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DIET, BODY SIZE, AND RISK OF BREAST CANCER

A case-control study

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Contents

Abstract

Männistö S. Diet, body size and risk of breast cancer - a case control study (dissertation). Helsinki: National Public Health Institute, 1999.

Breast cancer is the most important female malignancy in the industrialized countries, and in recent decades its incidence has consistently increased. This development can in part be explained by hormonal and reproductive factors. However, no realistic preventive strategy for decreasing the high incidence of breast cancer exists at present. Useful risk factors which women themselves could influence include, for example, dietary habits, alcohol consumption and obesity.

The main aim of this study was to investigate whether food consumption, nutrient intake, lifetime alcohol consumption, toenail selenium concentration, and body-size indicators were associated with risk of premenopausal and postmenopausal breast cancer. This case-control study is a part of the Kuopio Breast Cancer Study, which is a multi-disciplinary collaborative project conducted by the University of Kuopio, Kuopio University Hospital, and the National Public Health Institute in Helsinki.

The Kuopio Breast Cancer Study included all women (n=1919) who were referred to the Kuopio University Hospital for further breast examination between 1990 and 1995. Of them, 516 were diagnosed as having breast cancer, and 686 were diagnosed as healthy (=referral controls). Women with benign breast disease (n=717) were excluded. Population controls (n=663) were drawn from the National Population Register. About 310 breast cancer cases, 440 population controls and 500 referral controls, aged 25-75, years participated in the dietary studies. In all, 97% of breast cancer cases, 72% of population controls and 99% of referral controls were willing to participate in the Dietary Study. The final participation rates after exclusion were 81%, 68%, and 92%, respectively.

A validated self-administered food frequency questionnaire (FFQ) and an interview-based questionnaire on lifetime alcohol consumption (AQ) were used. Population controls (n=152) who were recruited to the Validation Study filled in a 14-day diet record, which was used as a reference for the FFQ. In addition to the FFQ and the AQ, body-size indicators (e.g., height, weight, waist and hip circumferences) were measured, a sample of toenail clippings was collected, and general information was obtained on socioeconomic background, medical history, reproductive factors, and lifetime habits. All this information was collected before the subject's diagnosis was known.

Based on comparisons between the breast cancer cases and the population controls, waist-to-hip ratio was found to be a better marker for breast cancer risk than body mass index. Premenopausal women in the highest quintile for waist-to-hip ratio had a 4.6-fold risk (95% CI 2.0-10.7) of breast cancer compared to women in the lowest quintile. The corresponding relative risk for postmenopausal women was 2.6 (95% CI 1.3-5.1). Height and high body fat percent (near-infrared interactance) were also associated with an increased risk of breast cancer, especially in postmenopausal women (OR 2.3, 95% CI 1.1-4.6; OR 2.0, 95% CI 1.0-4.0, respectively).

When recall bias was taken into account after comparison of the referral controls with the population controls (the highest vs. lowest quintile), high consumption of milk (OR 2.2, 95% CI 1.0-4.9) tended to increase the risk, and that of poultry (OR 0.4, 95% CI 0.2-0.9) decrease the risk of premenopausal breast cancer. High consumption of oil (OR 0.4, 95% CI 0.2-0.8) decreased the risk in postmenopausal women while consumption of cream (OR 1.9, 95% CI 1.0-4.0) increased the risk. High intake of n-3 polyunsaturated fatty acids (OR 0.3, 95% CI 0.1-0.6), n-6 polyunsaturated fatty acids (OR 0.4, 95% CI 0.2-0.8), and vitamin E (OR 0.5, 95% CI 0.2-1.0) decreased premenopausal breast cancer risk, whereas beta-carotene (OR 0.5, 95% CI 0.2-1.0) decreased postmenopausal breast cancer risk.

Current and past alcohol consumption were not associated with an increased risk of breast cancer, but the consumption levels were too low to exclude increased risk with high regular consumption. No association was also found between toenail selenium concentration and risk of breast cancer.

In summary, high waist-to-hip ratio was a clear risk factor for breast cancer both in premenopausal and postmenopausal women. Dietary factors did not play an important role in the occurrence of breast cancer. However, a dietary pattern characterized by high intake of oil, unsaturated fatty acids, vitamin E, and beta-carotene seemed to be protective factors against breast cancer.

List of original publications

This dissertation is based on the following original publications which are referred to by their Roman numerals (I-V) in the text:

I   Männistö S, Pietinen P, Pyy M, Palmgren J, Eskelinen M, Uusitupa M. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. Int J Cancer 1996;68:8-13.

II   Männistö S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. J Clin Epidemiol 1996;49:401-409.

III   Männistö S, Pietinen P, Virtanen M, Kataja V, Uusitupa M. Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias? J Clin Epidemiol 1999;52:429-439.

IV   Männistö S, Virtanen M, Kataja V, Uusitupa M, Pietinen P. Lifetime alcohol consumption and breast cancer - a case-control study in Finland. Public Health Nutrition (In press).

V   Männistö S, Alfthan G, Virtanen M, Kataja V, Uusitupa M, Pietinen P. Toenail selenium and breast cancer - a case-control study in Finland. Eur J Clin Nutr (In press).

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1. Introduction

Breast cancer is the most common cancer among women in the industrialized countries (WHO 1997). In Finland, breast cancer incidence has increased considerably during the last decades, accounting currently for one-third of the total cancer incidence in women (Finnish Cancer Registry 1997). In 1995, the number of new breast cancer cases was 3125, three times the number in the late 1960s. This trend toward an increase is expected to continue to the period 2008-2012, when 3860 new cases per year are predicted (Engeland et al. 1993). This trend is mainly explained by an increase in the number of elderly women in the population and strengthening of the effects of risk factors for breast cancer.

In spite of the increasing incidence, breast cancer mortality has remained largely unchanged because of improvements in diagnostic and treatment methods (see Harris et al. 1992). For example, the Finnish nationwide screening program since 1987 has decreased the breast cancer mortality of the participants by 24% (Hakama et al. 1997). In 1995, the number of deaths caused by breast cancer among Finnish women was 838 (Finnish Cancer Registry 1997).

A woman whose first-degree relative has had breast cancer is at increased risk herself (Hulka and Stark 1995). This risk is even higher if more than one first-degree relative has had breast cancer and if the cancer was diagnosed before the age of 60. In these situations, the estimated risk for breast cancer is two- to six-fold compared to women without a family history (see Harris et al. 1992). The discovery of the BRCA1 and BRCA2 tumor-suppressor genes in the 1990s has been an important milestone in breast cancer research (Miki et al. 1994, Wooster et al. 1994). Mutations in BRCA1 may account for 45% of the hereditary breast cancer, and almost all of hereditary cases in families with combined breast and ovarian cancer (Easton et al. 1993), while about 30% of high-risk breast cancer families are carriers of BRCA2 mutations. The initial estimates of the lifetime risk of breast cancer in BRCA1/BRCA2 carriers based upon studies in selected cancer-prone families were rather high, up to 84% by the age of 70 years (Ford et al. 1998). It has been estimated that inherited forms of breast cancer explain only 5% of all cases (Eeles et al. 1994). In Finland, however, low proportions of BRCA1 and

BRCA2 mutations (altogether 21%) were found in breast cancer families (Vehmanen et al. 1997a, Vehmanen et al. 1997b). More evidence is needed for other susceptibility genes.

The constant increase in breast cancer incidence, geographical variation in breast cancer occurrence, and migrant studies offer evidence that risk factors other than genetic susceptibility exist. The known risk factors for female breast cancer, such as early menarche, late first full-term pregnancy, low number of births, and late menopause, are associated with endogenous hormones (Hulka and Stark 1995, World Cancer Research Fund 1997). There is also evidence that exogenous hormonal treatments, such as oral contraceptives or postmenopausal estrogen replacement therapy, may increase the risk, but the findings are inconclusive (Collaborative Group on Hormonal Factors in Breast Cancer 1996, Willis et al. 1996, Collaborative Group on Hormonal Factors in Breast Cancer 1997, Grodstein et al. 1997, Hankinson et al. 1997).

High hormone level, especially that of estrogens, plays a major role in the promotional phase of breast carcinogenesis by stimulating, together with other growth factors, the division and growth of breast tumor cells (Lipworth 1995). Insulin and insulin-like growth factor I (IGF-I) have also received attention as potential biological factors in the development of breast cancer (Del Giudice et al. 1998, Hankinson et al. 1998). Insulin and IGF-I decrease the level of blood sex hormone-binding globulin, and thus increase the level of bioavailable estrogens. It seems that these two substances may explain some of the observed associations between dietary factors and breast cancer. For example, high fat intake has been indicated as enhancing insulin resistance and increasing the level of insulin and insulin-like growth factors (see Stoll 1996). These associations may be explained by free fatty acids that affect insulin-signaling mechanisms and reduce insulin binding (Smith 1994).

The known risk factors have been estimated to explain less than half of the sporadic breast cancer (see Hankin 1993). Thus, some other factors, such as dietary factors and alcohol, may be related to its development. Doll and Peto (1981) reported that diet accounts for 10-70% of all cancer deaths in the United States, but revised the range to 20-60% in the early 1990s (Doll 1992). An expert panel has recently estimated that high vegetable consumption, regular physical activity, abstinence from alcohol, and maintenance of normal

body weight may prevent more than 33% of breast cancer cases (World Cancer Research Fund 1997). However, only high alcohol consumption has consistently been associated with an increased risk of breast cancer, whereas the results for other dietary factors have been inconclusive. Genetic and hormonal factors are more often related to premenopausal breast cancer, whereas environmental factors are related to postmenopausal breast cancer (Henderson and Patek 1997).

This dissertation summarizes the results of associations between dietary factors, total lifetime alcohol consumption, toenail selenium concentration, body-size indicators, and risk of breast cancer in the Kuopio Breast Cancer Study. This case-control study was carried out in eastern Finland, where breast cancer incidence is somewhat lower than in southern or southwestern Finland. Dietary habits have been quite traditional in the east compared to the more modern habits of southern Finland, although the differences are diminishing rapidly. This study belongs to the field of nutritional epidemiology, which means that methods of nutrition science and cancer epidemiology were utilized in the analyses. All the patients were subjected to normal diagnostic procedures including clinical examination with inspection and palpation, radiological examinations (mammography or ultrasonography), and fine needle, core needle, or surgical biopsy, if necessary. In addition, the cytopathological or histopathological diagnoses were made according to the current practice at Kuopio University Hospital.

2. Diet, body size, and breast cancer

A number of reviews on the associations between diet, obesity and risk of breast cancer have been published during recent years (Hunter and Willett 1996, Steinmetz and Potter 1996, Kohlmeier and Mendez 1997). Thus, the purpose of this section is not to offer an exhaustive review on the topic. Instead, the emphasis is on background to aid the reader in understanding the contents of Studies I-V presented in this dissertation.

2.1 Diet and carcinogenesis

Cancer is a cell disorder in which the structure and function of genetic information coded in the DNA have changed. Such a malignant transformation may increase the capacity of cells to grow rapidly in an uncontrolled manner, producing abnormal growth. Although more than a hundred cancer types have been identified, the basic causes of tumor development seem to be quite similar. The model of chemical carcinogenesis and the role of diet in this process are briefly presented below. The presentation is based mainly on the following publications: Sorsa (1985), Weinberg (1996), and the World Cancer Research Fund (1997).

Covalent binding of the chemical carcinogen with DNA appears to be the most important event in carcinogenesis. Several well-known carcinogens have been identified, such as cigarette smoke, and exposures in the diet and workplaces (Figure 1). These factors may cause direct DNA damage (e.g., tobacco), or it is possible that procarcinogens (e.g., N-nitroso compounds in the diet) are converted into carcinogens through normal metabolic pathways. The common feature of many chemical carcinogens is that they are strong electron-deficient molecules (electrophilic), which react easily with electron-rich molecules such as proteins and DNA. The electrophilic metabolite that binds to cellular DNA is termed an "ultimate carcinogen" (Simic and Bergtold 1991). The enzymatic biotransformation processes (phase I enzymes, including the cytochrome P450 system) tend to make foreign chemicals more water-soluble so that they can be excreted in urine, but at the same time enzymes may change a particular chemical to a reactive form that binds to DNA. Phase II detoxification enzymes, found especially in plant
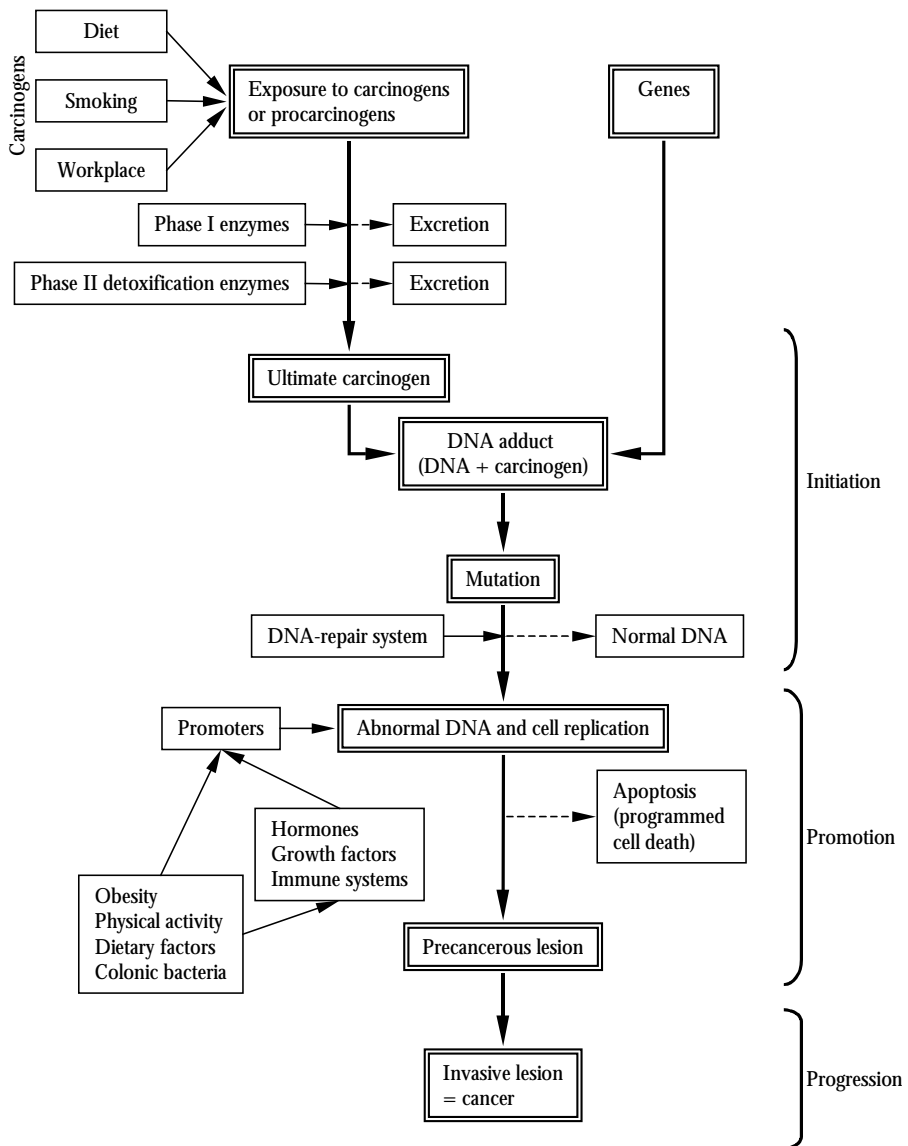
Figure 1. Model of chemical carcinogenesis (adapted from Sorsa 1985, World Cancer Research Fund 1997).

compounds, may prevent tumor development by detoxifying carcinogens in the diet.

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Although there is no clear evidence of the multistep carcinogenic process in the mammary epithelial cells, many chemical carcinogens that are lipophilic substances (e.g., heterocyclic amines) can be stored in the adipose tissue of the breast (Morris and Seifter 1992, Ghoshal and Snyderwine 1993). It has also been suggested that hormones stimulate mitotic division of initiated cells at a promotional stage of breast carcinogenesis.

The three stages of carcinogenesis (initiation, promotion, and progression) have been demonstrated in animal models. In human cancer development, these stages are not necessarily sequential, and they may overlap. When the probability of cancer is assessed, the balance between factors that induce or prevent mutations is important.

Dietary factors may affect carcinogenesis in different ways. Natural carcinogens in the diet (e.g., aflatoxins in moldy nuts) and substances formed by metabolism (e.g., N-nitroso compounds in protein rich food) or cooking (e.g., heterocyclic amines and polycyclic aromatic hydrocarbons) may increase risk of cancer. Other substances mainly derived from plant compounds, such as phytochemicals and compounds found in the cabbage family (Steinmetz and Potter 1996), inhibit the development of cancer by increasing metabolic detoxification. Dietary fiber enhances the passage of materials and waste products through the intestine, thus in theory decreasing the risk of colon cancer. Some dietary factors, such as fat or energy intake, have been found to induce tumor promotion, whereas selenium and vitamin D may have protective effects. Evidence of the role of obesity in promotion of cancer has been obtained in studies on breast, endometrium, colon, and kidney cancer. The role of the diet is not clear in the DNA-repair system and progression.

2.2 Body size and energy

A modest positive association between height and risk of breast cancer was shown in a review of eight cohort studies (Hunter and Willett 1996). The largest of these studies, including 570,000 Norwegian women, found that height was significantly directly related to breast cancer incidence in all women and to mortality in women over 50 years of age (Tretli 1989). These results were not, however, adjusted for the known risk factors for breast cancer. In the Nurses' Health Study, postmenopausal women over 168 cm had a slightly higher risk of breast cancer (OR 1.3, 95% CI 1.0-1.7) than

women under 160 cm (London et al. 1989). The review also included two cohort studies from the Netherlands, which found contradictory results. The first one from the 1970s showed a two-fold increase in the risk of postmenopausal breast cancer for each 15 cm difference in height (de Waard and Baanders-van Halewijn 1974), while the more recent study found no relationship between adult height and risk of postmenopausal breast cancer (den Tonkelaar et al. 1994). The multiethnic cohort study in Hawaii, not included in the review by Hunter and Willett (1996), found that risk of breast cancer increased linearly across the tertiles of height in postmenopausal women but not in premenopausal women (Galanis et al. 1998). In case-control studies, a positive association has been reported (Kalish 1984, Swanson et al. 1996) as well as results close to no association (Zhang et al. 1996).

One explanation for the relationship between height and risk of breast cancer is that height reflects the energy balance in youth (see de Waard and Trichopoulos 1988). Animal studies have strongly supported the hypothesis that energy restriction reduces the occurrence of mammary tumors, as reviewed by Welsh (1994). In a Norwegian cohort study, tallness seemed to be a risk factor for breast cancer only in women who lived their pubertal period during World War II, thus suggesting that a remarkable energy restriction in a critical growth period may decrease the lifetime risk of breast cancer (Vatten and Kvinnsland 1990). Another possible explanation is that the tallest girls mature and experience menarche earlier than do shorter girls. Early menarche has been related to increased risk of breast cancer by three biological pathways: regular menstrual cycles at earlier ages, high total lifetime estrogen levels, and earlier onset of hyperinsulinemia (Kelsey et al. 1993, Stoll 1998). However, no relationship between diet and age at menarche was found among girls in two cohort studies in Canada and the United States (Moisan et al. 1990, Maclure et al. 1991). On the other hand, diets rich in fat and low physical activity were associated with early menarche in a German cohort study (Merzenich et al. 1993). In all these three studies, height, weight, and obesity were inversely associated with early menarche.

