HRT

Compared to the reference group of women not using HRT and with an N1 pattern the observed joint relative risk of HRT and N1, P1 or P2 was close to unity and not significant. In contrast, women using HRT and with a DY breast pattern were at an increased risk of breast cancer (RR=11.6, 95% CI 2.5-53.6) which was statistically significant. (Table 2) The association could not be accounted for by the potential confounders of age, BMI and number of pregnancies, i.e. those known risk factors of breast cancer which in our material were also related to changes in mammographic parenchymal patterns. The expected relative risks (assuming multiplicative joint effect) were very close to the observed ones among women using HRT and either with a P1 or P2 pattern. Among women using HRT and with a DY pattern, the observed relative risk was 11.6 and the expected relative risk was only 1.5 (0.6x2.5) assuming a multiplicative joint effect. The difference between the observed RR (11.6) and the expected one (1.5) is an indication of synergism even if the interaction term did not reach statistical significance in the multivariate analysis.

Table 2. The adjusted relative risks with 95% confidence intervals (in parenthesis) of breast cancer by HRT and mammographic parenchymal pattern and expected relative risk of breast cancer assuming a multiplicative joint effect of HRT and mammographic parenchymal pattern.

Mammographic parenchymal pattern	HRT		
	No	Yes Observed	Expected
N1	1	0.6 (0.2-2.0)	0.6
P1	1.3 (0.6-2.9)	1.1 (0.4-3.1)	0.8
P2	2.4 (1.1-5.4)	1.3 (0.4-4.3)	1.4
DY	2.5 (0.3-20.2)	11.6 (2.5-53.6)	1.5

Adjusted for age, BMI and number of pregnancies.

6 Discussion

6.1 Reliability of the material and methods

The study material was based on a pilot population-based breast cancer screening programme which was initiated by the Finnish Cancer Society in the beginning of the 80's. The participation rate for the mammography screening program was high (86%). The information on cancer cases was based on the Finnish Cancer Registry, and its accuracy and coverage is good. Different check-ups have indicated that the Registry covers more than 99% of all malignant tumours diagnosed in Finland. (Teppo et al. 1994.)

By using a prospective cohort design and assuming that the assessment of mammographic parenchymal patterns was done at least 6 months before the diagnosis of breast cancer, the high risk pattern precedes the development of cancer and therefore, is not a consequence of cancer.

The study material differs from the present screening practice. The material included young women (aged 40-47 at entry). One mammogram was taken from each woman and one radiologist interpreted the mammograms. Furthermore, the breast imaging techniques have improved substantially since the beginning of the 1980's. Especially the contrast and resolution of conventional film images have increased (Sickles 2000).

In our study the high degree of unknown information about HRT and use of contraceptive pills is due to the fact that these were not elicited at the initial screening round. This weakens the HRT and especially the contraceptive pill exposure information. There was no reliable questionnaire information available on the duration of HRT use or on the type of used hormones. Because of the memory bias we chose not to use the questionnaire data on the duration of HRT use.

The number of unfavourable changes was small (200) compared to the number (1260) of favourable changes and one may wonder whether the changes were in fact due to a misclassification bias. All the mammograms over the five rounds were read by the

same radiologist who also had the previous mammograms and other data available. The numbers were also sufficient to result in statistically significant risk estimates. These facts argue against a nondifferential misclassification bias as the explanation of our results. However, there was no information on intra- or interindividual reliability of the classifications.

Subsequent to the original classification by Wolfe (1976b), other classifications with quantitative estimates of breast density have been developed and used (Brisson et al. 1989, Oza and Boyd 1993, Kato et al. 1995). However, since our material stems from a time prior to the development of more refined quantitative methods measuring breast density we were unable to evaluate these more recent classification measures.

Most of the changes in parenchymal patterns took place between the first and second screening round. This means that those recordings took place at a younger age when the women were at an increased risk of an unfavourable parenchymal pattern change. Therefore, our results are based on few cases only and subjected to large random variation.

