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LIFESTYLE FACTORS AND BREAST CANCER IN FINLAND

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ACADEMIC DISSERTATION

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1 ABSTRACT

Breast cancer is the most common cancer in women in Finland. It is often considered as a disease of affluent, Western societies with many known risk factors such as late age at first birth, small number of children, and sedentary lifestyle, among others. In addition, there are more novel exposures that are popular in modern Western societies and carry suspected carcinogenic potential, including use of hormonal contraceptives and personal use of hair dyes. The aim of the thesis was to evaluate the roles of such lifestyle factors and to assess how they contribute to the risk factor spectrum. The thesis is composed of four sub studies; Study I estimating the association between the use of hormonal contraceptives and breast cancer risk and Study II aiming at determining whether the use of hair dyes independently increases risk of breast cancer. Study III estimated the proportion of women who had an opportunistic mammography before the age 50 years and assessed the roles of breast cancer family history and educational level in having a mammography. Study IV investigated the impact of major life events in breast cancer-specific mortality.

Self-reported survey data was used as source of exposure information in all sub studies. Information on the outcomes of interest, namely breast cancer diagnosis and breast cancer-specific deaths were retrieved from the Finnish Cancer Registry. In Studies I and II, analyses by conditional logistic regression were conducted to estimate odds ratios (OR) and 95% confidence intervals (CI). In Study III, percentages of women reporting opportunistic mammography were calculated either directly or by Kaplan-Meier method. In Study IV, different Cox models were used to estimate breast cancer-specific mortality hazard ratios and 95 % confidence intervals.

Use of hormonal intrauterine device (HR IUD) increased the risk of breast cancer in post-menopausal women by 52% (OR 1.52, 95% CI: 1.14-2.02), relative to users of copper IUD. Use of other hormonal contraception was by contrast associated with risk of breast cancer in younger women (OR 1.32, 95% CI: 1.08-1.61), when compared to never-users. An OR of 1.23 (95% CI: 1.11-1.36) was observed for women using hair dyes, relative to those who had never dyed their hair. Opportunistic mammography was also found to be very common, with more than 60% of responders reporting having had a mammography before screening age. Mammographies were also more common in women who had breast cancer family history and/or higher education. A large number of experienced negative life events was associated with 4% higher risk of breast cancer-specific mortality, some positive events accordingly lowering it.

The prevalence of classical breast cancer risk factors, such as obesity and alcohol use have increased markedly over the past decades in Finland. Parity and total fertility are continuing to decline. These factors are more and more

commonly complemented by risk effects produced by use of exogenous hormones and cosmetics such as hair dye. Considering increasing usage, further research on the effects of HR IUD use is needed with other populations and a prospective study design. More research is also needed on the long-term effects of hair dye use.

With respect to opportunistic mammography, it would be important to start registering the examinations to be able to take them into account in evaluation of the practices and effectiveness of organized screening. Women should also be more extensively informed of the harms of opportunistic mammography, such as accumulating radiation burden and the potential consequences of false positive or negative findings. The observed negative effects of negative life events and positive effects of some positive life events in breast cancer mortality give grounds for more holistic planning of treatment and patient follow up.

2 FINNISH SUMMARY

Rintasyöpä on naisten yleisin syöpä Suomessa. Vaikka siitä selviytyminen on merkittävästi parantunut viime vuosina, on se edelleen myös suomalaisten naisten yleisin syöpäkuoleman syy.

Rintasyöpää on usein pidetty rikkaiden, länsimaisten yhteiskuntien sairautena ja sen tunnettuja riskitekijöitä ovat muun muassa myöhäinen ensisynnytysikä, alhainen lasten lukumäärä ja vähäinen fyysinen aktiivisuus. Näiden lisäksi on joukko uudempia, rintasyövän kokonaisriskiin mahdollisesti vaikuttavia tekijöitä, joiden rooli on epäselvä. Tällaisia ovat esimerkiksi hormonaaliset ehkäisy menetelmät ja kosmetiikan, kuten hiusvärien, käyttö. Tämän tutkielman tavoitteena oli muun muassa arvioida tällaisten elintapatekijöiden roolia rintasyövän etiologiassa, ja kuinka ne ovat osaltaan vaikuttamassa tämän päivän suomalaisen naisen rintasyövän riskitekijöiden kirjoon.