Although most case-control studies have found no statistically significant association between obesity and risk of premenopausal breast cancer (see the World Cancer Research Fund 1997), an apparent inverse association (RR=0.69, p=0.0002) was summarized in a meta-analysis of 12 case-control

studies when body mass index between the highest and lowest quintile was 10kg/m² (Howe et al. 1990). Based on another meta-analysis, including 19 case-control studies, the estimated risk was 0.88 for premenopausal women (95% CI 0.76-1.02) for a BMI difference of 8kg/m² (Ursin et al. 1995). Cohort studies, mostly carried out in the Scandinavian countries or in the United States, have found obesity to be associated with decreased risk of premenopausal breast cancer (Le Marchand et al. 1988, Tretli 1989, Vatten and Kvinnsland 1992, Törnberg and Carstensen 1994, Huang et al. 1997). No association, however, appeared in a recent cohort study in the United States (Yong et al. 1996).

Obesity has been positively associated with increased occurrence of postmenopausal breast cancer in case-control studies (see Howe et al. 1990, World Cancer Research Fund 1997). However, because the results of cohort studies have been contradictory, it has been concluded that obesity does not seem to be among the major risk factors for postmenopausal breast cancer (Swanson et al. 1988, London et al. 1989, Tretli 1989, Ballard-Barbash et al. 1990, Törnberg and Carstensen 1994, Yong et al. 1996, Kaaks et al. 1998). A cohort study in Hawaii indicated that the association between obesity and breast cancer was strongest for women aged 65 years or more (Galanis et al. 1998).

The inverse association between obesity and premenopausal breast cancer may be explained by anovulatory menstrual cycles more common in obese women. Infrequent ovulatory cycles have been related to low breast cancer incidence (see Pike 1990). For example, it has been found that women with a body mass index between 18 and 23 kg/m² have the lowest anovulatory infertility (Rich-Edwards et al. 1994). In obese postmenopausal women, the level of endogenous estrogens remains high because of the conversion of androgens to estrogens in adipose tissue (Ballard-Barbash 1994). High body mass index at younger ages may also protect against breast cancer after menopause (Willett 1998).

It seems that body mass index cannot entirely explain the association between obesity and risk of breast cancer. Some other factors, such as adult weight gain and body fat distribution, were assumed to be more informative as regarding sex-steroid metabolism, glucose metabolism and insulin-like growth factors (Ballard-Barbash 1994, Stoll 1996). In the Nurses' Health

Study, weight gain after the age of 18 increased the risk of breast cancer (Huang et al. 1997). The relative risk in this study was 1.99 (95% CI 1.43-2.76) for postmenopausal women who had gained more than 20 kg in weight but never used postmenopausal estrogen replacement therapy. A high waist-to-hip ratio has also been associated with increased risk of breast cancer in some studies (Ballard-Barbash et al. 1990, Folsom et al. 1990, Kaaks et al. 1998).

2.3 Fat

The leading dietary hypothesis about breast cancer until the mid-1980s was that high fat intake increases the risk of breast cancer. This hypothesis was based mainly on animal and ecological studies (Hunter et al. 1996).

Since the 1940s, animal studies have shown that high fat intake is associated with development of spontaneous breast tumors as well as those induced by chemicals (Tannenbaum 1942). In general, n-6 polyunsaturated fatty acids have been shown to be more potent in promoting mammary tumors than saturated fatty acids, whereas n-3 polyunsaturated fatty acids may even inhibit breast tumors (Wynder et al. 1994, Fay and Freedman 1997). However, if the required level for linoleic acid was achieved, only a small additional effect of polyunsaturated fatty acids on breast cancer appeared (Ip 1987).

Animal studies have been criticized because many of them have not considered energy intake in high-fat diets. Some recent studies, however, have shown that energy restriction may be more efficient in inhibiting mammary carcinogenesis than is fat restriction (Ip 1993). In a large experimental study including over 10,000 rats and mice, the daily dose of corn oil was fed at different levels of fat and energy intake, but no marked differences were found in mammary tumor incidence (Appleton and Landers 1986). Three meta-analyses of animal studies did not achieve any agreement whether or not the effect of fat intake is independent of total energy intake (Birt 1986, Albanes 1987, Freedman et al. 1990).

Ecological studies have shown a strong correlation between fat consumption and breast cancer incidence and mortality (r=0.7-0.9) (Armstrong and Doll 1975, Rose et al. 1986, Hursting et al. 1990), and the relationship has remained statistically significant after adjustment for the known risk factors

(Prentice et al. 1988). An ecological study of 65 Chinese counties where the fat intake ranged from 6% to 25% found a weaker correlation between fat consumption and breast cancer mortality in postmenopausal women (r=0.4, p<0.10) (Marshall et al. 1992).

The results of case-control studies have been inconsistent. Some of them - but not all - have shown an increased risk of breast cancer with high fat intake (see the World Cancer Research Fund 1997). When studies were stratified by geographical location, the association between fat and breast cancer was stronger in Europe (OR 1.45, 95% CI 1.26-1.67) than in North America (OR 1.00, 95% CI 0.90-1.11) or other places (OR 1.01, 95% CI 0.85-1.20) (Boyd et al. 1993). The authors suggested that the difference in results between Europe and North America may be caused by larger variation in fat intake in Europe. A meta-analysis of 12 case-control studies indicated a statistically significant increase in risk of postmenopausal breast cancer when fat intake was high (OR 1.46 for a 100 g increase in daily fat intake, p<0.0001) (Howe et al. 1990). This meta-analysis did not include the large case-control study (2,024 breast cancer cases) conducted in the United States, which found no increase in the risk with high fat intake (Graham et al. 1982). On the other hand, a recent case-control study in Italy, including 2,569 breast cancer cases, reported an inverse association (p=0.01) (Franceschi et al. 1996). This association could be explained by unsaturated fatty acids, and possibly their high correlation with the consumption of raw vegetables.

Total fat intake was not associated with the risk of breast cancer in a pooled analysis of seven cohort studies including 4,980 cases from 337,819 recruited women (Hunter et al. 1996). The energy-adjusted relative risk for the highest quintile of fat intake was 1.05 (95% CI 0.94-1.16). It should be noted that all these cohorts were carried out in Western countries, where fat intake is rather high: four in the United States (Mills et al. 1989, Graham et al. 1992, Kushi et al. 1992, Willett et al. 1992), one each in Canada (Howe et al. 1991a), the Netherlands (van den Brandt et al. 1993), and Sweden (Holmberg et al. 1994). In the Nurses' Health Study (Willett et al. 1992), the relative risk for the highest versus lowest quintile of fat intake was 0.96 (95% CI 0.73-1.26) in premenopausal and 0.91 (95% CI 0.73-1.14) in postmenopausal women. It has been criticized that the follow-up times of the cohort studies (on average five years) have not been long enough to cover the latent period between exposure and the disease (Kushi et al. 1992). However, no differences

between fat intake and risk of breast cancer were found after 4, 8, 12, and 14 years of follow-up in the Nurses' Health Study (Willett et al. 1987a, Willett et al. 1992, Willett 1998, Holmes et al. 1999).

As a consequence of the null findings in cohort studies, it has been suggested that, in the development of breast cancer, the type of fat may be more relevant than its total amount. In particular, high consumption of olive oil has been associated with decreased risk of breast cancer in the Mediterranean countries (Landa et al. 1994, Martin-Moreno et al. 1994, La Vecchia et al. 1995, Trichopoulou et al. 1995). This association may be explained by monounsaturated fatty acids rich in olive oil. A 4-year follow-up study in Sweden indicated an inverse association with monounsaturated (OR 0.45, 95% CI 0.22-0.95) but a positive association with polyunsaturated fatty acids (OR 1.69, 95% CI 1.02-2.78) (Wolk et al. 1998). That study comprised 674 breast cancer cases among 61,471 women between 40 and 76 years of age. As mentioned, n-3 polyunsaturated fatty acids have also been related to a lower risk of breast cancer in animal studies (see Wynder et al. 1994). The low rates of breast cancer in Alaskan Eskimos (Lanier et al. 1989) and in Norwegian fishermen's wives (Lund and Bønaa 1993) support the hypothesis that also a diet rich in fish may protect against human breast cancer. Epidemiological studies, in general, have not related n-3 polyunsaturated fatty acids or fish consumption to the risk of breast cancer (Willett 1997). Two case-control studies have analyzed the association between trans-fatty acids in adipose tissue and risk of postmenopausal breast cancer. The EURAMIC study showed an increased risk of postmenopausal breast cancer (OR 1.40, 95% CI 1.02-1.93) between the highest and lowest quartile of trans-fatty acids in adipose tissue (Kohlmeier et al. 1997). Another study in the United States found no association between trans-fatty acids in adipose tissue and risk of breast cancer (London et al. 1993).

Epidemiological studies have been inconsistent in their findings concerning specific high-fat foods and risk of breast cancer. Meat has been found to be a risk factor for breast cancer in some studies (Vatten et al. 1990a, Toniolo et al. 1994, Gaard et al. 1995) but not in all (Ambrosone et al. 1998). In a meta-analysis of cohort and case-control studies by Boyd (1993), a weakly increased risk of breast cancer was found for subjects who consumed a lot of meat, milk, and cheese. None or an indirect association has been found in

studies not included in the meta-analysis (van't Veer et al. 1989a, Toniolo et al. 1994).

Although the metabolic effects of fat on the development of breast cancer have not been completely understood, various mechanisms have been proposed. One explanation for the relationship may be that the level of circulating estrogens has been shown to correlate positively with fat intake (Wynder et al. 1994). In a randomized trial, serum estradiol concentration decreased after 6 months on a low-fat diet in postmenopausal women whose baseline estradiol concentration was high (Rose et al. 1993). Further, it has been found that vegetarian women had lower serum estrogen than did non-vegetarians (Goldin et al. 1982, Prentice et al. 1990). Increased exposure to estrogen may enhance risk of breast cancer by stimulating the division of tumor cells (Lipworth 1995). Fat may also affect free-radical reactions, membrane alterations, immune responses, and activation of oncogene expression (see Hankin 1993, Wynder et al. 1994). Animal studies have shown that high fat intake has more effect on promotion than on initiation of carcinogenesis (World Cancer Research Fund 1997).

2.4 Dietary fiber

Fibers are complex carbohydrates which can be classified into two groups according to whether they are soluble or insoluble in water (Weisburger et al. 1993). Important dietary sources of water-soluble fibers are fruit, vegetables, and certain grains, such as oats, whereas the main source of water-insoluble fibers is cereal grains. A high amount of fiber in the diet inhibits the intestinal reabsorption of estrogen excreted in bile, and thus it may be a protective factor for breast cancer. An experimental study in premenopausal women indicated that the level of serum estrogen sulfate was 36% lower in a low-fat high-fiber diet than in the diet usually consumed in industrialized countries (Woods et al. 1989).

In two cohort studies conducted in the United States (Graham et al. 1992, Willett et al. 1992), high fiber intake was not associated with a decreased risk of breast cancer, whereas a cohort study in Canada showed an inverse association between fiber intake and breast cancer risk (RR=0.68, 95% CI 0.46-1.00, the highest vs. lowest quintile) (Rohan et al. 1993). In the same way, a recent case-control study in New York associated high fiber intake

(the highest vs. lowest quartile) with a decreased risk of breast cancer in women aged 40 or over (OR 0.52, 95% CI 0.32-0.85) (Freudenheim et al. 1996). The association with fruit and vegetable fiber was more relevant (OR 0.48, 95% CI 0.30-0.78) than that with cereal fiber (OR 1.03, 95% CI 0.64-1.65). Case-control studies in southeast England failed to find any relationship for dietary fiber (Cade et al. 1998).

There is a general consensus that diet with high fruit and vegetable content is related to a lower than average occurrence of cancer, although the evidence is not consistent for hormone-related cancers (Block et al. 1992a, Steinmetz and Potter 1996). According to a review by Steinmetz and Potter (1996), 69% of the studies on breast cancer found an inverse association for at least one fruit or vegetable. A relatively low breast cancer mortality has also been found in vegetarians (Frentzel-Beyme et al. 1988), although the duration of membership in the Seventh-day Adventist church (mainly vegetarians) was not related to breast cancer incidence (Mills et al. 1989). Other dietary components besides fiber may also explain the observed inverse association, for example, fruit and vegetables include plenty of anticarcinogenic substances, such as antioxidants, flavonoids, folic acid, and isoflavones (Steinmetz and Potter 1996).

The relatively low incidence of breast cancer in Japanese women has attracted attention to phytoestrogens in soybean. Phytoestrogens have been shown to change estrogen metabolism in the gut, and thus to reduce the amount of free estradiol in blood. Because the structure of phytoestrogens resembles that of estrogens, they may also act as weak estrogens (on average 0.1% of normal estrogen activity) and compete with estradiol of target receptors. At the same time, phytoestrogens may increase the synthesis of serum sex hormone-binding globulin in the liver (Adlercreutz and Mazur 1997, World Cancer Research Fund 1997). In Finland, the most important sources of phytoestrogens are rye products rich in enterolactone. High consumption of rye bread has been suggested as explaining the difference between breast cancer incidence in Finland and the United States (Adlercreutz and Mazur 1997). Many animal studies have supported the hypothesis that phytoestrogens may prevent the development of breast cancer (Messina et al. 1994). Furthermore, one case-control study including 144 Australian breast cancer cases showed that women with high urinary

excretion of enterolactone and equol had a 60% lower risk of breast cancer than did women with low excretion (Ingram et al. 1997).

2.5 Vitamin A

Vitamin A is a lipid-soluble vitamin the chemical name of which is retinol. It is obtained directly from animal sources and indirectly from fruit and vegetables as carotenoids with provitamin A activity (for example beta-carotene), and carotenoids can be partially converted to retinol in the intestine. However, in dietary studies the variable "retinol" usually means retinol only from animal sources. Vitamin A may regulate differentiation of epithelial cells (Steinmetz and Potter 1996), inhibit cell proliferation (Phillips et al. 1993), and enhance cell-to-cell communication (Wolf 1994) and immune responses (Krinsky 1991). Beta-carotene is also a potent antioxidant, which may protect against free radicals (Steinmetz and Potter 1996). All these biological functions have been related to cancer pathogenesis.

Findings concerning the association between vitamin A intake and risk of breast cancer are mainly based on epidemiological studies. A weak protective effect for high vitamin A intake was found in some (Hunter et al. 1993, Rohan et al. 1993) but not all cohort studies (Graham et al. 1992, Kushi et al. 1996). Vitamin A supplements were found beneficial only in women with diets low in vitamin A (Hunter et al. 1993). Although it has in general been assumed that high beta-carotene intake may be more protective than retinol intake in the development of breast cancer, the women in the Nurses' Health Study in the highest quintile of retinol intake had a 20% reduction in risk of breast cancer, whereas no significant reduction was found for beta-carotene (Hunter et al. 1993).

A multinational case-control study conducted in Northern Ireland, Germany, the Netherlands, Spain, and Switzerland found no association between beta-carotene in adipose tissue and postmenopausal breast cancer (van't Veer et al. 1996). In fact, the beta-carotene concentration of adipose tissue was lowest in women residing in southern Europe, although breast cancer incidence is also relatively low in these areas. Some studies have shown that carotenoids other than beta-carotene may act as active agents, for example lycopene or lutein/zeaxanthin (Freudenheim et al. 1996, Dorgan et al. 1998).

The association of vitamin A intake and its status is only indirect. Thus, measurements of vitamin A in food and in body fluids should not be equated. This concerns especially retinol, which has limited interpretability in populations whose food consumption is adequate, and therefore a large reserve of vitamin A is in the liver (Olson 1984). Blood carotenoid level, however, is quite sensitive to dietary intake because it is not closely regulated by homeostatic mechanisms.

2.6 Vitamin E

Vitamin E is a term for eight different kinds of lipid-soluble substances: four tocopherols and four tocotrienols with vitamin E (α-tocopherol) activity. Several biological pathways have been suggested for the anticarcinogenic effect of vitamin E; vitamin E may protect polyunsaturated fatty acids in cell membranes from oxygen radicals and terminate free-radical chain reactions (Ames 1983, Knekt 1991). Further, vitamin E may strengthen the anticarcinogenic capacity of selenium (Steinmetz and Potter 1996) and immune responses (see Dorgan and Schatzkin 1991). Vegetable oil, margarine, whole grains, and eggs are sources of vitamin E.

High vitamin E intake has decreased the risk of breast cancer in many animal studies as reviewed by Wang et al. (1989), Knekt (1991), and Kimmick et al. (1997). This decrease was particularly found in studies with experimental diets rich in polyunsaturated fatty acids (Ip 1982).

Some of the case-control studies - but not all - have indicated an inverse association between vitamin E intake and risk of breast cancer as reviewed by Kimmick et al. (1997). No association was found in a recent case-control study in southeast England (Cade et al. 1998) or in the three cohort studies published thus far (Graham et al. 1992, Hunter et al. 1993, Rohan et al. 1993). Furthermore, a multicenter case-control study found no association between alpha-tocopherol in adipose tissue and risk of postmenopausal breast cancer (van't Veer et al. 1996). Studies on vitamin E concentration in blood and risk of breast cancer have involved only a small number of cases, however, and thus have suffered from methodological limitations in detecting small risk differences (Kimmick et al. 1997).

2.7 Vitamin C

Vitamin C is the most abundant water-soluble vitamin in the body, and is derived from fruit, berries, and vegetables. Vitamin C may protect against breast cancer as an antioxidant as well as affect collagen synthesis and immune responses (see World Cancer Research Fund 1997).

Epidemiological studies based on vitamin C intake or vitamin C concentration in blood have shown inconclusive results in terms of breast cancer risk. Three cohort studies carried out in the United States and Canada found a statistically non-significant reduction in the risk (Hunter et al. 1993, Rohan et al. 1993, Kushi et al. 1996). In addition, no association between vitamin C and risk of breast cancer was reported in a cohort study in the United States by Graham et al. (1982), whereas a significant inverse association (RR=0.53, 95% CI 0.33-0.86) was observed in their other study (Freudenheim et al. 1996). A meta-analysis of 12 case-control studies estimated a relative risk of 0.63 (for a 300 mg increase in daily vitamin C intake p<0.0001) for the highest quintile of vitamin C intake among postmenopausal women compared to the lowest quintile (Howe et al. 1990). This inverse association remained after adjustment for beta-carotene and dietary fiber (OR 0.73, p=0.03). Recent case-control studies, not included in the meta-analysis, have reported no association in Italy (Negri et al. 1996) or in the United Kingdom (Cade et al. 1998).

Consumption of vitamin C supplements was not related to decreased risk of breast cancer in a cohort study including 34,387 postmenopausal women in Iowa (Kushi et al. 1996).