The previous studies in relation to the associations between breast cancer risk factors and mammographic parenchymal patterns have mainly been cross-sectional (Bergkvist et al. 1987, Brisson et al. 1988, de Stavola et al. 1990, Beijerinck et al. 1991, Bartow et al. 1995) because the main interest in the studies related to parenchymal pattern has been its association with breast cancer risk, and only prevalences of mammographic patterns have been reported. Only a longitudinal design makes it possible to distinguish the incidence of a new risk pattern from the disappearance of an earlier risk pattern, both of which affect the prevalence, and to identify the direction of potential causality. This would have been possible in other studies but they were content with measuring two prevalences.

6.2 Changes to unfavourable and favourable mammographic parenchymal patterns

According to Wolfe (1976c), the changes in breast pattern occur mainly among women with breasts containing dysplastic tissue (DY). Most of such changes take place towards the category P2 but also towards N1 and P1. These changes usually take place at the age of 35 to 50. Van Gils et al. (1995), by following up women for 12 years, noted that 39% of women with either a P2 or DY pattern at their first examination changed to a N1 or P1 pattern over the years. Higher proportions of a favourable (e.g. N1, P1) mammographic parenchymal pattern with increasing age have been reported in cross-sectional studies (Brisson et al. 1988, de Stavola et al. 1990, Oza and Boyd 1993, Bartow et al. 1995), which is also consistent with our results where age was significantly associated with the incidence of an N1,P1 pattern. The women aged 45 or more had nearly two times higher incidence of favourable mammographic parenchymal pattern than younger women. We also showed that the incidence of a P2,DY pattern decreased by age. Therefore the high prevalence of N1,P1 parenchymal patterns at a high age is not only due to the increase of N1,P1 incidence but also due to the decrease of P2,DY incidence.

Postmenopausal status has been reported to increase the probability of an N1,P1 pattern (Brisson et al. 1988, Oza and Boyd 1993, Bartow et al. 1995), and it has been suggested to be even more closely related to mammographic parenchymal pattern than age (Oza and Boyd 1993, Gram et al. 1995). In our study, the age-adjusted relative incidence of a favourable pattern for menopausal status was close to unity (RR=1.1, 95 % CI 0.9-1.3) and without statistical significance, whereas the age-adjusted risk estimate of unfavourable change for postmenopausal women was statistically significant (OR= 0.6, 95% CI 0.4-0.9). Therefore, the increased prevalence of an N1,P1 pattern by menopausal status rather seems to be due to the decreased incidence of an unfavourable pattern than an increase in the incidence of a favourable pattern, if it is assumed not to be due to age.

Hitherto, information on the association between the mammographic parenchymal pattern and BMI has been based on cross-sectional studies (de Stavola et al. 1990, Beijerinck et al. 1991, Bartow et al. 1995,) which have shown that the proportion of the N1,P1 pattern is more common among women with a high BMI. In our study the crude

and adjusted relative incidence estimates of the N1,P1 pattern were significantly higher among women with a large BMI. Women with a large BMI were statistically significantly at lower risk of P2,DY patterns than women with a low BMI. Thus, not only is the N1,P1 pattern more prevalent among women with a large BMI, but such women with a P2,DY pattern are more likely to become favourable in the pattern than women with a small BMI. Also the incidence of a favourable change was statistically significantly higher among women whose BMI increased between the screenings compared to women whose BMI decreased. The risk of an unfavourable change seemed to be lower among women whose BMI changed (either decreased or increased) between the screenings.

Results from cross-sectional studies have included higher prevalencies of N1,P1 patterns among women with large breasts (Leinster et al. 1988, Bartow et al. 1995, Thurfjell et al. 1996). In our study the crude and age-adjusted risk estimate of both the favourable and unfavourable pattern for the breast size were also statistically significant. However, after further adjustment for BMI, this effect was no more statistically significant, which indicates that overweight is likely to be a more important determinant of mammographic parenchymal pattern than the breast size per se.

The results on breast cancer risk factors other than those directly related to radiolucency have been more contradictory. An association between nulliparity and the P2,DY pattern has been observed in prevalence studies (de Waard et al. 1984, Bergkvist et al. 1987, de Stavola et al. 1990, Kaufman et al. 1991b, Oza and Boyd 1993, Gram et al. 1995). In our study, three or more pregnancies indicated a small but statistically significant increase (RR=1.3, 95 % CI 1.1-1.6) also in the incidence of the N1,P1 pattern compared to nulliparous women. There was no relation between parity and incidence of unfavourable mammographic parenchymal pattern after the adjustment for age.