Tutkielma koostuu neljästä osatyöstä. Ensimmäisen osatyön tarkoituksena oli arvioida hormonaalisten ehkäisyvalmisteiden käytön ja rintasyövän riskin välistä yhteyttä ja toisen osatyön tavoitteena oli selvittää, lisääkö hiusvärien käyttö itsenäisesti rintasyövän riskiä. Kolmannessa osatyössä arvioitiin kuinka suuri osa alle 50-vuotiaista naisista oli käynyt opportunistisessa mammografiassa ja missä määrin mahdollinen rintasyövän perhehistoria ja koulutustaso vaikuttivat käynti-innokkuteen. Neljännessä osatyössä selvitettiin merkittävien elämäntapahtumien vaikutusta rintasyöpäkuolleisuuteen.

Kaikissa osatyöissä käytettiin pääasiallisena altisteiden tietolähteenä Naisten terveys ja hormonien käyttö-kyselytutkimusta vuodelta 2009. Kolmannessa osatyössä hyödynnettiin lisäksi Elintavat, elämänlaatu ja terveys-kyselyitä, jotka toteutettiin vuosina 2012 ja 2013. Tiedot syöpätapauksista ja syöpäkuolemista saatiin Syöpärekisteristä.

Hormonikierukkaa käyttäneiden post-menopausaalisten naisten rintasyövän riski oli kohonnut 52 % verrattuna kuparikierukan käyttäjiin. Muun hormonaalisen ehkäisyn käyttö vastaavasti lisäsi rintasyöpäriskiä nuoremmilla, enintään 50-vuotiailla naisilla 32 prosentilla, kun käyttäjiä verrattiin naisiin, jotka eivät käyttäneet hormonaalista ehkäisyä lainkaan. Hiusvärejä käyttäneiden naisten rintasyöpäriskin havaittiin olevan 23 % suurempi kuin naisilla, jotka eivät olleet koskaan värjänneet hiuksiaan. Yli 60 % kyselyihin vastanneista oli käynyt mammografiassa ennen seulontaikää. Mammografiat olivat myös yleisempiä naisilla, joilla oli rintasyövän perhehistoriaa ja/tai korkeampi koulutus. Suuri määrä koettuja kielteisiä elämäntapahtumia oli yhteydessä lievästi kohonneeseen rintasyöpäkuoleman riskiin, jotkin myönteisiksi koetut tapahtumat sitä vastoin alensivat rintasyöpäkuolleisuutta.

Monien klassisten rintasyövän riskitekijöiden esiintyvyys Suomessa on viime vuosikymmeninä merkittävästi lisääntynyt ja tätä joukkoa täydentävät yhä enenevässä määrin hormonaalisten ehkäisy menetelmien ja kosmetiikan käyttö. Ottaen huomioon hormonikierukan käytön lisääntyminen, sen vaikutuksista tarvitaan lisää tieteellistä näyttöä muilla tutkimusjoukoilla ja etenevällä tutkimusasetelmalla. Myös hiusvärien pitkäaikaisen käytön seurauksista ja elimistöön kertymisestä tarvitaan lisää tutkimuksia.

Opportunististen mammografia-käyntien yleisyys antaa aihetta tämän tiedon systemaattiseen keräämiseen, jotta tietoja voidaan hyödyntää organisoidun rintasyövän seulontaohjelman käytänteiden ja vaikuttavuuden arvioinnissa. Naisia tulisi myös valistaa turhien mammografioiden haitoista, kuten säteilykuorman kasvamisesta ja mahdollisista väärän positiivisen tai negatiivisen löydöksen seurauksista.

Havaitut kielteisten elämäntapahtumien kielteiset, ja myönteisten tapahtumien myönteiset vaikutukset rintasyöpäkuolleisuuteen antavat aiheen nykyistä kokonaisvaltaisempaan hoitojen suunnitteluun ja potilaan seurantaan, jossa psykososiaaliset tekijät huomioidaan aikaisempaa paremmin.