2.8 Selenium

Selenium is an essential micronutrient. It acts in attachment with glutathione peroxidase enzymes which act in various tissues as antioxidants. Selenium may also participate in immune responses, in the control of thyroid hormone (thyroid deiodinases) metabolism, and in the detoxification of heavy metals (Fleet and Mayer 1997, Holben and Smith 1999). Several ecological and animal studies have associated low selenium status with high mortality and high incidence of cardiovascular diseases and cancer, especially breast and colon cancer (Schrauzer et al. 1977, Fishbein 1986, Clark et al. 1991).

The association between selenium and human breast cancer is still uncertain, mostly because of methodological limitations of the studies. For example, most of the studies carried out thus far have included fewer than 100 breast cancer cases (see Willett et al. 1991). Three recent studies, a cohort study including the 434 breast cancer cases of the Nurses' Health Study (Hunter et al. 1990) and another cohort study in the Netherlands (355 postmenopausal cases) (van den Brandt et al. 1994), and a case-control study carried out in five European countries (van't Veer et al. 1996) including 374 postmenopausal cases, found no association between toenail selenium and risk of breast cancer. One case-control study has measured selenium status from various sources such as plasma, erythrocytes, and toenail and from diet (van't Veer et al. 1990). The results for all the measured factors were non-significant.

Interaction between selenium and other antioxidants is controversial. Some studies have found that the protective effect of selenium was strongest when the level of other antioxidants such as beta-carotene was low (van den Brandt et al. 1994, van den Brandt et al. 1994). In contrast, other studies showed that the effect of selenium may be reinforced by a high level of beta-carotene (Kok et al. 1987, Knekt et al. 1990). In a multicenter study of five European countries, however, no interaction existed between toenail selenium and other antioxidants (van't Veer et al. 1996).

Because the soil content of selenium and its bioavailability to plants in Finland is one of the lowest in the world, and many studies had reported a high risk of cardiovascular diseases and cancer among subjects whose serum selenium concentration was under 50 µg/l (Salonen et al. 1982, Salonen et al. 1985), the Finnish Ministry of Agriculture and Forestry decided in 1984 to supplement all commercial fertilizers with selenium (Aro et al. 1998). The nationwide selenium supplementation, a program unique in the world, has raised the serum selenium of the Finns to one of the highest in Europe (80 µg/l) (Alfthan and Neve 1996).

2.9 Alcohol

High alcohol consumption has been associated with increased risk of breast cancer in many countries and diverse cultures since 1977 (Williams and Horm 1977, Willett and Stampfer 1997). However, the evidence is weak, and there may be a threshold below which alcohol has no noticeable effect.

A pooled analysis of six cohort studies: four in the United States and Canada, one in the Netherlands, and one in Sweden, showed that women whose alcohol consumption was more than 30 g per day (2-3 drinks) had an increased risk of breast cancer (RR=1.41, 95% CI 1.18-1.69) compared to that of non-drinkers (Smith-Warner et al. 1998). That pooled analysis included 4,335 breast cancer cases diagnosed among 322,647 premenopausal and postmenopausal women. A positive dose-response relationship was found when the analyses of 38 cohort and case-control studies were combined (Longnecker 1994). The relative risks were 1.11 (95% CI 1.07-1.16), 1.24 (95% CI 1.15-1.34) and 1.38 (95% CI 1.23-1.55) for women whose daily alcohol consumption was one drink, two drinks, and three drinks, respectively, compared to non-drinkers. The relative risk of death from breast cancer was 2.10 (95% CI 1.18-3.72) in women who consumed alcohol over 60 g per day (about 5 drinks) compared to non-drinkers in the study of the American Cancer Society, the biggest cohort study thus far, including 2,933 breast cancer deaths from the follow-up data of 581,321 women (Garfinkel et al. 1988). A lower threshold value (15 g alcohol per day) for the increased risk was found in postmenopausal women of the Iowa Women's Health Study (Gapstur et al. 1992) and in premenopausal and postmenopausal women of the Nurses' Health Study (5 g per day) (Willett et al. 1987b). Cohort studies with the longest follow-up times have revealed the strongest direct association between alcohol consumption and risk of breast cancer (Longnecker 1994).

Based on the meta-analysis of six case-control studies, women whose alcohol consumption was more than 40 g per day had an increased risk of breast cancer (OR 1.69, 95% CI 1.19-2.40) compared to that of non-drinkers (Howe et al. 1991b). The largest case-control studies, one in the United States (6,662 breast cancer cases) (Longnecker et al. 1995) and one in Italy (2,402 cases) (La Vecchia et al. 1989), observed that high alcohol consumption was related to an increased risk of both premenopausal and

postmenopausal breast cancer, whereas another study in the United States (3,498 cases) found no such relationship (Chu et al. 1989). The accumulated evidence shows that the strongest associations (about 2.5-fold risk) were found in countries where alcohol is a regular component of the diet and the consumption per capita high. Studies from the Mediterranean countries and France are good examples (La Vecchia et al. 1989, Richardson et al. 1989, Toniolo et al. 1989, Ferraroni et al. 1991, Katsouyanni et al. 1994). Alcohol consumption explained 12% of the breast cancer incidence in a recent case-control study in Italy (Ferraroni et al. 1998). A much lower estimate (4%) was made in the United States, where alcohol consumption is low in general (Longnecker 1994).

No differences were found between various alcoholic beverages and the risk of breast cancer in a combined analysis of six case-control studies (Howe et al. 1991b). On the other hand, the alcoholic beverage consumed most within one country has tended to have the strongest association. Thus, it seems that amount of alcohol is more important than type of alcoholic beverage.

Some studies have provided information on past (Hiatt et al. 1988, La Vecchia et al. 1989, van't Veer et al. 1989b, Nasca et al. 1990, Freudenheim et al. 1995, Holmberg et al. 1995, Bowlin et al. 1997) or total lifetime alcohol consumption (Longnecker et al. 1995). These factors may be more important in the pathogenesis of breast cancer than is current alcohol consumption. The findings, however, have been inconsistent, and it is not known which is more relevant, alcohol consumption in early life or later on. Harvey et al. (1987) found that women who consumed alcohol before the age of 30 and then stopped and those who continued to drink alcohol had a similarly increased risk of breast cancer. A multicenter case-control study conducted in France, Switzerland, Northern Ireland, the Netherlands, and Spain indicated an increased breast cancer risk only for postmenopausal ex-drinkers (Royo-Bordonada et al. 1997). Both poor recall and current alcohol consumption may effect the reporting of alcohol consumption. For example, when ethanol grams per day and duration of consumption were simultaneously included in the multivariate model, duration was not important as a risk factor (Bowlin et al. 1997). Furthermore, the positive association between total lifetime alcohol consumption and risk of breast cancer disappeared after adjustment for current alcohol consumption (Swanson et al. 1997).

Ecological studies cannot be done to correlate alcohol consumption with breast cancer rates because per capita consumption usually reflects more men's than women's alcohol consumption (Longnecker 1994). For example, the proportion of women's of the total alcohol consumption in Finland is only 20-25% (Simpura et al. 1995, Männistö et al. 1997). In animal studies, alcohol has been found to increase the proliferation of mammary gland cells (Singletary et al. 1991). In a controlled trial in premenopausal women, 30 g alcohol per day increased total estrogen concentration and amount of bioavailable estrogens (Reichman et al. 1993). Alcohol may also act as a tumor promoter, induce free-radical production, inhibit the DNA repair system, and influence immune responses (Katsouyanni et al. 1994).

2.10 Summary of factors related to diet

Obesity may increase the risk of postmenopausal breast cancer, but nonexistent or even inverse associations have been demonstrated for premenopausal women. Because of the contradictory results between case-control and cohort studies, additional information about factors identifying obesity more accurately, for example in terms of body fat distribution and timing of weight gain, has been called for. Some findings have related high waist-to-hip ratio and weight gain to increased risk of breast cancer, but more studies are needed to reach a reasonable conclusion. Height has also been associated with increased risk of breast cancer, at least in postmenopausal women. The positive energy balance in youth and early menarche may explain this association.

The association between fat intake and risk of breast cancer is still uncertain. Ecological and animal studies have shown that high fat intake increases the risk of breast cancer, but it is possible that total energy intake acts as a confounder. Case-control studies have reported diverse results, whereas cohort studies have found no association. However, because of promising results between high consumption of olive oil and relatively low risk of breast cancer in Mediterranean countries, it has been suggested that the type of fat, e.g., monounsaturated fatty acids, n-3 polyunsaturated fatty acids, and trans-fatty acids, may be more important in the development of breast cancer than is total fat intake. A high amount of fiber in the diet may also be a protective factor against breast cancer, although the results from epidemiological studies have been contradictory. In this respect, Finland is an

interesting country because not only fat intake but also fiber intake is high, and because of the important role of dairy products in the Finnish diet.

A diet rich in antioxidants, such as beta-carotene, vitamins E and C, and selenium, may decrease breast cancer incidence by protecting breast tissue from oxidative damage. The results of human studies, however, have been inconsistent. To clarify the situation, more studies are needed, in particular those with adjustment for the known risk factors for breast cancer. Dietary supplements and combined benefits of other antioxidants have also seldom been considered. Finland is one of the countries where the soil content of selenium is very low. Because many studies had showed increased risks of cardiovascular disease and cancer among subjects whose selenium intake was low, it was decided in 1984 to supplement all commercial fertilizers with selenium. More than a decade after the beginning of supplementation, it may be possible to assess whether selenium intake now has reached a level at which it is no longer related to risk of diseases.

It seems that women who consume more than 30 g alcohol per day have an increased risk of breast cancer. This association has been found to be stronger in countries where alcohol is part of the normal diet, whereas in countries where alcohol consumption is low, the role of alcohol is still unclear. Furthermore, the critical time periods of women's lifetimes when alcohol consumption has the most substantial effect on the development of breast cancer have not yet been determined. Measuring past alcohol consumption is methodologically challenging, and validated innovative methods are needed.

3. Assessment of dietary exposure

3.1 Overview of food frequency questionnaires

Retrospective dietary assessment methods, such as short-term recall, dietary history, and the food frequency questionnaire (FFQ), are designed to assess the subject's past diet. Short-term recall, however, is seldom suitable for epidemiological studies, because long-term dietary intake is often more relevant than the current diet when associations between exposures and diseases are examined (Willett 1998). Compared to an interview-based dietary history, a self-administered FFQ is cheaper, requires less time to complete and is easier to enter into a mainframe computer. Because FFQ is easy for participants, it leads to a high response rate, which is the most important reason why FFQ is becoming the main method in large population studies (Thompson and Byers 1994).

FFQs are based on the detailed dietary history interview developed by Burke (1947). That interview included a checklist on which subjects indicated frequencies and amounts of consumed foods and drinks during a specified period. Although the present form of food frequency questionnaire was developed during the 1960s (Wiehl and Reed 1960, Stefanik and Trulson 1962), it did not become common until the 1980s when large cohort studies between diet and chronic diseases were initiated (Willett 1998). The main purpose of a FFQ is not to estimate absolute intakes, but to rank subjects into exposure categories according to food consumption or nutrient intakes, often over the entire past year (Thompson and Byers 1994). Such ranking is adequate for most epidemiological studies to assess the overall relative risk of disease.

The important issues concerning FFQs are a well-designed food list and frequency categories. Foods included in the list should be consumed reasonably often in the basic population, have a high between-person variance and cover the relevant contributors of nutrients of interest (Willett 1998). Often 10 to 15 foods can explain over 80% of the intake of a special nutrient (Byers et al. 1985). Callmer et al. (1987) found that individuals in developed countries regularly consumed 80 to 120 food items. Therefore, about 100 food items or aggregate foods are usually enough to assess the

intakes of most nutrients. An inquiry into the frequency of consumption has typically involved 5 to 10 frequency categories (Willett 1998). The increasing order of frequency categories, from never to frequently used food items or mixed dishes, is recommended because the decreasing order may increase the frequency responses for some food items (Kuskowska-Wolk et al. 1992). The overestimation was especially related to the consumption of bread, vegetables, and fish.

Three approaches on estimating portion sizes have been presented: a simple FFQ in which no information on portion sizes is collected, a semi-quantitative FFQ in which a certain portion size is specified for each food item or foods, and an open-ended FFQ in which subjects can select portion sizes freely (Willett 1998). Portion sizes are, however, difficult to evaluate (Guthrie 1984, Smith et al. 1991), mainly because of large within-person variation for each food (Hunter et al. 1988). Further, when FFQs with and without portion sizes were compared, no significant differences appeared (Humble et al. 1987, Tjønneland et al. 1992). Exceptions are studies by Block et al. (1990, 1992b) in which correlations between diet records and FFQs improved when gender and age-specific portion sizes were taken into account.

FFQs more often assess aggregate foods rather than individual food items. Questionnaires are also quite inflexible in measuring unusual diets (Thompson and Byers 1994, Lissner et al. 1998). FFQs are usually designed for specific populations, which implies that any new questionnaire should be evaluated against a more established method, such as diet records or biochemical indicators, in that population (Buzzard and Sievert 1994). The purpose of the evaluation is to yield guidance for the interpretation of the results in that particular study (Thompson and Byers 1994).

3.2 Reproducibility and validity of food frequency questionnaires

Reproducibility, i.e., reliability, refers to how consistently the same method repeats the diet of the same subject at different occasions without overlapping reference periods. In reproducibility studies of FFQ carried out in 1964-1997, correlation coefficients have ranged from 0.5 to 0.7 for nutrients and from 0.4 to 0.7 for food items (Willett 1998). Beverages have

had the highest and foods seldom consumed the lowest correlation coefficients (Colditz et al. 1987). The reproducibility of dietary factors resembles the values of many biological measurements, such as serum cholesterol and blood pressure, widely used in epidemiological studies (Willett 1998).

Validation, on the other hand, means how well the method measures what it is supposed to be measured. Diet records are regarded as a "gold standard" against other dietary assessment methods, although they have some weaknesses of their own (Thompson and Byers 1994). Nevertheless, diet records describe more accurately a subject's diet than FFQs, and their inherent inaccuracies are independent of those of FFQs (Willett 1998). To estimate most nutritional factors adequately requires 7 to 14 diet-record days (Jeor et al. 1983, Willett et al. 1985, Nelson et al. 1989, Hartman et al. 1990), although the motivation of subjects may decrease if the records are kept for more than 7 record days (Gersovitz et al. 1978).

The relative risks of a disease are often measured according to quartiles or quintiles of the exposure. Therefore, it is important to rank subjects into categories correctly. Willett et al. (1985) and Pietinen et al. (1988) have reported that about 75% of the subjects were classified into the same or adjacent quintile according to the FFQ and diet records.

3.3 Biochemical indicators

3.3.1 Overview of biochemical indicators

Use of biochemical indicators is a possible reference method to objectively assess the validity of dietary information furnished by the participants. In addition to validation, biochemical indicators can also be used as indicators of dietary intake or nutritional status, and for assessment of susceptibility to disease, and metabolic effects and risk of disease (Kohlmeier 1991).

Although human cells, tissues, and fluids offer a large number of biochemical parameters for monitoring of the nutritional status (Kohlmeier 1991, Kok and van't Veer 1991), only a few biochemical indicators are known to assess dietary intakes reasonably well. Good indicators exist for intakes of fatty

acids, vitamins, and some minerals, whereas for intakes of total fat, total carbohydrate, and cholesterol, just to mention a few, no biochemical indicators are available (Kohlmeier 1991, Hunter 1998). One difficulty in finding good markers is that associations between nutrient intakes and biochemical indicators are not always linear because of variation among subjects in nutrient absorption and metabolism (Willett and Lenart 1998). Another problem may be that other nutrients such as fat and carbohydrate may change the association between biochemical indicators and nutrient intake.

3.3.2 Toenail selenium concentration

Several biological sources are available for estimating selenium intake, for example, plasma, erythrocytes, urine, hair, and nails (Riboli et al. 1987). Of these, nails are best suited for epidemiological studies since they are easy to collect, transport, and store, and they are less exposed to environmental contamination than is hair. Nails also give a good estimate of long-term selenium intake (Longnecker et al. 1996, Hunter 1998).

Selenium intake has correlated well with toenail selenium concentration in some studies (Swanson et al. 1990), though not in all (Ovaskainen et al. 1993). A trial with three groups of four men consuming a high (4.9 μmol), a medium (2.6 μmol), or a control dose (0.41 μmol) of selenium per day showed that toenail selenium concentration provided an approximation of selenium intake over six to twelve months (Longnecker et al. 1993). It has also been reported that sex, obesity, current smoking, alcohol consumption, and intake of other antioxidants may affect the selenium status, and that these factors should thus be considered in the analyses (van't Veer and Alfthan 1991, Virtanen et al. 1996, Hunter 1998).

3.4 Summary of food frequency questionnaires and biochemical indicators

Food frequency questionnaires are widely used in large epidemiological studies since they are cheap, are easy for the participants, and they assess the past diet. Because the questionnaire is usually designed for a particular population, interpretation of the results requires information on the accuracy of the method (reproducibility and validity). Diet records are generally

regarded as the best reference method for FFQs, because the errors in records differ from those related to FFQs. It has been shown that FFQ measures relatively well the overall levels of food consumption and nutrient intake, although it may reflect the diet which participants would like to consume rather than what they really eat (Kimmick et al. 1997).

Biochemical indicators are objective, and thus highly recommended for use together with FFQs in epidemiological studies. The reason for this recommendation is that some nutrients can be measured accurately by a questionnaire, whereas some others can be measured less accurately or sometimes only by use of biochemical indicators (Willett 1991). The problem is that biochemical indicators have not yet been found for all dietary factors, for example, for total fat, total carbohydrate, and cholesterol. Good indicators exist for fatty acids, and for some vitamins and minerals, such as selenium.

4. Aims of the study

Dietary factors have been suggested to be significant determinants in the development of breast cancer. However, despite the extensive amount of study, only a few consistent findings between diet and breast cancer have emerged. In fact, there exists no realistic preventive strategy to reduce the high incidence of breast cancer. Identification of lifestyle factors that women themselves could influence would greatly help in developing such a strategy.

The main aims of this dissertation are:

1. To examine whether body-size indicators are associated with risk of premenopausal and postmenopausal breast cancer (I).

2. To assess how well the food frequency questionnaire designed for this study measures food consumption and nutrient intake (II).

3. To examine associations between the consumption of certain foods and risk of premenopausal and postmenopausal breast cancer (III).

4. To examine whether fat, fatty acids, fiber, or certain vitamins/antioxidants are associated with risk of premenopausal and postmenopausal breast cancer (III).

5. To assess the reporting bias resulting from the threat of disease, and how it influences the interpretation of the results on associations between dietary factors and risk of breast cancer (III).

6. To examine whether current and past alcohol consumption is associated with risk of premenopausal and postmenopausal breast cancer (IV).

7. To examine whether toenail selenium concentration is associated with risk of premenopausal and postmenopausal breast cancer a decade after the beginning of selenium supplementation of fertilizers in Finland (V).