Brisson et al. (1988) found only a very weak and irregular association between age at first birth and breast pattern, whereas Bergkvist et al. (1987) and Gram et al. (1995), for example, concluded that late age at first birth increased the probability of having a high-risk pattern. Likewise, Bartow et al. (1995) did not find parity related factors to be significant predictors of breast parenchymal pattern. In the present study, no statistically significant association was found between the age at first pregnancy and an

unfavourable parenchymal pattern. However, the incidence of a favourable parenchymal pattern increased with an increasing number of children (RR=1.3, 95% CI 1.1-1.6). In our study after an adjustment for age, there was an increased risk of an unfavourable parenchymal pattern among women who had their menarche at the age of 13 or later compared to women whose age at menarche was 12 or less. However, no linear trend was found with an increasing age. Incidence of favourable parenchymal patterns was not associated with age at menarche.

Stomper et al. (1990) noted that among postmenopausal women undergoing HRT there were mammographic changes consistent with an increase in breast density. Comparing the mammographic parenchymal patterns between mammograms taken before and one year after the initiation of HRT Laya et al. (1995) found that mammographic pattern was more dense compared with baseline values in 73% of subjects undergoing HRT. They also noted a shift in Wolfe's classification from lower to greater parenchymal density in 24% of subjects. Bergkvist et al. (1989) also found that estrogen replacement therapy was more common among women with a high risk than those with a low risk mammographic parenchymal pattern. However, the results of that case-control study did not allow the conclusion that the treatment itself could be responsible for the high proportion of P2,DY patterns. According to Kaufman et al. (1991a), HRT appears to inhibit involutonal process within the breast. Therefore, women undergoing HRT live for a longer period in the status of high risk parenchymal patterns. These studies, however, reported only the prevalences of mammographic parenchymal patterns at the beginning and at the end of the follow-up. In our study, we failed to find any effect of HRT on the incidence of a favourable mammographic parenchymal pattern, but we found that women receiving HRT had a significant two-fold age-adjusted risk of a P2,DY parenchymal pattern. Therefore, our results are consistent with those proposing that women with HRT and an N1,P1 pattern are at an increased risk of a P2,DY pattern. Our results do not, however, support the finding that women with HRT and P2,DY patterns are living longer in the status of a high risk pattern than women with a P2,DY pattern and without HRT.

6.3 Risk of breast cancer

The sequential mammograms enabled us to study the effect of change in the mammographic parenchymal pattern as well as the time between the mammogram and the diagnosis of breast cancer. The mammographic parenchymal pattern changed in general to a more favourable one, and the highest risk was found among women with a persistent high risk pattern. Also van Gils et al. (1999) observed an increased risk of breast cancer among women with consistently dense parenchymal patterns (OR=5.7, 95% CI 2.2-15.2) compared to women with consistently low density patterns. However, a greater risk was observed among women whose density increased during the follow-up (OR=6.9, 95% CI 2.1-22.9). The higher risk estimates in the study by van Gils et al. compared to our results are partly due to their use of a quantitative measure of mammographic density. These two studies confirm that repeated measurements give substantially improved information on the relationship between mammographic parenchymal pattern and breast cancer.

In their reviews, Boyd et al. (1984) and Saftlas and Szklo (1987) concluded that most carefully conducted epidemiological studies support a positive association between the mammographic parenchymal pattern and the risk of breast cancer. Mammographic parenchymal patterns persisted as a risk indicator of breast cancer for 4 (Saftlas et al. 1989) to 10 years (Oza and Boyd 1993). Our results are consistent with those by Carlile et al. (1985), Saftlas and Szklo (1987) and Saftlas et al. (1989) showing that the mammographic parenchymal pattern is an independent risk indicator of breast cancer. Furthermore, we found that the longer the lag between the definition of the breast pattern and the diagnosis of breast cancer, the higher the relative risk.

Low sensitivity (49%) and specificity (65%) of mammographic parenchymal patterns as a criterion for screening compared to validity of mammography screening, which in an organised, nationwide programme in Finland has a sensitivity of 77% (Joensuu et al. 1994) and specificity of 96% (Hakama et al. 1991), do not justify the selective screening based on patterns.