3 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals (I-IV):

I: Heikkinen S, Koskenvuo M, Malila N, Sarkeala T, Pukkala E, Pitkäniemi J. Use of exogenous hormones and the risk of breast cancer – Results from self-reported survey data with validity assessment. *Cancer Causes & Control*, 2015: 27(2), 249-258. DOI: 10.1007/s10552-015-0702-5

II: Heikkinen S, Pitkäniemi J, Sarkeala T, Malila N, Koskenvuo M. Does Hair Dye Use Increase the Risk of Breast Cancer? A Population-Based Case-Control Study of Finnish Women. *PLOS ONE*. 2015 Aug 11;10(8). DOI: 10.1371/journal.pone.0135190

III: Heikkinen S, Miettinen J, Koskenvuo M, Huovinen R, Pitkäniemi J, Sarkeala T, Malila N: Proportion of women with self-reported opportunistic mammography before organized screening. *Acta Oncologica*. 2016 Jul 2;55(7):865–9. DOI: 10.3109/0284186X.2016.1171392

IV: Heikkinen S, Miettinen J, Pukkala E, Koskenvuo M, Malila N, Pitkäniemi J: Impact of major life events on breast cancer-specific mortality – A case-fatality study on 8000 breast cancer patients. *Submitted*.

These publications have been reprinted with the permission of their copyright holders. In addition, some unpublished material is presented.

4 ABBREVIATIONS

AVTK	Health Behaviour and Health among the Finnish Adult Population
BMI	Body Mass Index
CI	Confidence interval
DALY	Disability-adjusted life-years
DNA	Deoxyribonucleic acid
EET	Breast Cancer Screening, Lifestyle and Quality of Life-study
FCR	Finnish Cancer Registry
FDA	US Food and Drug Administration
FINRISK	The National FINRISK Study
HC	Hormonal contraceptives
HR IUD	Hormone-releasing intrauterine device
IARC	International Agency for Research on Cancer
IUD	Intrauterine device
MI ratio	Mortality-to-incidence ratio
MR	Mortality hazard ratio
NK cells	Natural killer cells
NOCCA	Nordic occupational cancer study
OR	Odds ratio
OSF	Official Statistics Finland
PPD	P-phenylenediamine
PR	Percentage ratio
PRC	Population Registry Centre
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WHH	Women's Health and Use of Hormones – survey
WHO	World Health Organization
4-ABP	4-aminobiphenyl
4-MMPD	4-methoxy-m-phenylenediamine

5 INTRODUCTION

Breast cancer is the most common cancer in women in Finland. Although survival from breast cancer has greatly improved in recent years, it remains the most common cause of cancer death among Finnish women¹. Considering the high breast cancer prevalence worldwide², it is also likely to be one of the most studied cancer types. There is a long list of established risk factors contributing to breast cancer incidence, including many reproductive factors, family history of breast cancer, body mass index (BMI), physical activity and so forth. Regardless of extensive research and public health measures, breast cancer remains an indeterminate, life-threatening disease with many unknown factors. A great deal of effort has been put into both primary and secondary preventive measures in the form of identifying potential risk factors of breast cancer with extensive epidemiological and biomedical studies and with organized breast cancer screenings.

The overall risk of breast cancer of a Finnish woman is likely to derive from dozens of contributing factors. It is also apparent that the risk factors and exposure to them are continuously changing, along with the changing environment. New environmental risk factors with possible carcinogenic effects emerge regularly and, due to rapid changes in lifestyle-related habits, they may have vast effects on the overall breast cancer risk. Good examples of such relatively novel exposures that are immensely popular in today's Western societies are the use of hair dyes and extensive use of exogenous hormones. Also, chronic stress may be considered as such. Changes in health-related behavior have occurred also in other areas of life, as cancer prevention by organized screenings has become part of the routine health policy in Finland. Easy access to affordable mammography also outside the organized screening has led to massive popularity of so-called opportunistic screenings, and the consequences of such habits are unknown.