5. Subjects and Methods

5.1 Kuopio Breast Cancer Study

The Kuopio Breast Cancer Study is a multi-disciplinary cooperative project conducted by different departments of the University of Kuopio, Kuopio University Hospital, and the Department of Nutrition of the National Public Health Institute in Helsinki. The subjects of the project included all women who were referred to Kuopio University Hospital (North-Savo Health Care District) for breast examination between April 1990 and December 1995. The catchment area of the hospital is presented in Figure 2.
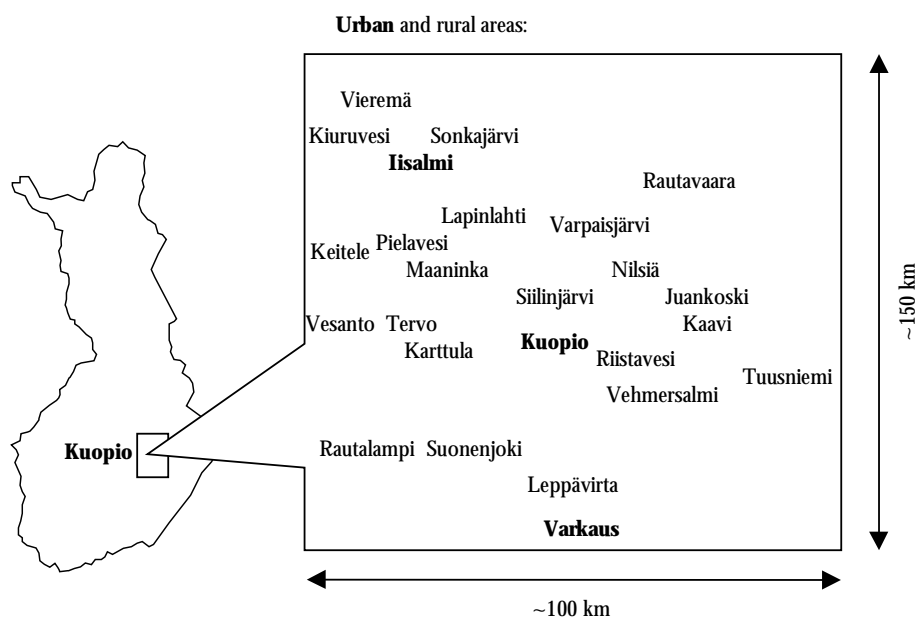
Figure 2. Catchment area of Kuopio University Hospital.

The project started as a case-control study, but all breast cancer cases could be followed up because they make their annual visits to Kuopio University Hospital. The long-term aim of this project is to decrease the incidence of and mortality from breast cancer in eastern Finland. The focus is on risk and protective factors for breast cancer, pathogenesis, diagnosis at an early stage of disease, estimation of prognosis, and improvement in treatment.

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The Kuopio Breast Cancer Study follows the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by the European Institute of Oncology in Milan (the collaborative study was initiated as a SEARCH program in the International Agency for Research on Cancer). The collaborative study is based on the assumption that breast cancer and colorectal cancer may have common risk factors, particularly in the diet, such as alcohol, fat, cholesterol, and vitamin A (Boyle 1990). Study centers of the breast cancer study are situated in Canada, Finland, Greece, Ireland, Italy, Russia, Slovakia, Spain, and Switzerland. Each of the centers must collect at least 400 breast cancer cases (Boyle 1989). The multicenter study expands the variation in breast cancer incidence and in exposure variables compared to that of a single case-control study.

The diet study of the Kuopio Breast Cancer Study concentrates on associations between dietary factors, body-size indicators, and risk of breast cancer. In this dissertation, five of these studies are presented: Body-size Study (I), Validation Study (II), Dietary Study (III), Alcohol Study (IV) and Selenium Study (V). All studies are based on the original case-control study design.

5.2 Subjects

5.2.1 Recruitment of cases and controls

Recruitment protocol of the Kuopio Breast Cancer Study

The recruitment protocol of subjects for the study in Kuopio University Hospital is shown in Figure 3. All those 1,919 women who had any suspected breast disease and who lived in the catchment area of the hospital during the study period from 1990 to 1995 were referred for further examination. All women were diagnosed and treated in Kuopio University Hospital. Originally, the subjects were referred to the hospital by a physician because of a suspected breast lump or breast symptom. Of these women, 516 (27%) were finally diagnosed with breast cancer, 717 (37%) had benign breast disease, and 686 (36%) were diagnosed as healthy (in terms of their breasts) after examination (later referred to as referral controls). Women with benign breast disease were excluded from Studies I-V. The clinical examination and

interview of the subjects were carried out before their diagnosis was confirmed. This means that all subjects, both those with cancer and the referral controls, were similarly interviewed, and the diagnosis or treatment of cancer had no influence on the results.
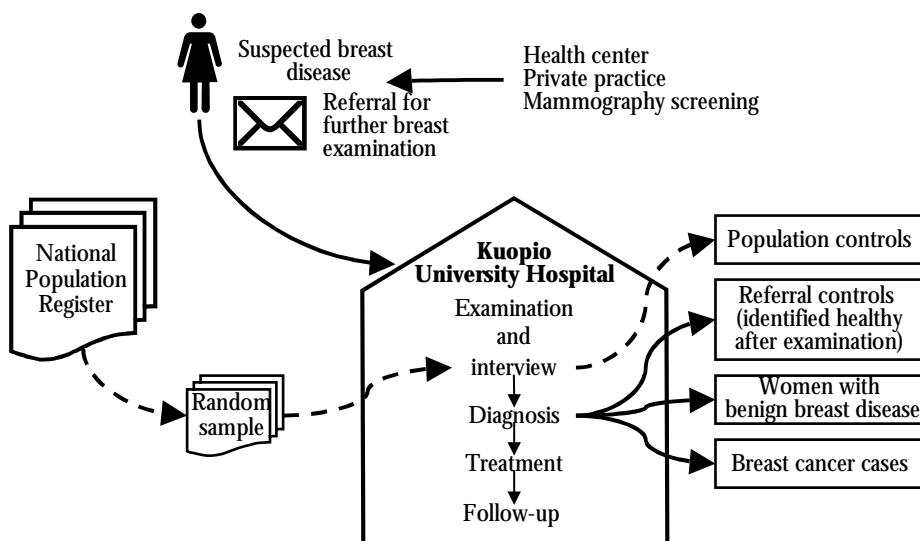
Figure 3. Recruitment protocol of the Kuopio Breast Cancer Study.

Cases

All cases (n=516, age range from 23 to 91) had newly diagnosed, histologically confirmed breast cancer. Subjects who had a previous history of cancer in the past five years were ineligible. Subjects were asked to participate in the Kuopio Breast Cancer Study at their first visit to the hospital. Only twelve of the women who were later diagnosed with breast cancer refused to participate. The diet study included cases between 25 and 75 years of age according to the protocol of the International Collaborative Study of Breast and Colorectal Cancer (one case was under 25, and 76 cases were over 75). The subjects should also have had the ability to participate in an interview of sufficient quality, and thus the age of 75 was set as the upper limit. The diet study began in October 1990, and thus the first 56 breast cancer cases (recruited between April 1990 and September 1990) did not furnish any information on diet. The data of the diet study thus included 383 breast cancer cases aged between 25 and 75.

Referral control

Referral controls (n=686) were women who were referred to the hospital because of a suspected breast lump or breast symptom, but who were subsequently diagnosed as healthy (as to their breasts). After the exclusions (53 referral controls under 25 or over 75, and 85 women recruited during April 1990 and September 1990 and for whom no information on diet was available), the data of the diet study included 548 referral controls 25 to75 years old.

Completeness of patient catchment

Our recruitment protocol missed 51 breast cancer cases and 5 referral controls within the hospital. These all were private patients who did not enter the hospital by the standard procedure. These missed subjects were recognized when clinical and pathology records of the hospital were compared to the data of the Kuopio Breast Cancer Study. Furthermore, eleven breast cancer cases and four referral controls were missed during the nurses' one-month strike in 1995.

The completeness of this data set was also tested by comparing the confirmed breast cancer cases (516+51+11=578) with the Finnish Cancer Registry. The comparison showed that 96% (578/604) of breast cancer cases who lived in the catchment area of Kuopio University Hospital were referred to the hospital; 26 breast cancer cases had been treated elsewhere.

In conclusion, the study material represents well the breast cancer cases in the catchment area of Kuopio University Hospital, since only 15% of eligible cases were missed (516 vs. 604).

Population controls

One population control was selected for each breast cancer case after the cancer diagnosis had been confirmed. Controls should reflect the exposure distribution of the population that generates those cases (Ahlbom and Norell 1990). Therefore, a randomly selected group of subjects was drawn from the Finnish National Population Register covering the same catchment area (Figure 3). The population controls were individually matched with the breast

cancer cases by the area of residence (urban/rural) and age (within ±5 years). The proportion of case-control pairs who lived in the same municipality was 87%, and the remaining pairs lived as near as possible, to keep the urban-urban or rural-rural matching.

In all, 663 population controls were invited to the hospital to be interviewed in parallel with the cases. Although the matching ratio was decided upon as 1:1, there were more population controls than breast cancer cases because one to four controls were selected for each case in the Validation Study (II) to ensure its completion on schedule. The participation rate of the population controls was 72% (64% during the Validation Study, 76% otherwise). The interval between the interview of a case and that of the corresponding population control was one to two months.

5.2.2 Body-size Study (I)

In Study I, the associations between body-size indicators, i.e., anthropometric measurements, and risk of breast cancer were examined according to the menopausal status of the women and estrogen-receptor status of the tumors. The subjects were 25 to 75-year-old women (339 breast cancer cases and 420 population controls) who were recruited to the Kuopio Breast Cancer Study during the first four years, from April 1990 to December 1994 (Figure 4). Seven cases and three population controls were excluded because of severe illness or inability to cooperate. Four breast cancer cases refused to participate in the study. The final data included 328 breast cancer cases and 417 population controls.

The body-size indicators with a value missing for less than 10 subjects were height, weight, body mass index, waist-to-hip ratio, or weight loss at age 22 to 44. Indicators with 10 to 20 missing values were body fat percent, fat weight, and lean body weight. Weight gain had a large number of missing values, especially in postmenopausal women (133). Estrogen-receptor status was not available for the tumors of 32 premenopausal and 52 postmenopausal women.

The mean age of the breast cancer cases was 54 years (SD 11), and 62% of them lived in towns. The corresponding values for the population controls were 53 years (SD 11) and 65%.

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Figure 4. Recruitment time axis and final number of subjects in Studies I-V.

The figure contains a timeline and the following table:
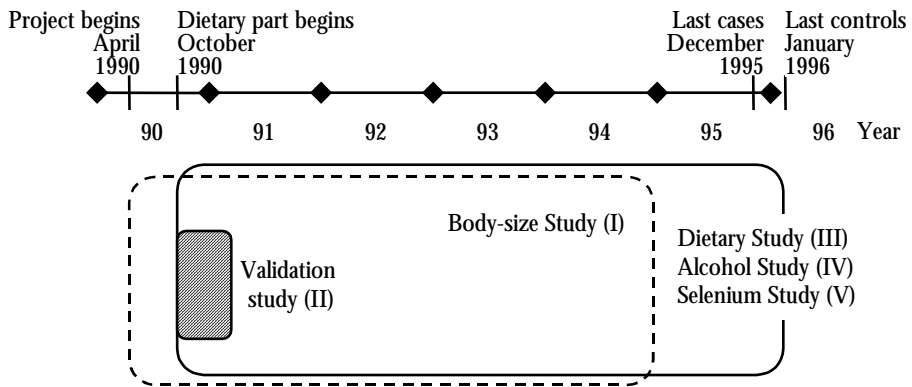
	Cases	Population controls	Referral controls
Body-size Study (I)	328	417	-
Validation Study (II)	-	152	-
Dietary Study (III)	310	454	506
Alcohol Study (IV)	301	443	-
Selenium Study (V)	289	433	-

Timeline labels: Project begins April 1990; Dietary part begins October 1990; Last cases December 1995; Last controls January 1996. Years: 90, 91, 92, 93, 94, 95, 96 Year. Body-size Study (I); Validation study (II); Dietary Study (III); Alcohol Study (IV); Selenium Study (V).

5.2.3 Validation Study (II)

The first 250 population controls of the diet study, recruited between October 1990 and February 1991, were invited to the Validation Study (II), in which the reproducibility and validity of the FFQ designed for the diet study were investigated (Figure 4).

The first food frequency questionnaire (FFQ1) was sent to the subjects along with the invitation letter to attend the examination and interview. The purpose of the study and the importance of obtaining healthy population controls were explained in the letter. The controls were not paid for their participation, but a free health examination with laboratory analyses and anthropometric measurements was offered. Of the 250 eligible subjects, 198 visited the hospital and filled in the FFQ1 (79%), of these 188 agreed to continue, and 167 returned the first 7-day diet record (Figure 5). The second food frequency questionnaire (FFQ2) was sent to the subjects after an interval of three months (n=167); 160 of them returned it as well as the

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repeated 7-day diet record two weeks later. In analyses, the two 7-day diet records were combined into a 14-day diet record.

Eight women were excluded because of pregnancy, breast-feeding, fasting (more than two days), or incompletely filled in forms. As a result, the final Validation Study (II) included 152 population controls. Three women had only 13 diet-record days and two only 12 days because of fasting, illness, or unknown reasons. The aim was to collect over 100 subjects, which is a reasonable size for validation studies (Willett and Lenart 1998) .

250 eligible subjects
198 visited the hospital

| October 1990 – February 1991 **FFQ1** | November 1990 – April 1991 **DR1** | | February – May 1991 **FFQ2** | March – August 1991 **DR2** |

2 weeks   3 months   2 weeks

n=198   n=167   n=160   n=160

(Final data: 152 subjects;
8 subjects excluded)

Legend:
FFQ = Food frequency questionnaire
DR = Diet record
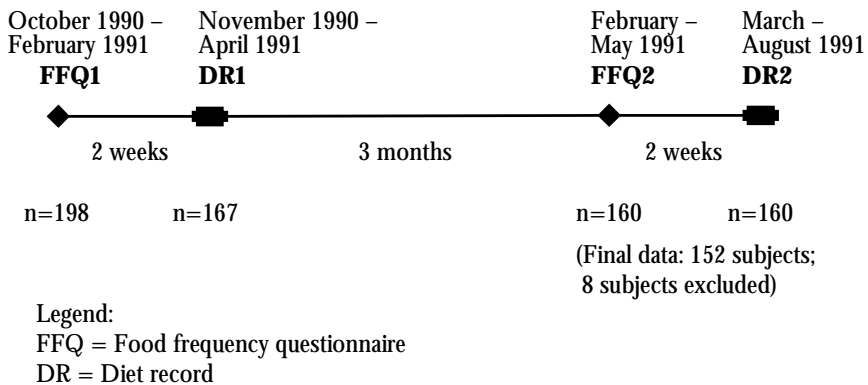
Figure 5. Design of the Validation Study (II).

Study II was divided into two parts: the FFQ1 was compared with the FFQ2 in the reproducibility part, and both the FFQ1 and the FFQ2 with the 14-day diet record in the validation part. The interval of three months between the questionnaires was chosen because a few months' period between the original and the repeated questionnaire is recommended if the questionnaire concerns the intake over the past year. If the interval is too short, subjects may also remember their previous answers, which increases reproducibility artificially. On the other hand, with a long interval, reproducibility reflects not only the repeatability of the questionnaire but also the true changes in diet (Willett and Lenart 1998). The seasonal variation in the Finnish diet

seems also to be covered, because the data were collected during 11 months (from October to August).

The mean age of the 152 subjects was 51 years (SD 9) and more than half of them (64%) lived in an urban area. The mean age of the original 250 population controls was 50 years (SD 9) with 62% of them living in an urban area.

5.2.4 Dietary Study (III)

The main aim of Study III was to examine associations between dietary factors (foods and nutrients such as fat, fiber, and vitamins) and risk of breast cancer. Furthermore, recall bias due to worry caused by the threat of disease was also examined. Because all subjects were diagnosed after the interview, it was possible to assess whether the self-reporting of diet between two control groups, the population controls and the referral controls, varied.

Study III included all breast cancer cases (n=383), population controls (n=663), and referral controls (n=548) aged 25 to 75 who were invited to the Kuopio Breast Cancer Study after October 1990 when the diet study began (Table 1, Figure 4). Exclusion criteria for participation in the Dietary Study (III) were as follows: refusal, pregnancy, or lactation during the Validation Study (II), inability to cooperate, other severe disease, or an unacceptable food frequency questionnaire (Table 1). The FFQ was not accepted if the energy intake per day was under 800 kcal, if more than 10 food items were skipped, if more than five food items had "unreasonably" high frequencies or if only one or two frequency categories were used repeatedly. These criteria had been modified from those reported by Block et al. (1990). Half of the population controls (n=90) who refused to participate were those who did not want to participate in the Validation Study (II) at the beginning of the project. Finally, the data of the Dietary Study included 310 breast cancer cases, 454 population controls, and 506 referral controls (81%, 68% and 92%, respectively, of enrolled 25- to 75-year-old women).

Table 1. Participation (n) and reasons for exclusions in Study III.

	Cases	Population controls	Referral controls
Enrolled (25-75 year-old women)	383	663	548
Exclusions			
Not willing to participate	12	188	2
Pregnancy or lactation during the			
Validation Study (II)	-	5	-
Controls who developed breast cancer	-	2	6
Unable to cooperate or too ill	25	8	9
Food frequency questionnaire missing			
or unacceptable	36	6	25
Total	73	209	42
Final number of subjects in the Dietary			
Study (III)	310	454	506
Premenopausal	119	178	324
Postmenopausal	191	276	182

5.2.5 Alcohol Study (IV)

The association between lifetime alcohol consumption (current consumption, consumption at age of first use, cumulative consumption before age 30, and cumulative lifetime alcohol consumption) and risk of breast cancer was examined in Study IV. Two different kinds of measurements for alcohol consumption were used: the self-administered FFQ and an interview-based Lifetime Alcohol Consumption Questionnaire (AQ) designed for this study. The validity of the current alcohol consumption rates was assessed by comparing the results of both methods.

Study IV was based on the breast cancer cases (n=310) and the population controls (n=454) of the Dietary Study (III) (Figure 4). However, nine breast cancer cases and eleven population controls were excluded because of missing AQs. Thus, the final data included 301 breast cancer cases and 443 population controls.

5.2.6 Selenium Study (V)

The Selenium Study (V) was designed to assess the association between toenail selenium concentration and risk of breast cancer.

Study V was based on the breast cancer cases (n=310) and the population controls (n=454) of the Dietary Study (III) (Figure 4). Some exclusions, however, were made (21 breast cancer cases and 21 population controls) because of missing or insufficient samples, or unreasonably high selenium concentration (>3SD), which usually originates from selenium-containing anti-dandruff shampoo. The final data of Study V included 289 breast cancer cases and 433 population controls.