6.4 Joint effect of mammographic parenchymal patterns and HRT on the risk of breast cancer

In our material there was no statistically significant overall effect of HRT on the risk of breast cancer. The hormone exposure was quite common but the time of the actual exposure (use) was short which may partly explain the lack of association. However, HRT among women with a DY mammographic parenchymal pattern affected the risk of breast cancer. There was a statistically significant over 11-fold risk of breast cancer among women with DY patterns and undergoing HRT. The point estimate supports a synergistic joint effect. Our data was small and therefore we cannot totally rule out that in fact the joint effect was multiplicative. However, assuming a multiplicative joint effect, the expected relative risk was 1.5 while the observed one was 11.6. On that basis, our observation supports more the hypothesis of a synergistic than multiplicative joint effect. This association could not be accounted for possible confounders i.e. age, BMI and number of pregnancies which were found in our previous studies to be associated with the incidence of mammographic parenchymal patterns.

Our study is consistent with those showing young age and low weight (i.e. factors inversely related to radiolucency) and HRT to be risk factors for an unfavourable mammographic parenchymal pattern. Other risk factors for breast cancer were not strongly nor consistently related to the incidence of a P2,DY pattern. The incidence of lucent mammographic pattern was related to old age, large BMI and multiparity. Therefore, a change in the mammographic parenchymal pattern either from favourable to unfavourable or vice versa is an indirect indicator of exposures to personal habits (a diet that results in overweight and thus, in a large breast size) and physiological ageing (age that results in menopausal status) which are known or proposed risk factors for breast cancer. Exogenous hormones (HRT) are risk factors in an unfavourable change (incidence of a P2,DY pattern) whereas endogeneous hormonal or reproductive risk factors in breast cancer are related only to a favourable change (incidence of an N1,P1 pattern). Adjusted relative risk of breast cancer among women with high risk patterns (P2,DY) was almost three times higher than among women with low risk patterns (N1,P1). The risk increased to almost 12 when taking into account the joint effect of the

use of HRT and DY mammographic parenchymal pattern.

These results should be confirmed using a modern digitalised technology which allows more objective assessment of mammographic patterns and which is also more insensitive to variations in mammographic techniques.

7 Summary

Population-based pilot screening material (n=4090) from Kotka area was used to evaluate the effect of breast cancer risk factors on the change of mammographic parenchymal patterns and the association of those patterns with the risk of breast cancer. Women under study were 40-47 years old at the entry and were invited to be screened every other year from 1982 to 1990. In each screening round information on breast cancer risk factors was recorded and Wolfe's classification of breast pattern based on mammography was applied. The follow-up was extended up to 1993 for the diagnosis of breast cancer. Logistic regression (I), Cox proportional hazard model (II; III) and Poisson regression model (IV) were used in the analysis of the data.

The change to an unfavourable pattern (i.e. P2,DY) by breast cancer risk factors was estimated by using the data of 1890 women with a mammographic pattern either N1 or P1 at the initial screening. The incidence of an unfavourable pattern was 1.9/100 woman years. After age-adjustment, the risk of change was 2.0 (95% CI 1.0-3.9) among women with hormonal replacement therapy (HRT), 0.6 (95% CI 0.4-0.9) among postmenopausal women, 0.2 (95% CI 0.1-0.4) among women with large breasts and 0.2 (95% CI 0.1-0.3) among women with a large BMI. After multivariate adjustment only the effect of BMI remained statistically significant with risk of 0.2 (95% CI 0.1-0.6) for women with a BMI 25 or more compared to women with a BMI less than 20. (I)

The change to a favourable pattern (i.e. N1,P1) by breast cancer risk factors was estimated by using the data of 1947 women whose mammographic parenchymal pattern at the initial screening was unfavourable (either P2 or DY in Wolfe's classification). The incidence of favourable transition was 12.5/100 woman years and it was significantly related to old age, large body mass index (BMI) and multiparity. The relative risk of N1,P1 pattern adjusted for other risk factors for women aged 45 years or more was 1.7 (95% confidence interval (CI) 1.5-1.9) compared to younger women. The adjusted relative risk of N1, P1 pattern among women with a BMI of 25 or more was 2.1 (95% CI 1.6-2.8) compared to women with a BMI of less than 20; women with more than 2 pregnancies had a 30% higher adjusted relative risk (RR=1.3, 95% CI 1.1-1.6) than women with no pregnancies. (II)