The main aim of the thesis was to evaluate the roles of novel lifestyle-related factors in breast cancer outcomes in Finland. These factors have increased in popularity over the past few decades and potentially contribute to the overall risk of – and survival from - breast cancer among Finnish women. Another aim was to place these findings into larger cultural and societal contexts. The studies explore potential associations between certain breast cancer risk factors, namely the use of hormonal contraceptives and hair dyes, and breast cancer incidence. The use of opportunistic mammography before screening age was also assessed, as were patterns of breast cancer-specific mortality with respect to pre- or post-diagnostic major negative and positive life events.

6 REVIEW OF THE LITERATURE

6.1 EPIDEMIOLOGY OF BREAST CANCER

Wade Hampton Frost described epidemiology as “*something more than the total of its established facts. It includes their orderly arrangement into chains of inference, which extend more or less beyond the bounds of direct observation*”³. The fast changing world with increasingly complex and multifaceted structures in society presents a challenge for epidemiologists. Resolving a full etiology of a disease is considered nearly impossible, and the “truth” must be composed of evidence from countless different sources. Dressler, a medical anthropologist, stated in his writings that disease risk varies in relation to culture as culture defines the context – the surrounding social and economic conditions.⁴ Dixon in turn summarized the concept of culture in health by stating that “*culture can be causal, contributory or protective in relation to ill health*”⁵. Figure 1 illustrates the multidimensional effect of culture on health and disease. While all the different levels of culture, from macro to micro, are interconnected, also the impact on health outcomes is diverse and multifaceted. In addition to the pronounced effects of the cultural context on physical health outcomes, the mental well-being of the individual and community is also greatly influenced by it.

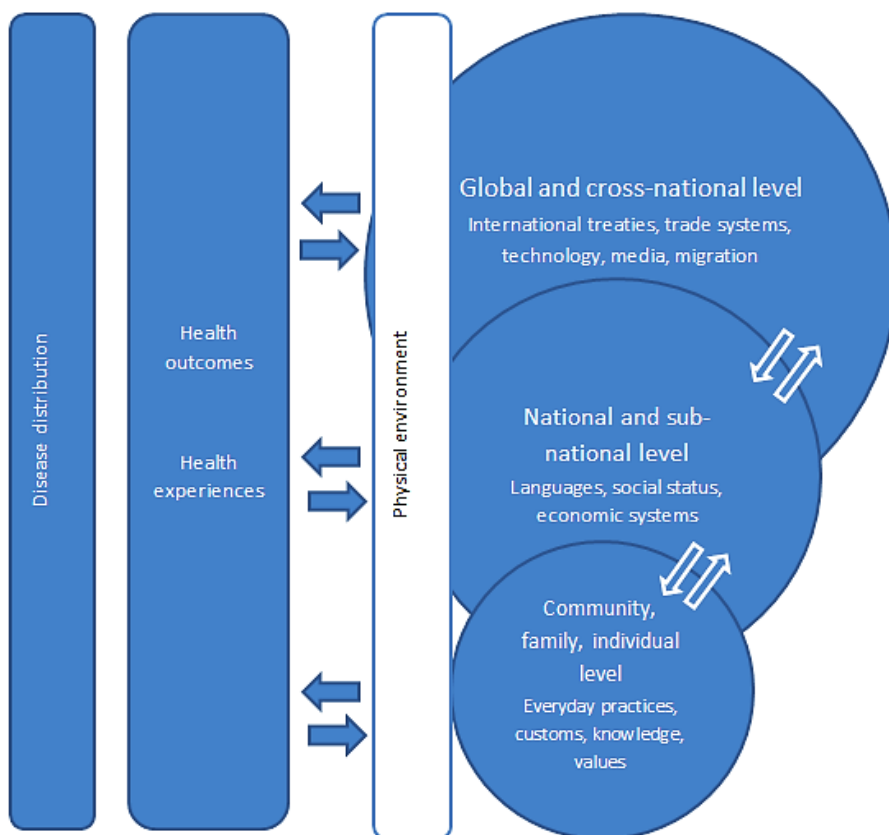


Figure 1. Multidimensional effect of culture on health and disease.