5.2.7 Characteristics of the subjects

The main characteristics of the breast cancer cases, population controls and referral controls of the Dietary Study (III) are summarized in Table 2. The distributions by age, area of residence, and education were similar between the cases and the population controls both in premenopausal and in postmenopausal women. The first-degree relatives (mother and sisters) of the breast cancer cases had more diagnosed breast tumors than did relatives of the population controls (13% vs. 5% for premenopausal and 9% vs. 5% for postmenopausal women). The referral controls were the youngest both among premenopausal and among postmenopausal women, had the highest education among the premenopausal women and had the highest percentage of breast cancer in their family among the postmenopausal women.

5.2.8 Ethics

The Kuopio Breast Cancer Study was approved by the Joint Ethics Committee of the University of Kuopio and Kuopio University Hospital. Participation was based on written consent by which subjects gave permission to use their medical records, and to monitor them for any future health conditions.

Table 2. Selected characteristics of the subjects in the Dietary Study (III).

	Cases	Population controls	Referral controls
Premenopausal women			
Number of subjects	119	178	324
Age (years)	45	44	38
Urban (%)	65	66	63
More education than comprehensive school (%)	43	44	56
Family history of breast cancer (%)	13	5	6
Postmenopausal women			
Number of subjects	191	276	182
Age (years)	60	60	58
Urban (%)	60	59	56
More education than comprehensive school (%)	24	20	20
Family history of breast cancer (%)	9	5	12

5.3 Methods

5.3.1 Food frequency questionnaire

The semi-quantitative food frequency questionnaire (FFQ) was developed for the Kuopio Breast Cancer Study from the longer questionnaire of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the ATBC Study) in Finland (Pietinen et al. 1988). The FFQ was designed to assess the subject's entire diet during the year before diagnosis. It included separate 110 food items, mixed dishes, and alcoholic beverages. Frequency of use was described by nine categories from "never" to "six or more times a day". The usual portion size was predefined in the FFQ, for example, a slice of bread, a banana, or a cup of coffee. Subjects were also asked to assess the frequency and quantity of dietary supplements used, and they were allowed to report additional foods consumed frequently but not listed in the FFQ.

For the subjects who reported using butter in cooking and usually ate homemade food (29%), butter was assumed to be the cooking fat in all

recipes. For the other subjects, the cooking fat was assumed to consist of butter, margarine, and oil in equal proportions. This assumption was made, because a large proportion of Finnish employees have their lunch (the daily main meal) outside the home and are unaware of the types or amounts of fats used in cooking. The type of salad dressing usually chosen (oil and vinegar, mayonnaise, juices, or low-caloric) was also included individually in the analyses. Further, a limit for "unreasonably" high frequency was determined for 60% of food items or mixed dishes in order to exclude impossibly high consumption. In the analyses, unreasonably high frequencies were converted to one above the defined maximum so that the ranking between the subjects was still maintained. For example, "yogurt six or more times a day" was not accepted and was converted to "twice a day" (the highest reasonable frequency for yogurt was determined as "once a day"). However, less than 1% of frequencies were converted during the analyses and these conversions concerned 15% of subjects.

The FFQ was sent to the subjects along with a letter inviting them to a breast examination. The questionnaire was completed at home, and returned to the study nurse during the interview visit.

5.3.2 Diet record

The subjects of the Validation Study (II) were asked to report all foods and beverages they consumed for two specified 7-day periods. The amounts of foods were estimated by a picture booklet including 126 color photographs of foods in varying portion sizes (Haapa et al. 1985) or by common household measurements whichever was more appropriate. Dietary supplements were not included in the diet record.

5.3.3 Questionnaire of lifetime alcohol consumption

The lifetime alcohol consumption questionnaire (AQ) was completed together with the study nurse during the interview visit. The subjects were allowed freely to define any different drinking periods (age at start and end of drinking). Alcohol drinkers were especially asked to recall all special events in their life that were likely to be associated with changes in alcohol consumption, for example, leaving the parental home, pregnancy, divorce, and unemployment. The maximum number of drinking periods reported

(when the subject used to drink alcohol in a constant pattern) was between two and five depending on alcoholic beverage. The subjects were asked to describe the number of predefined portions and the frequency of use for all alcoholic beverages consumed (beer, long-drink, wine, fortified wine and spirits) during each interval.

The following variables were calculated from the AQ: current consumption of alcohol (ethanol g/week), age at first use, alcohol consumption during the first year alcohol was consumed (g/week), total cumulative consumption before age of 30 (cumulative sum of all ethanol) and total lifetime alcohol consumption (cumulative sum). In this dissertation, the terms "alcohol consumption" and "alcohol intake" refer to intake as absolute alcohol.

5.3.4 Food composition database

All food frequency questionnaires and diet records were entered into the mainframe computer at the National Public Health Institute by students of nutrition science. The final approval was given by the nutritionist who used the exclusion criteria mentioned in sections 5.2.4.

Dietary data were converted into individual daily food consumption and nutrient intakes by the software and food composition database (FINELI) of the National Public Health Institute. This database, which is also the official Finnish National Food Composition Database, includes about 1,600 of the most important food items and mixed dishes in the Finnish diet, and over 200 dietary factors (Ovaskainen et al. 1996). The supplement database includes 778 dietary supplements, of which 75% had a known nutritional content (Kaartinen et al. 1997).

The food groups were selected on the basis of importance as macronutrient and micronutrient sources in the Finnish diet, or because of relation to reported risk of breast cancer. Thus, 17 of 32 food groups designed for the ATBC Study were chosen for this study. These groups are rye products, vegetables, fruit and berries, butter, soft margarine, oil, total milk, low-fat milk, sour milk, cream, cheese, beef and pork, poultry, fish, coffee, tea, and sugar. The formation of food groups has been explained in detail in Study III. For example, the group "Milk" consisted of all milk consumed in the diet

independently of whether it was recorded as a milk item or derived from mixed dishes, e.g., from porridge made with milk.

Of the nutrients, the intakes were calculated of fat (total fat and fatty acids), fiber (total fiber and water-insoluble noncellulosic polysaccharide), vitamins (retinol, beta-carotene, vitamins E and C, with supplements), and alcohol. These nutrients were selected because earlier studies have suggested that they may be related to the development of breast cancer.

5.3.5 Toenail selenium

An envelope with instructions to cut clippings from the toenails was mailed to the subjects with the invitation letter to the hospital. They were asked to return the sample to the study nurse.

The toenails were analyzed for selenium at the National Public Health Institute. The nail samples were cleaned with 1% sodium dodecylsulfate for one hour. After one minute of ultrasonication, the samples were rinsed thoroughly with demineralized water and dried. The selenium concentration of the samples was analyzed by acid-digestion fluorimetry by use of 2,3-diaminonaphthalene to produce the piaselenole (Alfthan 1984). A standard reference material (BCR, Bovine Liver 185, Community Bureau of References, Brussels) was analyzed in each series (n=23), the mean $\pm$ SD value being 0.47 ± 0.01 mg/kg compared with the certified value of 0.47 ± 0.01 mg/kg. All analyses were done by the same laboratory personnel who were blinded for the case-control status of the subjects.

5.3.6 General interview

During the personal interview visit, which lasted approximately one hour, the study nurse filled in a questionnaire on socioeconomic background, medical history, family history of breast cancer, reproductive factors, physical activity, smoking, and current alcohol consumption. The same study nurse interviewed the subjects during the whole study, with the exception of the Validation Study (II), in which the information was collected by a student of nutrition science.

5.3.7 Body size and body composition

Height and weight were measured, and body mass index was calculated as weight (kg)/[height (m)]^2. Waist-to-hip ratio was measured by two measures of waist and hip circumferences. Waist circumference was measured midway between the lower rib margin and the iliac crest, and the hip circumference at the widest circumference over the greater trochanters. Body composition was measured by near-infrared interactance (FUTREX 5000; Futrex, Gaithersburg, MD, USA). The device transmits near-infrared light into the biceps of the dominant arm at a wavelength that allows fat to absorb the light and lean mass to reflect it back. The light absorption is measured to determine percent body fat, and from that were calculated the values of fat weight (kg) and lean weight (kg). The weakness of this method is that it analyzes only the amount of fat at the point of measurement (biceps of the arms). Near-infrared interactance and skinfold thickness are both useful field techniques, since they are inexpensive, safe, simple, and rapid. Near-infrared interactance was chosen in order to eliminate observer errors.

Because near-infrared interactance measures adiposity indirectly, the degree of error deserves extensive attention. No such data, especially from the perspective of epidemiological studies, exist. However, the errors related to indirect measurements of obesity imply that its health effects may be underestimated in epidemiological studies (Willett 1998).

5.3.8 Estrogen receptors

The samples for estrogen-receptor analysis were rapidly frozen (within 15 min of operation) in liquid nitrogen. Tumor blocks were cut into 8-μm slices which were mounted on glass slides coated with the tissue adhesive provided in the ER-ICA kit. The estrogen receptors were assayed using an ER-ICA kit (Abbot, North Chicago, IL, USA) at the laboratory of the Department of Pathology of Kuopio University Hospital. The laboratory and the assay is submitted to an inter-laboratory quality control program (Labquality, Helsinki, Finland). The immune-staining was performed according to the manufacturer's instructions. This method utilizes a monoclonal antibody and the peroxidase-anti-peroxidase (PAP) technique for visualization of estrogen receptors in a frozen section. A positive control slide provided by Abbott

(North Chicago, IL, USA) was used along with a negative control slide (frozen section of the sample without antibody).

Tumors with strong staining (ER) were coded as strong expression (ER++) and completely ER-negative tumors as ER-. Tumors with weak or moderate cytoplasmic expression of ER were coded as ER+.

5.3.9 Statistical methods

One population control (or 1-4 in Study II) was selected for each breast cancer case by individual matching for age (±5 years) and area of residence (urban/rural) in order to have similar distribution of these variables in both groups. However, because the individual matching was quite permissive and was based exclusively on age and area of residence, group matching was used in the analyses.

Analysis of variance (likelihood ratio test) was carried out to compare the distributions of selected variables between the cases and the population controls (and the referral controls in Study III). The accepted level of type I error was $p < 0.05$. The data were analyzed with the SAS statistical software package of the National Public Health Institute computing system (SAS Institute Inc. 1989).

Associations between exposures and risk of breast cancer were evaluated by logistic regression using odds ratios (OR) and corresponding 95% confidence intervals (95% CI) by quintiles. Body-size indicators, consumption of foods and alcohol, intakes of nutrients, and toenail selenium concentration were the explanatory variables in the analyses. The matching variables, age and area of residence (urban/rural), were included in all models (Ahlbom and Norell 1990). Further adjustment was made for known risk factors for breast cancer including age at menarche, age at first full-term pregnancy, use of oral contraceptives, use of postmenopausal estrogen replacement therapy, family history of breast cancer, history of benign breast disease, education, current alcohol intake (except for Study IV), smoking, physical activity, body mass index, and waist-to-hip ratio (except for Study II). In addition, Study V also included a factor for the year of recruitment, because the selenium level annually changed in Finland as a result of selenium supplementation through fertilizers, and factors for intakes of retinol, beta-carotene, vitamin E, and

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vitamin C. Further, when past alcohol consumption was examined, a factor for the duration between age at interview and the age at first alcohol use was added to the models, whereas total alcohol consumption before age 30 was adjusted for the duration between age at interview and age 30.

Before calculating odds ratios, the dietary factors were log-transformed to reduce skewness and improve normality as required by most statistical methods. The formula $\log(x+1)$ was used because all subjects did not consume each food item, and the non-transformed value would then have been zero. We also employed the residual method by Willett (1998) to make the dietary factors independent of total energy intake. The summary of log-transformation, energy adjustment, and factors included in the multivariate models is presented in Table 3.

The study design to examine recall bias using two control groups (the population controls and the referral controls) in the Dietary Study (III) has been reported in detail in Study III. In this dissertation, the terms "recall bias" and "reporting bias" are used synonymously.

The data were analyzed separately for premenopausal and postmenopausal women. Women who were over 50 and used postmenopausal estrogen replacement therapy were classified as postmenopausal; otherwise the self-reported menopausal status was used. Tumors were also classified according to estrogen-receptor (ER) status in the Body-size Study (I).

Certain additional statistical methods were employed in the Validation Study (II). Intraclass correlation coefficients were calculated to measure agreement of the food consumption and nutrient intakes based on the original FFQ1 and the repeated FFQ2. The intraclass correlation coefficient is defined as the ratio of between-person variation to total variation. Thus, high intraclass correlation implies low within-person variation. The Pearson correlation coefficient was used to assess correlation between the food consumption (or nutrient intake) in the FFQ1 and in the 14-day diet record. Within-person variation in FFQ measurements induces attenuation in the correlation coefficient. This was corrected using the formula:

$r_c = r_o * (1 + s^2_{intra}/s^2_{inter})^{1/2}$

where r_c denotes the corrected correlation, r_o the observed correlation, s^2_{intra} intraindividual variance, and s^2_{inter} interindividual variance for the FFQ measurements. Because epidemiological data are often analyzed categorically, for example as quartiles, or quintiles, the degree of misclassification needs to be measured. The proportion of subjects correctly categorized in the same or adjacent quintile of food consumption and nutrient intakes was calculated based on the FFQ1 and the 14-day diet record.

The Pearson correlation coefficients and the degree of misclassification were also determined when the consumption of alcohol was assessed on the basis of the FFQ1 and the AQ in Study IV. Furthermore, the validity between toenail selenium concentration and dietary selenium intake was evaluated by the Pearson correlation coefficient.

Table 3. Summary of log-transformation (Log), energy adjustment by residual method and the covariates in multivariate models (known risk factors for breast cancer and other factors) used in studies I-V.

Exposure	Log	Residual method	KRF[2]	Other factors
Body-size indicators	No	No	Yes	
Food groups	Yes	Yes	Yes	
Nutrients	Yes	Yes	Yes	
Vitamin supplements	Yes	No	Yes	
Current alcohol consumption	(Yes)[1]	(Yes)[1]	Yes	Body mass index
Past alcohol consumption	No	No	Yes	Body mass index
				Time between age at interview and age at first alcohol use
				Time between age at interview and age 30
Toenail selenium	Yes	No	Yes	Body mass index
				Year of recruitment
				Intake of antioxidants

[1] Since log-transformation and energy-adjustment did not affect the results for current alcohol consumption, only the results without these adjustments are presented.
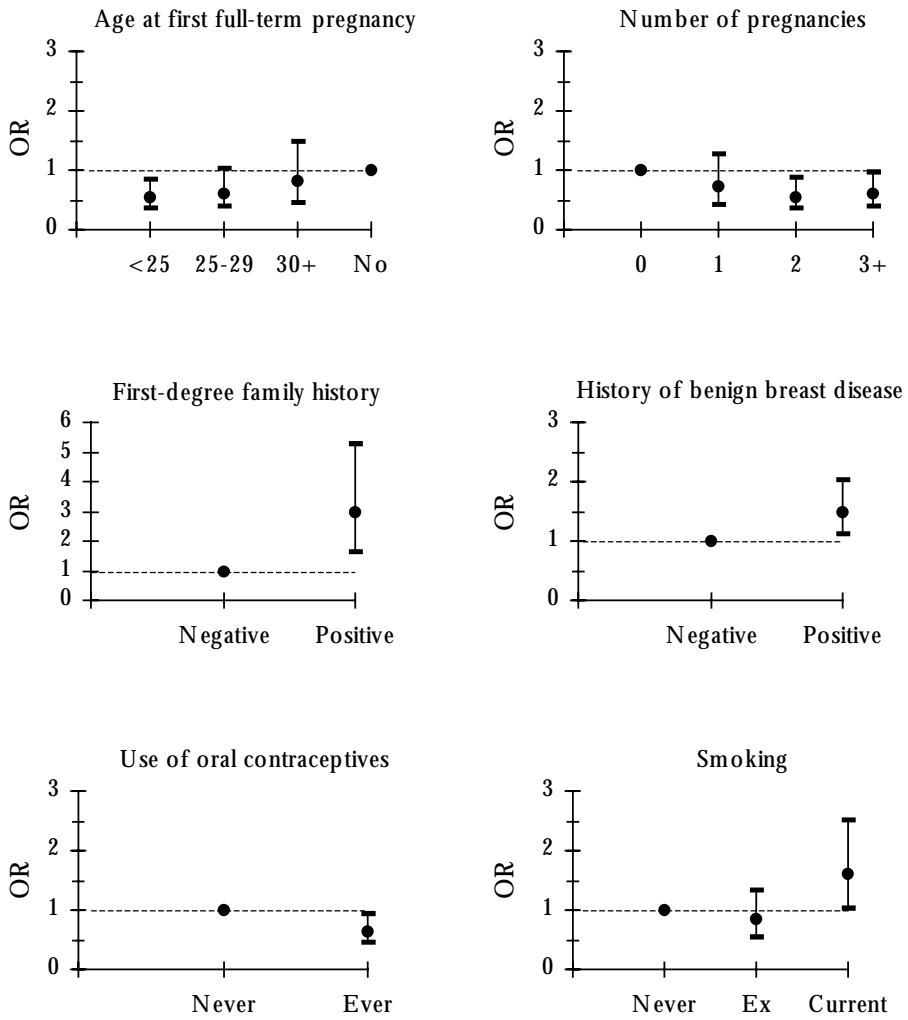
[2] Known risk factors.

6. Results

6.1 Associations between known risk factors and breast cancer (I)

Women who had delivered their first child under 30 years of age, had at least two children, or had ever used oral contraceptives had a lower risk of breast cancer than did other women (Figure 6). On the other hand, diagnosed breast cancer in first-degree relatives, other breast diseases earlier in their lifetime, or current smoking increased the risk. The most educated women had a relative risk of 1.4, and women who exercised physically once a week a relative risk of 0.7, but the associations were not statistically significant. No associations were found between breast cancer and factors related to menstrual cycle: age at menarche, age at menopause, or menopausal status.

6.2 Body-size indicators and risk of breast cancer (I)

Height was associated with risk of breast cancer. However, the association was not linear, since only the tallest women, in the fifth quintile, showed an increased risk. The relative risk of breast cancer was 1.8 (95% CI 0.8-4.2) for premenopausal women at least 169 cm tall and 2.3 (95% CI 1.1-4.6) for postmenopausal women at least 166 cm tall compared to those under 160 cm and 156 cm, respectively.

Weight and BMI were not associated with risk of breast cancer. Women whose waist-to-hip ratio (WHR) was high had an increased risk of breast cancer compared to those with a low WHR (Figure 7). The odds ratio was 4.6 (95% CI 2.0-10.7) for premenopausal women with a WHR at least 0.87 compared to women who had the lowest ratio (below 0.79). In postmenopausal women, the odds ratio between the highest (at least 0.89) and lowest quintiles of WHR (below 0.80) was 2.6 (95% CI 1.3-5.1). High body fat percent increased the risk of postmenopausal breast cancer in the highest quintile (OR 2.0, 95% CI 1.0-4.0) compared to the lowest one, whereas weight loss over ten kilograms after the age of 45 modestly decreased the risk (OR 0.6, 95% CI 0.3-1.2) when compared to figures for those who maintained their weight. Weight gain was related to risk of breast cancer neither in premenopausal nor in postmenopausal women.

Figure 6. Known risk and protective factors for breast cancer.

The proportion of ER-positive tumors was lower (47%) in premenopausal than in postmenopausal women (57%). No consistent associations were found between body-size indicators and estrogen receptor status (ER-, ER+ or ER++) of the tumor.