The relationship between a sequential mammographic parenchymal pattern and breast cancer was estimated and the results were applied to selective screening using the whole data set. The age-adjusted relative risk of breast cancer was 2.5 (95% CI 1.7-4.9) among women with high risk mammographic parenchymal patterns (P2,DY) at the screening preceding cancer diagnosis compared to women with low risk patterns (N1,P1). Further adjustment for BMI, number of pregnancies and size of the breast increased the risk to 2.8 (95% CI 1.7-4.9). If the mammographic P2,DY patterns had been used for selective screening the sensitivity would have been 49% and specificity 65%. (III)

Finally, the joint effect of the mammographic parenchymal pattern and HRT on the risk of breast cancer was evaluated. The use of HRT was not related to the risk of breast cancer (RR=0.7, 95% CI 0.4-1.4) whereas, the mammographic parenchymal pattern was significantly associated with the risk of breast cancer. The age-adjusted relative risk of breast cancer among women with a P2 versus N1 pattern was 2.5 (95% CI 1.3-4.8) and with a DY versus N1 pattern 4.9 (95% CI 1.6-15.1). Women using HRT and with a DY pattern were at substantially increased risk of breast cancer (RR=11.6, 95% CI 2.5-53.6) compared to women not using HRT and with an N1 pattern. However, the synergistic interaction was not statistically significant compared to the expected multiplicative effect. (IV)

As a conclusion, the change in the mammographic parenchymal pattern is an indirect indicator of exposures to personal habits and physiological ageing which are known or proposed risk factors for breast cancer. Exogenous hormones (HRT) are a risk factor for unfavourable change whereas endogenous hormonal or reproductive risk factors for breast cancer are related only to favourable change. Furthermore, the mammographic parenchymal pattern is also an independent risk factor for breast cancer but it is not strong enough to be used as a criterion for selective screening. The results related to a high risk of breast cancer among women with high risk patterns and using HRT should be confirmed by other studies before concluding whether the DY mammographic parenchymal pattern can be considered as a contraindication of HRT.

8

Acknowledgements

The present study was carried out at the Tampere School of Public Health, the Finnish Cancer Registry and the STUK - Radiation and Nuclear Safety Authority.

I would like to express my warm gratitude to my supervisor Professor Matti Hakama, D.Sc., Director of the Tampere School of Public Health, University of Tampere for his guidance, support and most of all patience. You have given me many valuable lessons.

Sincere thanks are due to Docent Ahti Anttila, Ph.D. and radiologist, Docent Tapani Tikkakoski, M.D., Ph.D. for their constructive criticism and careful review of the manuscript.

I want to thank the Cancer Society of Finland, the Kymenlaakso Cancer Society and the Kotka Screening Committee. I am grateful especially to radiologist Ulla Svinhufvud, M.D., radiologist Kari Godenhjelm, M.D. and Ms Marita Nenonen as well as to all women participating in the Kotka pilot screening programme. You made this study possible.

This work gave me the possibility to get to know two marvellous women radiologist Irma Saarenmaa, M.D. and Ms Minna Heikkilä who also were my co-authors. Thank you for your help and support. I really enjoyed working, discussing and also having fun with you.

I am thankful to Ms Marita Hallilla for technical advice in the final preparation of thesis, Raili Salmelin, Ph.D. for the help with the figures and Mr Bengt Söderman and Mr Esko Voutilainen for the help with data processing.

My good friend Katja Mäntylä, M.A. deserves sincere thanks for revising the English language of the thesis.

I want to thank the personnel of the Tampere School of Public Health, the Finnish Cancer Registry and the Pirkanmaa Cancer Society. You always made me feel welcome.

I am very grateful to my friends for their continuous support in all stages. Our conversations on everything under the sun gave me faith and strength to finish this thesis. Thank you for being there.

My mother I want to thank for love, support and care. I also wish to thank my sister Tarja and her family for reminding me about what is important in life.

The financial support of Doctoral Programs in Public Health, the Pirkanmaa Cancer Society, Finnish Cancer Organisations, Foundation for the Finnish Cancer Institute and the Scientific Foundation of the City of Tampere is gratefully acknowledged.

Tampere, August 2000

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