Source: Dixon J, Banwell C, Ulijaszek S. When Culture Impacts Health. In: When Culture Impacts Health. Elsevier; 2013 [cited 2016 Apr 12]. p. 1–11. Available from: <http://linkinghub.elsevier.com/retrieve/pii/B9780124159211000014>

Breast cancer is the second most common cancer in the world, following lung cancer and it is the most common cancer in women in 140 countries. While it is more prevalent in the developed, high-income regions, the incidence rates are also steadily rising in less developed low- and middle-income areas. Currently, the incidence is highest in Western and Northern Europe and in Northern America, and lowest in East Asia and Middle Africa (Figure 2). Overall, there is a greater than twofold difference in breast cancer incidence rates between less developed and highly developed countries.⁶

The risk of breast cancer has increased in both developed and less developed countries until the 1980s, but has since levelled off or declined in some developed countries while continuing to increase in the less developed

areas⁷. It has been suggested that the somewhat lowered breast cancer incidence in parts of Europe and the United States is at least partly attributable to the decreasing use of hormone replacement therapy⁷. Smoothing in the incidence was observed also in some Nordic countries in 2003-2009, not however in Finland, and the trend in all Nordic countries has turned upwards in recent years⁸.

While developed countries have high breast cancer incidence, they also have low breast cancer mortality in relation to incidence (Figure 3)². This phenomenon can be seen from the mortality-to-incidence ratios (MI ratios) presented by Forouzanfar and colleagues in a large systematic analysis of breast and cervical cancer in 187 countries between 1980 and 2010. The breast cancer MI ratios of women in developed countries are lower than those of women in less developed countries. The ratios for both developed and less developed countries have decreased steadily since the mid-1980s, but the difference in the ratios between the countries has remained more or less the same over time.⁹ In 2008, Porter reported the breast cancer MI ratio to be 0.69 in Africa, as compared with 0.19 in North America¹⁰.

Declined breast cancer mortality rates observed especially in the developed countries are considered to result from a combination of improved detection and earlier diagnosis through population-based screening and more effective treatment regimens, such as adjuvant hormonal treatment and introduction of second- and third-generation chemotherapy agents and aromatase inhibitors^{6,7}.