Premenopausal women

Body mass index

Waist-to-hip ratio

Postmenopausal women

Body mass index

Waist-to-hip ratio

Body fat percent
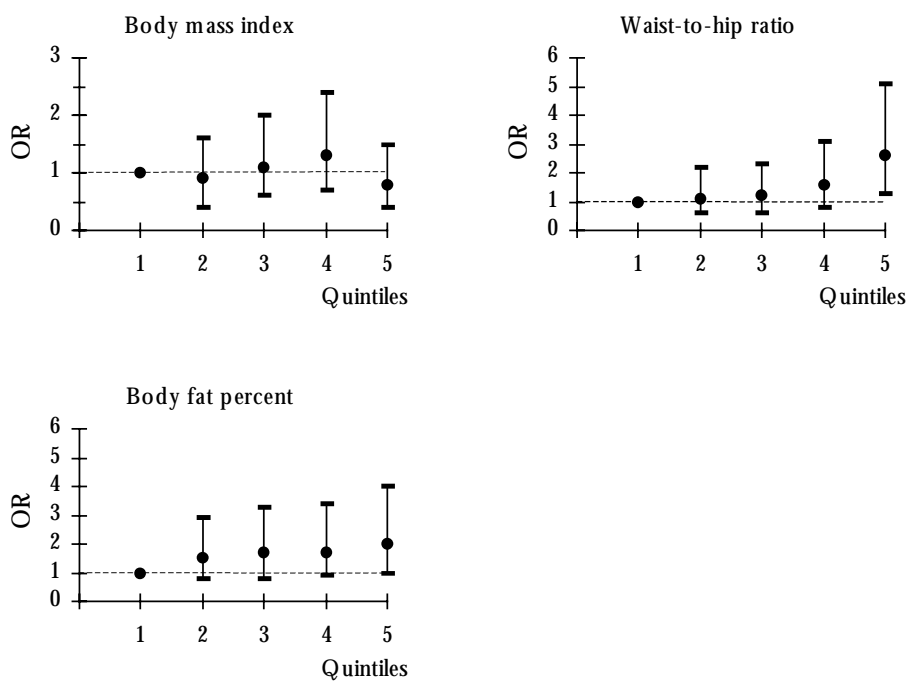
Figure 7. Selected body-size indicators and risk of breast cancer by menopausal status.

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6.3 Quality of food frequency questionnaire (II)

The aim of the Validation Study (II) was to assess whether the FFQ used in the Kuopio Breast Cancer Study measured what it was intended to measure. Overall, 29 food groups and 36 nutrients were included in the analyses, but in this section the focus is on the dietary factors (17 food groups and 14 nutrients) that were further examined in Studies III-IV.

Mean food consumption and nutrient intakes in the FFQ were generally lower than in the 14-day diet record (Figure 8). The consumption of sour milk, sugar, soft margarine, coffee, and tea were underestimated by more than 20% in the FFQ compared to figures in the diet records, whereas overestimation was more than 20% for vegetables and low-fat milk. Alcohol was underestimated by more than 20%, whereas overestimation was above 20% for retinol and beta-carotene (Figure 9).
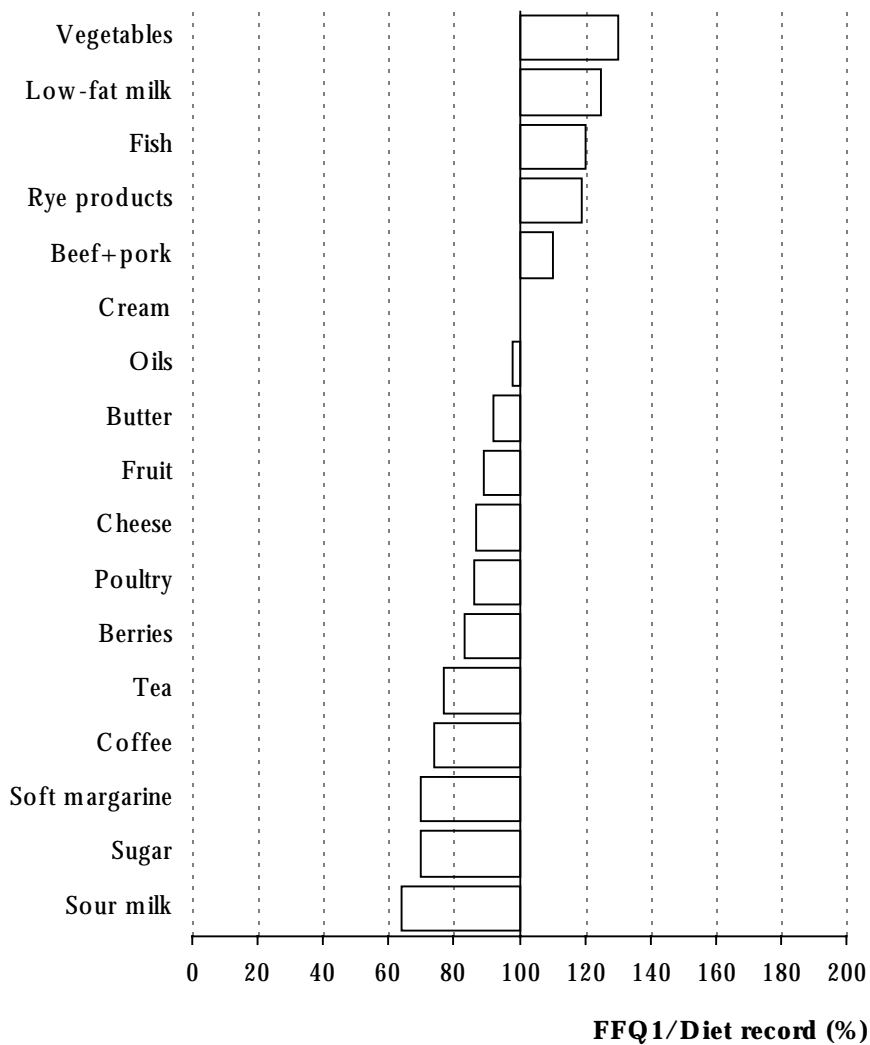
Figure 8. Mean consumption of foods based on the FFQ1 compared to the 14-day diet record.
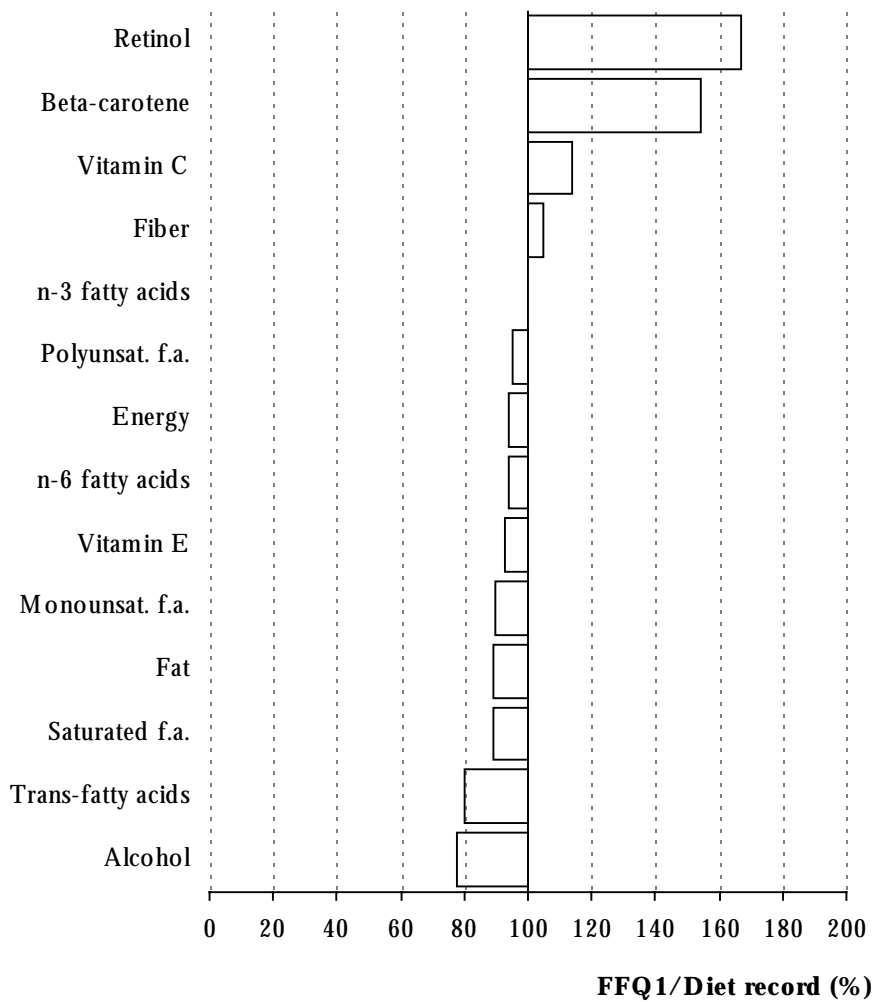
Figure 9. Mean intake of nutrients based on the FFQ1 compared to the 14-day diet record.

Figure 10 shows the positive association between reproducibility and validity of foods, i.e., good reproducibility was generally related to good validity and vice versa. Reproducibility or validity is good if the value is at least 0.70, acceptable if the value is between 0.50 and 0.69, and it should be at least 0.40 to avoid serious attenuation in the results (Willett and Lenart 1998). According to these limits, both reliability and validity were good (>0.7) for low-fat milk, soft margarine, and coffee, whereas none of these foods was measured extremely poorly (<0.4). The range of reproducibility varied between 0.5 and 0.8; berries, soft margarine, coffee, and most of the dairy products had a correlation over 0.7. The range of validity was quite large, ranging between 0.3 and 0.9. The validity was under 0.4 for oils and meat.

The range of reproducibility was very narrow, between 0.6 and 0.7, for nutrients (Figure 11). Alcohol consumption had a high validity (>0.7), whereas retinol, total fat, and monounsaturated fatty acids had low values (<0.4).

Energy adjustment improved the validity for nutrients more than that for foods, whereas the correction for the attenuation due to within-person variation was similar for nutrients and foods. The energy adjustment improved the correlation coefficient for foods on average 0.02 (between -0.05 and 0.06) and for nutrients on average 0.10 (between -0.04 and 0.24). The correction for the attenuation improved the values for foods on average 0.08 (between 0.04 and 0.12) and for nutrients 0.08 (between 0.06 and 0.10).

When quintile classifications were compared between the FFQ1 and the 14-day diet record, consumption of rye products, sour milk, and poultry were seriously misclassified (Table 4). Total fat, saturated fatty acids, trans-fatty acids, retinol, and vitamin C were the nutrients most often misclassified (Table 5).

In summary, validity was low for oil and meat (Figure 10). Misclassification may also attenuate associations between risk of breast cancer and rye products, sour milk, and poultry (Table 4). Among the nutrients, validity was low for retinol, total fat, and monounsaturated fatty acids (Figure 11), while saturated fatty acids, trans-fatty acids, and vitamin C were most often misclassified (Table 5).

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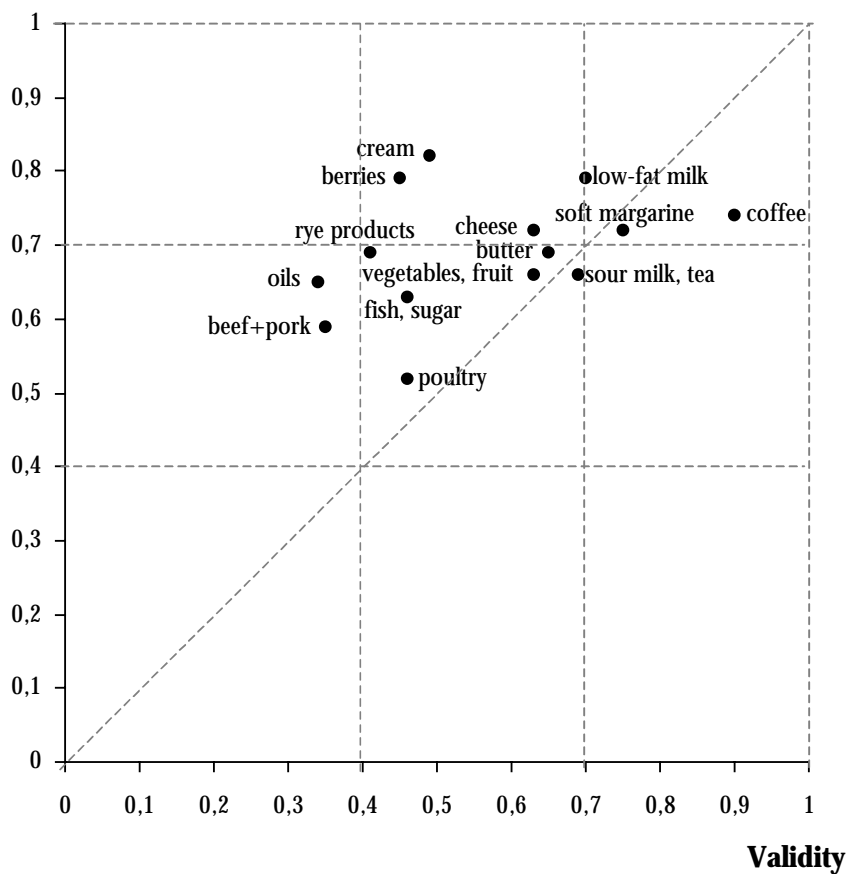
Reproducibility

Figure 10. Reproducibility and validity for energy-adjusted foods.

Reproducibility
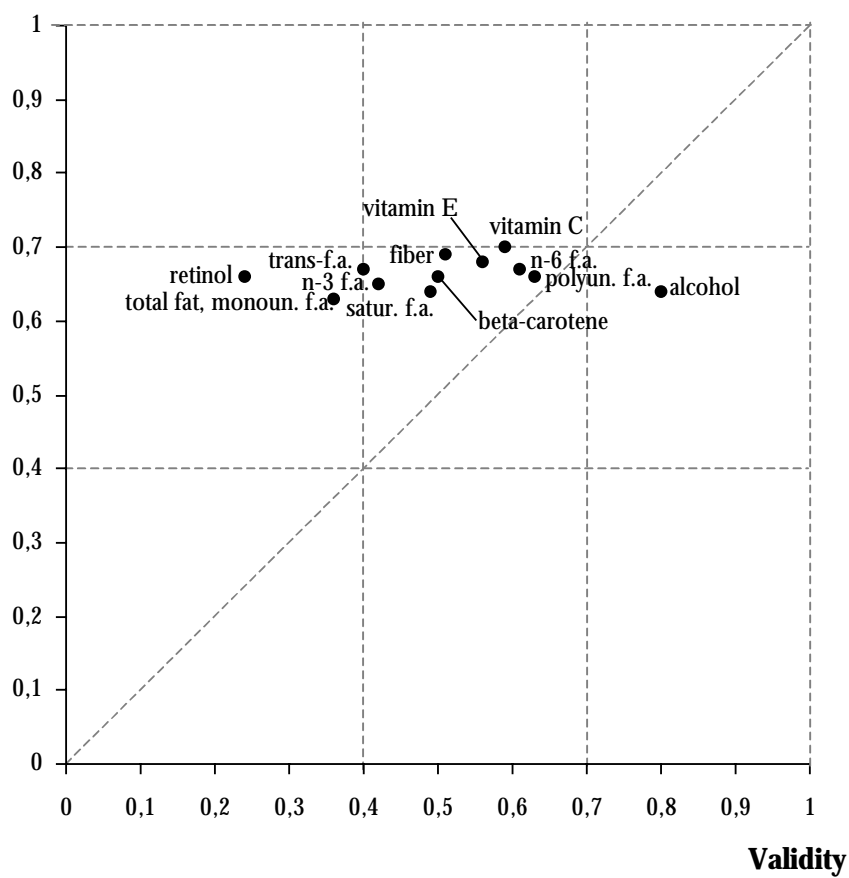
Figure 11. Reproducibility and validity for energy-adjusted nutrients.

Table 4. Cross-classification of food consumption between FFQ1 and diet records.

Food	Same or adjacent quintile based on both methods (%)	1st quintile on record but 5th quintile on FFQ (%)
Rye products	66	17
Vegetables	72	3
Fruit	68	7
Berries	69	10
Butter	80	3
Soft margarine	88	4
Oil	64	7
Low-fat milk	82	3
Sour milk	83	17
Cream	62	3
Cheese	72	7
Beef + pork	61	3
Poultry	57	14
Fish	63	10
Coffee	77	3
Tea	85	6
Sugar	78	7

Table 5. Cross-classification of nutrient intake between FFQ1 and diet records.

Nutrient	Same or adjacent quintile based on both methods (%)	1st quintile on record but 5th quintile on FFQ (%)
Total fat	59	13
Saturated fatty acids	69	13
Monounsaturated fatty acids	66	3
Polyunsaturated fatty acids	68	3
n-3 fatty acids	64	7
n-6 fatty acids	68	3
Trans-fatty acids	71	17
Fiber	61	7
Retinol	62	17
Beta-carotene	70	7
Vitamin E	59	7
Vitamin C	66	13
Alcohol	93	2

6.4 Food consumption and risk of breast cancer (III)

Associations between foods and risk of breast cancer as well as recall bias due to the threat of breast disease were examined in the Dietary Study (III). Comparison of breast cancer cases and population controls is the classical way of presenting results in case-control studies. The possible recall bias could be assessed by comparing the results in terms of two control groups (population controls and referral controls). Comparisons between the breast cancer cases and the referral controls are considered to result in "unbiased" odds ratios.

Consumption of low-fat milk and poultry was inversely related to the risk of premenopausal breast cancer, while sour milk seemed to increase the risk (Table 6). After the examination of reporting bias, high consumption of milk increased (OR 2.2, 95% CI 1.0-4.9) and poultry decreased (OR 0.4, 95% CI 0.2-0.9) risk of premenopausal breast cancer compared to that in women whose consumption was low.

Butter, oil, cheese, and coffee were related to postmenopausal breast cancer when analyses were carried out in the classical manner between the breast cancer cases and the population controls (Table 6). After the examination of reporting bias, the results showed that high consumption of cream (OR 1.9, 95% CI 1.0-4.0) was associated with increased risk, and high consumption of oil (OR 0.4, 95% CI 0.2-0.8) with decreased risk. There was also suggestive evidence that high consumption of milk and coffee may decrease, and butter increase the risk of postmenopausal breast cancer.

The reporting bias observed explained well the differences in results from use of population controls, referral controls and breast cancer cases. When the food consumption was under-reported or over-reported under the threat of disease, the estimated risk of breast cancer (between the breast cancer cases and referral controls) increased or decreased, respectively.

Table 6. Associations between foods and risk of breast cancer by menopausal status.

Food	Cases vs. Population controls	Cases vs. Referral controls	Reporting "under threat of breast cancer"
Premenopausal women			
Rye products	-	-	-
Vegetables	-	-	-
Fruit + berries	-	-	-
Butter	-	-	-
Soft margarine	-	-	-
Oil	-	-	-
Total milk	-	↑	underestimation
Low-fat milk	↓	-	underestimation
Sour milk	↑	-	(overestimation)
Cream	-	-	-
Cheese	-	-	-
Beef + pork	-	-	-
Poultry	↓	↓	-
Fish	-	-	-
Coffee	-	-	-
Tea	-	-	underestimation
Sugar	(↓)	-	(underestimation)
Postmenopausal women			
Rye products	-	-	-
Vegetables	-	-	-
Fruit + berries	-	-	-
Butter	↑	(↑)	-
Soft margarine	-	-	-
Oil	↓	↓	-
Total milk	(↑)	(↓)	overestimation
Low-fat milk	-	(↓)	(overestimation)
Sour milk	(↑)	-	(overestimation)
Cream	-	↑	underestimation
Cheese	↓	-	underestimation
Beef + pork	-	-	-
Poultry	-	-	-
Fish	-	-	-
Coffee	↓	(↓)	-
Tea	-	-	-
Sugar	-	-	-

6.5 Nutrient intake and risk of breast cancer (III)

In premenopausal women, no association between nutrient intake and risk of breast cancer was found in the comparison between the cases and population controls. However, some fatty acids were over-reported under the threat of breast cancer, especially n-3 polyunsaturated fatty acids (Table 7). Thus, after taking the reporting bias into account, a high intake of polyunsaturated fatty acids (OR 0.4, 95% CI 0.2-0.9), n-3 polyunsaturated fatty acids (OR 0.3, 95% CI 0.1-0.6) or n-6 polyunsaturated fatty acids (OR 0.4, 95% CI 0.2-0.8) was related to decreased risk of premenopausal breast cancer compared to risk in women whose intake was low. The association between polyunsaturated fatty acids and breast cancer disappeared when saturated, monounsaturated, and polyunsaturated fatty acids were mutually adjusted in the analyses. There was also some evidence that, under the threat of breast cancer, monounsaturated fatty acids were overestimated. Without overestimation, they may actually have been related to decreased breast cancer risk. This result was, however, not statistically significant. The intakes of total fat, saturated fatty acids, trans-fatty acids, and dietary fiber were not associated with premenopausal breast cancer. Although bias was shown in reporting vitamin intake, only high intake of vitamin E was found to decrease risk of breast cancer (OR 0.5, 95% CI 0.2-1.0).

In postmenopausal women, retinol increased and polyunsaturated fatty acids decreased risk of breast cancer in the comparison between the cases and population controls (Table 7). The association between polyunsaturated fatty acids and risk of breast cancer disappeared when saturated, monounsaturated, and polyunsaturated fatty acids were mutually adjusted in the analyses. High intake of beta-carotene decreased risk when the cases were compared to the referral controls (OR 0.5, 95% CI 0.2-1.0).

Table 7. Association between nutrient intake and risk of breast cancer by menopausal status.

Nutrient	Cases vs. Population controls	Cases vs. Referral controls	Reporting "under threat of breast cancer"
Premenopausal women			
Total fat	-	-	-
Saturated fatty acids	-	-	-
Monounsaturated fatty acids	-	-	-
Polyunsaturated fatty acids	-	↓1	(overestimation)
n-3 fatty acids	-	↓	overestimation
n-6 fatty acids	-	↓	(overestimation)
Trans fatty acids	-	-	-
Dietary fiber	-	-	-
Retinol	-	-	-
Retinol with supplements	-	-	underestimation
Beta-carotene	-	-	-
Beta-carotene with supplements	-	-	underestimation
Vitamin E	-	↓	overestimation
Vitamin E with supplements	-	-	-
Vitamin C	-	-	-
Vitamin C with supplements	-	-	-
Postmenopausal women			
Polyunsaturated fatty acids	↓1	-	-
Retinol	↑	-	-
Retinol with supplements	-	-	-
Beta-carotene	-	-	-
Beta-carotene with supplements	-	↓	-

↑ = increased risk, p<0.05, ↓ = decreased risk, p<0.05, ( ) = suggestive effect, - no association.
1 No association when saturated, monounsaturated and polyunsaturated fatty acids were mutually adjusted in the analyses.

6.6 Comparison of different methods of assessing alcohol consumption (IV)

Reported alcohol consumption was somewhat higher in the interview-based AQ than in the self-administered FFQ. The mean consumption of alcohol was 28 g/week for the premenopausal cases and 24 g/week for the premenopausal population controls based on the AQ, while the figures were 15 g and 14 g for the postmenopausal women. Based on the FFQ, the difference in alcohol consumption between the cases and population controls was statistically significant (p=0.03) only for postmenopausal women (9 g/week for cases and 14 g/week for population controls). About 30% of premenopausal and 60% of postmenopausal women were classified as abstainers.

The Pearson correlation coefficient between the AQ and the FFQ was 0.60 for the current alcohol consumption in all women, being high for the premenopausal women (0.80) and quite low for the postmenopausal women (0.40). No noteworthy difference, however, was found when current alcohol consumption was categorized into quintiles by the two alcohol measurement methods. In all, 64% of premenopausal and 70% of postmenopausal women were categorized in the same quintile. The percentages decreased to 59% and 57%, respectively, when only alcohol drinkers were compared. Reported lifetime non-drinking and ex-drinking levels were less accurate in postmenopausal than in premenopausal women. Ten postmenopausal women were maximally misclassified, but none of the premenopausal women. The overall proportion of ex-drinkers was quite low, 4% for premenopausal and 5% for postmenopausal women.

Current alcohol consumption was correlated with lifetime alcohol consumption in all women (r=0.74), but not so much with alcohol consumption at the age of first use (r=0.48) or with alcohol consumption before age 30 (r=0.42).

6.7 Current and past alcohol consumption and risk of breast cancer (IV)

Current alcohol consumption, based on the AQ, was not associated with risk of premenopausal or postmenopausal breast cancer. The odds ratios were around 1.0 for all alcohol consumption categories, with one exception for premenopausal ex-drinkers (OR 1.4, 95% CI 0.3-6.2). The results of the FFQ were comparable to those observed in the AQ.

Cumulative lifetime alcohol consumption was not associated with risk of breast cancer in premenopausal or postmenopausal women. In addition, alcohol consumption at early ages (before age 30) did not increase the risk.

6.8 Toenail selenium concentration and risk of breast cancer (V)

The mean toenail selenium concentration was 0.80 mg/kg in premenopausal cases and 0.84 mg/kg in the population controls, whereas the concentrations were 0.77 mg/kg and 0.80 mg/kg, respectively, in postmenopausal women. The relative risk of breast cancer between the highest and the lowest quintile of toenail selenium concentration was 1.1 (95% CI 0.4-3.2) for premenopausal women and 0.7 (95% CI 0.3-1.5) for postmenopausal women. Intakes of retinol, beta-carotene, vitamin E, and vitamin C did not modify these associations.

7. Discussion

7.1 Limitations of case-control studies

7.1.1 Study design

Ecological, case-control, cohort, and experimental study designs are used to assess relationships between diet and chronic diseases (Howe 1994). Ecological studies examine associations at the population level, which means that confounding factors such as economy and education may produce biased findings. Dietary data are collected by food balance sheets, which describe inaccurately the food consumption of individual subjects. Ecological studies generate hypotheses rather than test associations. Case-control and cohort studies, on the other hand, take into account food consumption and confounding factors at the individual level. Case-control studies have been more common, because they are easier, quicker, and cheaper to carry out than cohort studies. Case-control studies, however, are susceptible to selection and recall biases (Hebert and Miller 1988), and thus cohort studies in which subjects are recruited before the onset of disease are recommended although not always possible. Experimental studies investigate biological mechanisms and relevant timing of exposure. All these four designs are needed to gain deeper understanding of associations between dietary factors and diseases.

7.1.2 Selection bias

Selection bias occurs if exposed subjects participate selectively in a study (Howe 1994). The overall voluntary participation in medical studies has decreased during the last decades in the Western countries. This has been observed also in Finland where response rates have traditionally been quite high. For example in the FINRISK Surveys among Finnish adults, carried out every fifth year since 1972, the response rate has decreased from 91% to 76% for men and 94% to 85% for women living in Kuopio Province (Vartiainen et al. 1994). No data about the dropouts are available in this survey, but factors associated with non-response in the dietary survey among participants in the 1992 FINRISK Survey were young age, loss of spouse,

divorce, and less healthy dietary habits (e.g., consumption of fat and vegetables) (Roos 1998). Furthermore, obese men and male smokers as well as less educated women and female heavy drinkers had low response rates. On the other hand, women with a high education and healthy lifestyle are more likely to volunteer in epidemiological studies (Criqui et al. 1978, Rimer et al. 1996). In the Kuopio Breast Cancer Study, the response rate of the population controls was 72%. The reasons for non-response were not assessed in this study. The prevalence of smokers (14%), however, was somewhat lower than in another study carried out in Kuopio province (19%) (Vartiainen et al. 1994). Although the present study included more old women who smoked less, the possibility of a slight selection bias in terms of smoking cannot be excluded.

Selection bias is an important factor also when results are interpreted and generalized to different populations. A noteworthy feature of the study design was the attempt to recruit all breast cancer cases in the catchment area of the hospital. This aim was quite well achieved, which was shown by comparisons between the Finnish Cancer Registry, the clinical and pathological registers of the hospital and the register of the Kuopio Breast Cancer Study. In all, only 15% of all eligible breast cancer cases were missed. It is, however, possible that educated and wealthy women are over-represented in this group of non-participants, and thus difference between the cases and the population controls may have further widened with respect to health-consciousness. This may have theoretically biased the results as follows: if health-conscious subjects (more in population controls) tend to over-report foods that are considered healthy (e.g., fruit), it may increase the effects of protective factors, whereas if they underestimate foods possibly hazardous for health (e.g., fat), it may increase the effects of risk factors.

With certain reservations, the results of this study can be extrapolated to differing groups of women. It has been assumed that a dietary factor related to risk of breast cancer in one population is also probably an apparent risk or protective factor in other populations with a similar level of dietary exposure (Hebert and Miller 1988).

7.1.3 Recall bias

Another important bias related to case-control studies is recall bias, which occurs, for example, if cases report their food consumption differently from controls. This may happen because patients have often thought about their previous exposure in order to find causes for their disease. It has also been shown that subjects who are aware of exposure-disease relationships may over-report or under-report their consumption of certain food items. In the Kuopio Breast Cancer Study, the subjects with potential breast disease were interviewed before the diagnosis was known. However, the possibility of interviewer bias between the subjects referred to the hospital for breast examination and the population controls could not be eliminated.

Recall bias between diet and risk of breast cancer has been examined in only a few studies. The Adventist Health Study (Lindsted and Kuzma 1989, Lindsted and Kuzma 1990) and the Canadian National Breast Screening Study (Friedenreich et al. 1991a, Friedenreich et al. 1991b, Friedenreich et al. 1993) found no recall bias between the diets reported by cases and controls. The Nurses' Health Study found by comparing the 1986 questionnaire to the 1989 questionnaire a non-significant increase in relative risk, from 0.87 to 1.43, between fat intake and breast cancer (Giovannucci et al. 1993). On the other hand, in Sweden, breast cancer patients reported the consumption of meat, snacks, coffee, and tea differently from healthy women (Holmberg et al. 1996). None of these studies examined the possible effects of the threat of disease.

The approach examining recall bias in this study was different from the approach of earlier studies, in which the recall bias has been evaluated by comparing the reported diet before and after the diagnosis of breast cancer. We used two different control groups: population controls and referral controls. Because the diagnosis was not known at the time of interview, it was possible to evaluate whether worry about possible breast cancer changed the reporting of diet by comparing the results obtained from the two control groups.

This study showed that reporting bias due to the threat of breast cancer may change the results for some foods and nutrients. The premenopausal women tended to misreport the consumption of liquid milk products, tea and sugar.

The reporting of some fatty acids and vitamins was also different between the two control groups. The postmenopausal women misreported the consumption of milk products (all milk consumed, low-fat milk, sour milk, cream, and cheese). Despite the suspicion that recall bias is related to case-control studies, only one previous study on breast cancer has explicitly shown some recall bias in its data (Holmberg et al. 1996). That Swedish study was conducted in the 1990s, while the other studies on recall bias are from the 1980s when associations between diet and breast cancer had not yet been widely discussed in the media. It is also possible that the subjects under the threat of disease describe their diet as they wish it to be. This hypothesis is supported by a study in which the twin sisters of breast cancer cases reported changes in dietary habits that had not occurred (Richardson et al. 1993).

The enrollment methods of this study between the two control groups were not identical. The population controls were drawn from the Finnish National Population Register, whereas the referral controls comprised women who were referred to further breast examination but were later diagnosed as healthy. The question remains how much the control groups differed from each other. The referral controls were younger, had had more mammography examinations, and they reported more regular self-monitoring of their breasts than did the population controls (Study III). Therefore, the referral controls may have been more worried about their risk of breast cancer. All results, however, were adjusted for the known risk factors for breast cancer. Further adjustment for mammography examinations, self-monitoring, and seasonal variation in participation did not change the results. Nevertheless, the possibility of hidden premalignant breast disease in the referral controls cannot be ruled out. It is also possible that the threat of disease was not exactly the same between the breast cancer cases and the referral controls. No questions concerning this issue were presented in our study and no information on conversations between the first physician at the local health center and the subject was available. These issues should be kept in mind in future studies.

7.2 Other methodological considerations

The potential pitfalls of nutrition research, mainly related to dietary assessment methods, are briefly summarized here.

The imperfections of food composition databases add to the inaccuracy of information measured by dietary assessment methods (Hebert and Miller 1988, Kohlmeier and Mendez 1997). The official Finnish National Food Composition Database, which was used in this study, is of very high quality but certainly not perfect. For example, loss of vitamins in cooking could not be considered in the analyses, with some exceptions (potatoes and cooked vegetables) (Ovaskainen et al. 1996).

Another problem of nutrition research is that some subjects (e.g., female, obese and more educated subjects) tend to under-report their food consumption. This tendency has increased during the last decades because of increasing health-consciousness. In the 1992 Dietary Survey of Finnish adults, over 40% of subjects underestimated their energy intake when estimated basal metabolic rate was used as a reference method (Hirvonen et al. 1997). Another study observed that 46% of subjects admitted having altered their diet during the period when they completed a 7-day weighed food record (Macdiarmid and Blundell 1997). Two main reasons for misreporting were the knowledge of unhealthy dietary habits and neglect in recording all food items accurately. Although energy adjustment is used to correct under- and overestimation of FFQs (Willett 1998), it is possible that misclassification may dilute associations between diet and diseases.

Undiagnosed illness may change the appetite and thus alter the subject's reporting of diet. This concerns especially cancers of the digestive tract, whereas the effect is minor in breast cancer, which is often diagnosed at an early stage. In the Kuopio Breast Cancer Study, most of the tumors were diagnosed at an early stage: 60% were axillary-node negative, and only 2% of the patients had stage IV disease (distant metastases) at the time of the diagnosis.

Other factors, such as alcohol consumption, smoking, and education, may correlate with dietary factors, and thus confound associations between diet and diseases (Franceschi 1993). In this study, the results were adjusted for the known risk factors for breast cancer (the most important factors were first-degree family history of breast cancer, history of benign breast disease, age at first full-term pregnancy, and use of oral contraceptives). In most of the models, interpretation of the results was quite similar between the basic model (including age and area of residence) and the multivariate model.

7.3 Associations between diet, body size, and breast cancer

Body-size indicators and risk of breast cancer

High body mass index did not increase risk of breast cancer in the Kuopio Breast Cancer Study, whereas waist-to-hip ratio was linearly related to risk. Relative risk was 4.6-fold in premenopausal women and 2.6-fold in postmenopausal women categorized into the highest quintile of waist-to-hip ratio compared to the lowest one. High waist-to-hip ratio is an independent predictor of metabolic disturbances in sex-steroid metabolism, glucose metabolism, and insulin-like growth factors (see Ballard-Barbash 1994, Stoll 1996). Besides these factors, behavioral characteristics such as weight cycling, smoking, high alcohol consumption, low physical activity, and high parity may explain a high waist-to-hip ratio (Seidell 1991, Kahn et al. 1997, Han et al. 1998). Our result on waist-to-hip ratio is compatible with earlier findings (Table 8) such as a recent cohort study including 11,663 subjects in the Netherlands, in which the relative risk of breast cancer in women with natural menopause was 2.63 (95% CI 1.09-6.35) for high waist-to-hip ratio compared to women with a low ratio (Kaaks et al. 1998).

In a clinical setting, waist-to-hip ratio can be measured accurately, and thus women with an increased risk of breast cancer are easily identified (Roberts et al. 1997). In Finland, obesity (Pietinen et al. 1996, Lahti-Koski et al. 1999a) and waist-to-hip ratio (preliminary results, Lahti-Koski et al. 1999b) have significantly increased since the 1970s. The National Academy of Sciences (1989) has recommended that waist-to-hip ratio should not exceed 0.80. In this study, only 20-30% of premenopausal and postmenopausal women had a waist-to-hip ratio within the recommended limits.

High body fat percent doubled the risk of postmenopausal breast cancer in this study. This may be explained by an elevated estrogen level in obese postmenopausal women due to the conversion of androgens into estrogen in adipose tissue after the menopause (see Ballard-Barbash 1994).

In the Nurses' Health Study, weight gain seemed to be a potential risk factor in those postmenopausal women whose weight was low at the age of 18 and who had never used postmenopausal estrogen replacement therapy (RR=1.99, 95% CI 1.43-2.76) (Huang et al. 1997). No association between

adult weight gain and breast cancer was found in the Kuopio Breast Cancer Study (Table 8). However, the lowest weight in adulthood, causes for gaining weight, and weight cycling were not asked about.

It is well known that height may modestly increase risk of breast cancer (see Hunter and Willett 1996) (Table 8). In this study, the tallest women had a two-fold risk of breast cancer compared to the shortest ones with the analyses adjusted for age at menarche.

Table 8. Comparison of findings in earlier studies and in the Kuopio Breast Cancer Study.

	Summary of earlier studies	Kuopio Breast Cancer Study
Nutrients		
Total fat	-	-
Saturated fatty acids	-	-
Monounsaturated fatty acids	($\downarrow$)	-
Polyunsaturated fatty acids	-	-
n-3 fatty acids	($\downarrow$)	$\downarrow$pre
n-6 fatty acids	-	$\downarrow$pre
Trans-fatty acids	-	-
Fiber	-	-
Beta-carotene	($\downarrow$)	$\downarrow$post
Vitamin E	-	$\downarrow$pre
Vitamin C	-	-
Non-nutrients		
Alcohol	$\uparrow$	-
Other factors		
Height	$\uparrow$	$\uparrow$
Body mass index	($\uparrow$post, $\downarrow$pre)	-
Waist-to-hip ratio	$\uparrow$	$\uparrow$
Adult weight gain	($\uparrow$)	-

$\uparrow$, $\downarrow$ Convincing effect
$\uparrow$pre Convincing effect for premenopausal women
$\uparrow$post Convincing effect for postmenopausal women
( ) Suggestive effect
 - No association

Diet and risk of breast cancer

The findings between fat intake and risk of breast cancer in epidemiological studies have been inconclusive (Table 8). In a review of case-control studies, high fat intake was modestly related to an increased risk of breast cancer (Boyd et al. 1993). Because fat intake, however, did not appear to increase the risk in a pooled analysis of seven cohort studies (Hunter et al. 1996), it has been suggested that type of fat may be more important than total amount of fat (Table 8). Different kinds of fatty acids may have diverse effects on carcinogenesis of breast cancer, and thus flatten out the importance of total fat. In this study, no relation to total fat was found (after exclusion of reporting bias), whereas a high intake of n-3 and n-6 polyunsaturated fatty acids (and perhaps monounsaturated fatty acids) was related to a lower risk of breast cancer, especially in premenopausal women. The intakes of saturated fatty acids and trans-fatty acids were not associated with breast cancer. It seems that the types of fats considered beneficial against other major diseases, such as cardiovascular diseases and diabetes, may also decrease the occurrence of breast cancer.

A diet rich in olive oil has been related to the low breast cancer incidence in the Mediterranean countries, and monounsaturated fatty acids have been suggested to play a central role in this relationship. Rapeseed oil, which is the most consumed oil in Finland, consists of plenty of monounsaturated fatty acids as well as α-linoleic acid (n-3 series fatty acid). In Sweden, where fatty acid composition of the diet is quite similar, monounsaturated fatty acids decreased and polyunsaturated fatty acids increased the risk of breast cancer in a cohort study of 674 breast cancer cases aged 40 to 76 (Wolk et al. 1998). Although oil consumption has become more common in Finland since the 1980s, mean consumption is still low, only 3.5 g per day (National Public Health Institute 1998). It is therefore possible that oil does not have an effect of its own but acts as an indicator of oil consumers' healthy lifestyles. It should also be noted that intakes of fatty acids are difficult to assess without biochemical indicators because dozens of new soft margarine products with various fatty acid compositions have been developed during the last years. It is difficult to separate the intakes of monounsaturated and polyunsaturated fatty acids due to reporting inaccuracies and due to difficulties in keeping food composition databases up-to-date with the fast product development.

Some studies have associated dairy products, such as fermented milk, cheese, and yogurt (Le et al. 1986, van't Veer et al. 1989a), with decreased risk of breast cancer. By altering the intestinal bacterial activity, these products may influence the formation and function of estrogenic compounds. Furthermore, micro-organisms provided by cultured dairy product may stimulate immunological activity in the host. It is also possible that the conjugated linoleic acid (CLA) found especially in dairy products and meat may prevent the development of mammary tumors (Ip and Scimeca 1997), even in small quantities (under 1% in the diet) (Ip et al. 1995). CLA, which is produced from linoleic acid by microflora in the rumen (Kepler et al. 1966), may be one explanation for the inverse association between milk consumption and breast cancer found in a Finnish cohort study (Knekt et al. 1996). Human studies specifically focusing on CLA and breast cancer have not yet been published. In the Kuopio Breast Cancer Study, high consumption of milk products tended to decrease postmenopausal breast cancer. However, high milk consumption increased the risk of breast cancer in premenopausal women. No relationship was found for sour milk, either in the premenopausal or postmenopausal women.

Lignans and isoflavonoids are food components that are converted to biologically active hormone-like substances by intestinal microflora and may have anticarcinogenic effects (Adlercreutz et al. 1992). Rye bread, which is the most important contributor of fiber to the Finnish diet, also contains high amounts of lignans (enterolactone). However, no association was found between rye products and risk of breast cancer in this study, although the mean daily consumption of rye product varied from 34 g to 120 g in quintiles. Misclassification of rye products was high, apparently because of the large variation in the bread types consumed in Finland. Serum enterolactone concentration has been analyzed in the Kuopio Breast Cancer Study, and the results will be presented later. The only human study published thus far showed that high urinary excretion of enterolactone and equol predicts a lower risk of breast cancer compared to that of women with low excretion levels (Ingram et al. 1997).

High consumption of fruit and vegetables rich in fiber and vitamins has been found to decrease the risk of all cancers. The association, however, has been more consistent for cancers of the lung and stomach than for hormone-related cancers (Steinmetz and Potter 1996). A cohort study in the United

Kingdom found that after a 17-year follow-up the all-cause mortality of 11,000 vegetarians and health-conscious subjects was only one half that of the general population (Key et al. 1996). However, no decrease was found in breast cancer mortality. Most vitamin studies have focused on the possible protective effects of beta-carotene. Many of them, however, have been too small to detect any differences (see Kohlmeier and Mendez 1997). In this study, neither fruit nor vegetables were associated with the risk of breast cancer, but the increased intake of beta-carotene decreased the risk of postmenopausal breast cancer (Table 8). The associations between vitamins and breast cancer did not change when the dietary supplements were added to the nutrient intake. It may be that the protective effects of supplements exist only in a situation where the antioxidant intake is low, or consumption has been continued for a long time (Blot et al. 1993). In this study, it was impossible to separate subjects who had recently begun to use supplements from long-term users. It is also possible that beta-carotene may act as a marker for other potential factors, such as other carotenoids, flavonoids, phenols, or plant sterols.

Food frequency questionnaire of the Kuopio Breast Cancer Study

The validity of nutrient intakes measured by FFQ was compared between the Nurses' Health Study (Willett et al. 1985), the ATBC Study (Pietinen et al. 1988), and the Kuopio Breast Cancer Study (Table 9). It seems that the results of the present Validation Study (II) were comparable to the validation study which included 173 female nurses (Willett et al. 1985), whereas the 168 Finnish men had slightly better correlation coefficients, especially for saturated fatty acids, fiber, and vitamin E (Pietinen et al. 1988). Women are more health-conscious than men, and thus tend to misreport their diet by responding in a manner better matching social norms and beliefs (Hebert et al. 1997).

The Validation Study (II), however, showed that it may be impossible to detect associations between rye products, total fat, saturated fatty acids, trans-fatty acids, vitamin C, and risk of breast cancer.

Table 9. Validity of the food frequency questionnaire against the diet records in the Nurses' Health Study (Willett et al. 1985), in the ATBC Study (Pietinen et al. 1988), and in the Kuopio Breast Cancer Study. Nutrient intakes adjusted for total energy intake.

Nutrient	Nurses' Health Study	ATBC study	Kuopio Breast Cancer Study
Total fat	0.48	0.39	0.35
Saturated fatty acids	0.49	0.62	0.49
Monounsaturated fatty acids	-	0.38	0.36
Polyunsaturated fatty acids	0.42	0.69	0.63
n-3 fatty acids	-	-	0.42
n-6 fatty acids	-	-	0.61
Trans-fatty acids	-	-	0.40
Fiber	0.51	0.72	0.51
Vitamin A[1]	0.28	0.31	0.26
Vitamin E[1]	-	0.66	0.56
Vitamin C[1]	0.52	0.58	0.59
Alcohol	-	0.80	0.80

[1] Without supplements

Toenail selenium concentration and risk of breast cancer

Ecological and animal studies have found a strong relationship between low selenium intake and cancers of the breast and colon (Schrauzer et al. 1977, Willett et al. 1991). In case-control and cohort studies, selenium deficiency is more related to cancers of the digestive tract and lung than to breast cancer (Willett et al. 1991).

In this study, selenium status was analyzed in toenails, which are considered as appropriate material for assessing selenium intake over 6 to 12 months (Longnecker et al. 1993). Selenium was not associated with premenopausal breast cancer. In postmenopausal women, the relative risk of breast cancer was below unity in all three upper quintiles, but the findings were not statistically significant. This result was similar to that of a Finnish cohort study carried out between 1968 and 1972. In that study, the relative risk for the highest four quintiles of selenium intake was 0.52 compared to the lowest, but it was not statistically significant (Knekt et al. 1990). Low toenail

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selenium concentration was not associated with risk of breast cancer in a large cohort study in the United States (Hunter et al. 1990), in the Netherlands (van den Brandt et al. 1994), nor in a multicenter case-control study (van't Veer et al. 1996). Furthermore, the multicenter study found no interaction between toenail selenium and other antioxidants in adipose tissue (beta-carotene and alpha-tocopherol). Our results showed that the intake of retinol, beta-carotene, vitamin A, and vitamin C, used as covariates in the model, did not change the association between toenail selenium and breast cancer.

The most important question in the Selenium Study (V) is whether the selenium supplementation through fertilizers has changed the ranking of subjects by their selenium intake. It was possible to examine the question in the ATBC Study including 29,000 men (Hartman et al. 1998). No notable difference in ranking (r=0.83) was observed when selenium intake was calculated from the same food consumption data using a database based on pre-supplementation values, and then using that based on post-supplementation values. Another important question is the time frame between the recruitment of the case and the matched population control that was meant to be limited to one to two months. The interval was longer for a few subjects, but never more than one year. The time of recruitment was controlled for in the analyses.

Current and past alcohol consumption and risk of breast cancer

There is a consensus based on epidemiological studies that more than two to three alcoholic drinks per day increase risk of breast cancer (Howe et al. 1991b, Smith-Warner et al. 1998). In the present study, the current alcohol consumption was not related to the risk of premenopausal or postmenopausal breast cancer. The alcohol consumption was, however, quite low, because the premenopausal women consumed, on average, only two drinks and postmenopausal women about one drink per week, and because 30% and over 50% of them were categorized as abstainers, respectively. The proportion of abstainers was quite high, but did not differ from the results of a preanalysis of lifetime alcohol consumption by birth cohorts (35- to 76-year-old subjects in the United States) (Russell et al. 1997). In that study, about 40% of subjects were abstainers in all birth cohorts through the decades. It should also be noted that variation in social norms of alcohol

consumption affects differently cohorts born at different times (Lemmens 1998). Postmenopausal women in Finland belong to a female generation that has never consumed much alcohol. In the 1982 Dietary Survey of Finnish adults, the 55- to 64-year-old women consumed only 3 g alcohol per week, whereas the 25- to 34-year-old women consumed 17 g per week (Kleemola et al. 1994); the values were 10 g and 25 g per week in the 1992 Survey, respectively (National Public Health Institute 1998). Furthermore, it is possible that older women report their drinking habits more inconsistently than do younger women, which tendency was also observed in this study.

Consumption of coffee and alcohol seem to be negatively related to each other (Le Marchand et al. 1989, La Vecchia et al. 1992, Männistö et al. 1996). Therefore, it has been suggested that coffee and alcohol may be competitors in the diet. Coffee may affect estrogen metabolism by increasing sex hormone-binding globulin, and thus decrease the risk of breast cancer (Ferrini and Barrett-Connor 1996). In a cohort study in Norway, including 14,593 premenopausal women, high coffee consumption decreased the risk of breast cancer in lean women (BMI<24) but increased the risk in others (Vatten et al. 1990b). In Finland, coffee consumption is one of the highest in the world, on average over 400 g per day for women (National Public Health Institute 1998). This study showed a decreased risk of breast cancer among postmenopausal women drinking over 480 g coffee a day.

A challenge for breast cancer studies is to define the most sensitive period in a woman's lifetime in the development of breast cancer. Food frequency questionnaires typically evaluate dietary habits over the preceding 12 months, which may be totally irrelevant in examining a disease with a long latency period. As a biological explanation, it has even been speculated that intrauterine factors may advance mutations in the mammary gland (Michels et al. 1996). The most powerful biological explanation, however, is related to the hypothesis that the period between menarche and the first full-term pregnancy is particularly important because of changes in the breast tissue (Moolgavkar et al. 1980, MacMahon 1993, Colditz 1995).

It has been suggested that lifetime alcohol consumption may predict the alcohol exposure more accurately than would current alcohol consumption (Longnecker et al. 1995). The lifetime alcohol consumption questionnaire (AQ) was used in the Kuopio Breast Cancer Study to obtain information on

alcohol consumption during different times (age of first use, before the age of 30, and cumulative lifetime consumption). In contrast to a study in the United States (Longnecker et al. 1995), no evidence on an association between past alcohol consumption and risk of breast cancer was found in this Finnish population.

The methods for assessing lifetime alcohol consumption have been reasonably good in reliability, between 0.67 and 0.90 (Lemmens et al. 1997). Although the validity for absolute amounts has been poor, the relative ranking has been reasonably stable, as shown by the validity for current alcohol consumption (between r=0.63 to 0.73) (Feunekes et al. 1999). It is, however, possible that all methods consistently measure alcohol consumption poorly, for example, with similar under-reporting. One study has examined the reporting of the initiation of alcohol and tobacco use among school children. When the questionnaire was repeated three times in 1989, 1991, and 1994, it was found that the older the students became, the older they reported the age when they started to drink alcohol (Engels et al. 1997).

In the Validation Study (II), the reliability of the current alcohol consumption was 0.64, and the validity between the first FFQ and the 14-day diet record was 0.80. Almost all subjects (95%) were categorized into the same or adjacent alcohol quintile by means of the FFQ and the diet records. The validity of the current alcohol consumption was also assessed by comparison of the first FFQ and the AQ, with the correlation was found to be higher for premenopausal women (r=0.80) than for postmenopausal women (r=0.40). In all, 64% of premenopausal and 70% of postmenopausal women were classified into the same category by the FFQ and the AQ. In general, the interview-based AQ yielded higher alcohol consumption figures than did the self-administered FFQ. The complexity of the lifetime alcohol consumption questionnaire may be lessened if it is administered by trained interviewers (Lemmens 1998).

Current alcohol consumption may influence the reporting of past alcohol consumption (Swanson et al. 1997), especially if the subject's drinking habits have changed many times (Lemmens 1998). In this study, the correlation between current alcohol consumption and lifetime alcohol consumption was high (r=0.74).

7.4 Future directions

The variation in diet is often too narrow in studies within one country compared to the worldwide range. Thus, it is possible that some potential risk or protective factors for a disease cannot be recognized. Multicenter studies and pooling projects have been initiated to combine the advantages of individual and population-based studies. One example is the European Prospective Investigation on Cancer and Nutrition (EPIC), a very large cohort study involving almost half a million participants from nine Western European countries. The pilot phase concerning the accuracy of dietary assessment methods in each study center has been reported (Kaaks et al. 1997). The second example is the International Collaborative Study of Breast and Colorectal Cancer, in which the Kuopio Breast Cancer Study is one of the nine study centers (Boyle 1990).

Pooling of large cohort studies is a new approach to assess associations between diet and cancers. The Harvard Pooling Project includes nine large cohort studies, and it has produced, for example, a pooled analysis on the association between alcohol consumption and risk of breast cancer (Smith-Warner et al. 1998). New analyses concerning foods are in progress.

Some on-going intervention studies in humans are also of interest, for example, the Women's Health Initiative. That randomized trial including 48,800 women aged 50 to 79 was begun to determine whether a low fat diet decreases occurrence of breast cancer (Self et al. 1988). The last subjects of the trial were recruited during the summer of 1998.

The methods of nutritional epidemiology need to be developed by improvement in study hypotheses, study designs, and contribution of statistical methods, such as new models of measurement error (Carroll et al. 1995). The challenge is to understand and estimate better the problems in dietary assessment methods, for example, variation between and within individuals. Study designs may be improved by use of more than one method to assess the same exposure. In addition, it would be beneficial to find more biochemical indicators to estimate nutritional status. This study used, two different kinds of methods to assess alcohol consumption, two control groups to examine reporting bias under the threat of disease, and toenail selenium as a biochemical indicators of selenium status.

More information is needed on the effects of the different stages of disease on diet and diet reporting, such as presymptomatic illness, the threat of disease, and diagnosed breast tumor (changes in metabolism caused by disease or treatment and intentional changes in dietary habits in an attempt to improve prognosis). It is also unknown how much of the changes in reporting are truthful and how much reflect merely the wish for better dietary habits. The role should also be clarified for different kinds of fatty acids and phytoestrogens, for weight gain and for factors related to abdominal obesity, as well as for the interaction between genes and environmental factors in the etiology of breast cancer. Moreover, better knowledge is needed of the most sensitive periods in a woman's lifetime in the development of the breast.

7.5 Summary of the main findings

This dissertation was part of the Kuopio Breast Cancer Study, a case-control study carried out in eastern Finland. The main objective of the diet study was to examine the possible role of body-size indicators, dietary factors and alcohol consumption in the development of breast cancer. Special attention was also paid to the study design and dietary assessment methods.

Weight and body mass index were not associated with risk of breast cancer. However, waist-to-hip ratio, which indicates body fat distribution more accurately, was a strong risk factor. Those premenopausal women categorized into the highest quintile of waist-to-hip ratio had a 4.6-fold and postmenopausal women a 2.6-fold risk of breast cancer compared to women in the lowest category. Further, in postmenopausal women, high body fat percent was associated with an increased risk of breast cancer.

The quality of dietary data was assessed by comparing the food frequency questionnaire (FFQ) to the 14-day diet record and by assessing recall bias under the threat of disease. The validity and reproducibility of the questionnaire were comparable to those in previous studies. This study showed that recall bias may distort the interpretation of results between dietary factors and disease in case-control studies. Those premenopausal women who were under the threat of breast cancer tended to misreport their consumption of milk products and tea. Recall bias was also related to the intake of fat and vitamins. In postmenopausal women, recall bias seemed to be associated with the reporting of milk products. It has been suggested that

the recall bias of case-control studies may explain the discrepancies in results between case-control and cohort studies. The interpretation of results can be improved by using different types of methods to assess the same dietary factors.

Dietary factors did not play an important role in the occurrence of breast cancer in this study. However, a diet rich in milk increased, whereas high consumption of poultry decreased the risk of premenopausal breast cancer. Consumption of oil was negatively, and that of cream positively associated with risk of breast cancer in postmenopausal women. Suggestive evidence was found for butter, milk, and coffee. Among nutrients, high intakes of n-3 and n-6 polyunsaturated fatty acids and vitamin E were related to decreased risk of premenopausal breast cancer, while beta-carotene decreased the risk in postmenopausal women. This study supports the evidence that the quality of fat may be more important than total fat intake in the development of breast cancer. It is possible that dietary factors have independent effects, but they can also be merely indicators of a healthy lifestyle.

Current and past alcohol consumption were not associated with premenopausal or postmenopausal breast cancer among women with generally low alcohol consumption. When the validity of current alcohol consumption was assessed by comparing the food frequency questionnaire to the lifetime alcohol consumption questionnaire, it was found that older women were somewhat more inaccurate in their reporting than were younger women.

No association was found between toenail selenium concentration and risk of breast cancer, and this result was not changed by adjusting for intake of beta-carotene, retinol, vitamin E, and vitamin C.

Conclusion. Epidemiological studies furnish information on healthy dietary habits. The aim of this study was to find means for decreasing risk of breast cancer. These include maintenance of normal body size throughout one's lifetime and avoidance of high abdominal fat and body fat percent. High intake of fatty acids such as n-3 and n-6 polyunsaturated fatty acids that are generally considered healthy, certain vitamins, and the consumption of oil were also related to decreased risk of breast cancer. On the other hand, women do not need to be worried about one to three alcoholic drinks per

week, although level of alcohol consumption was too low to exclude increased risk with high regular consumption. These findings are in line with general recommendations to lower the overall cancer incidence.

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