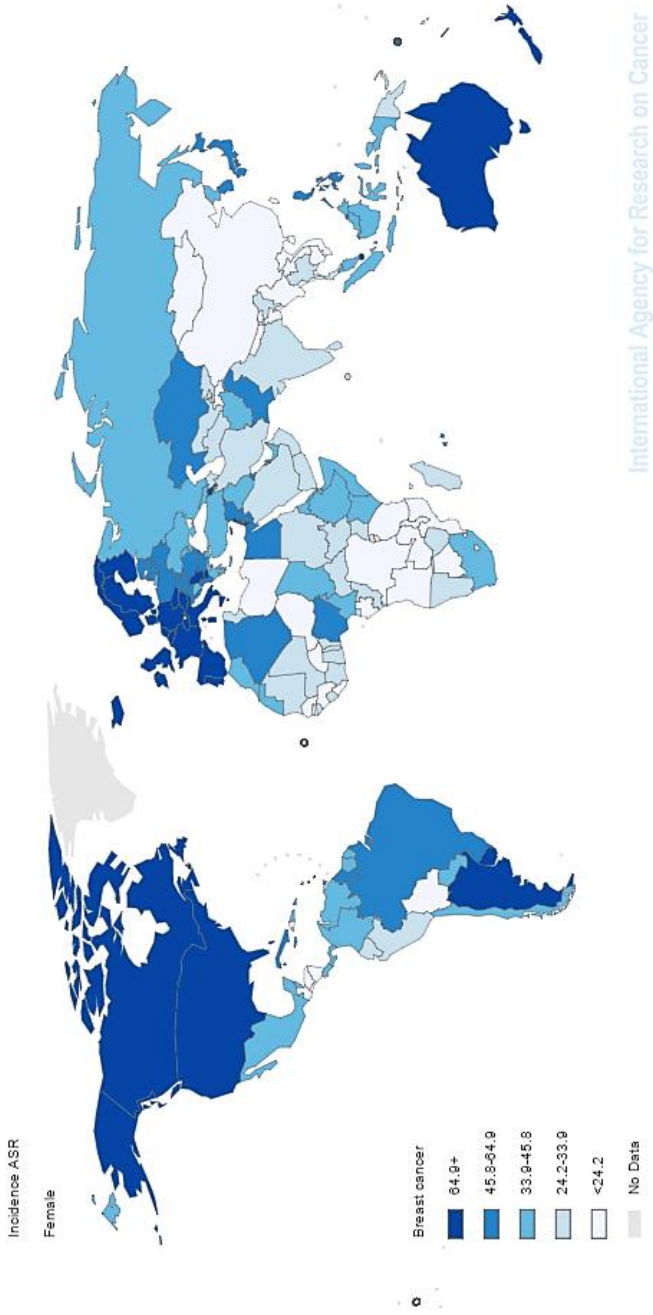


Figure 2. Breast cancer incidence worldwide in 2012, per 100 000 persons

Source: *GLOBOCAN 2012 (IARC)*, (Accessed 17/1/2017).

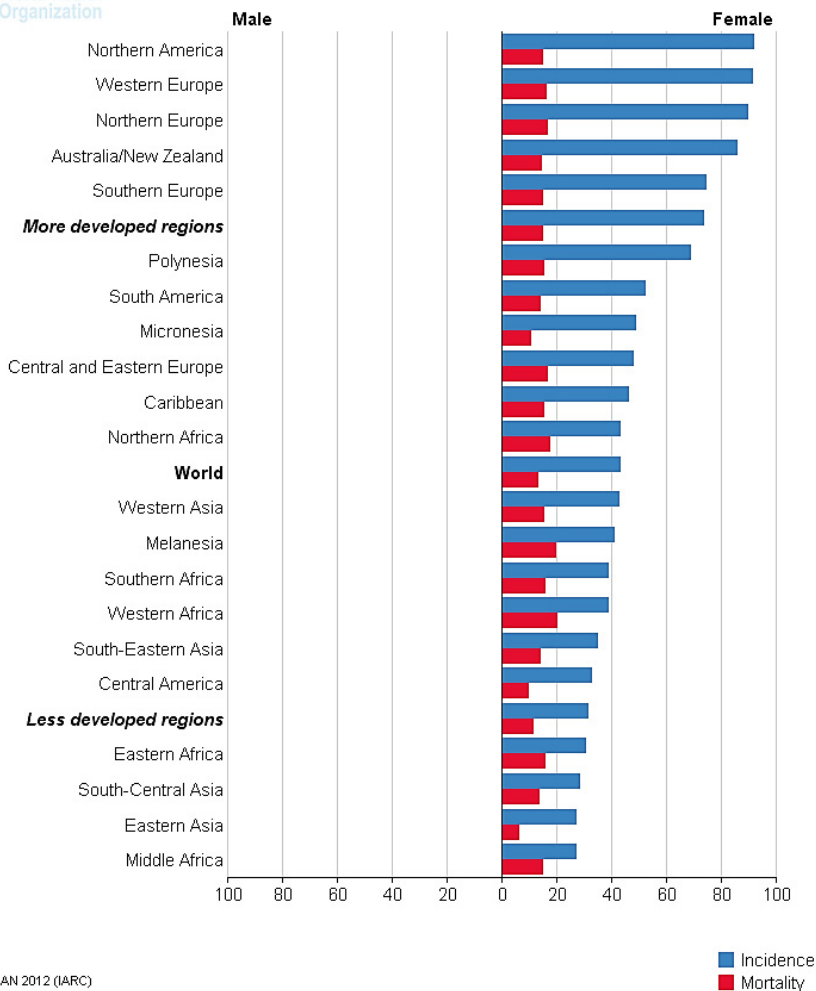


Figure 3. Estimated age-standardized (World) rates of breast cancer per 100,000 persons

Source: GLOBOCAN 2012 (IARC), Section of Cancer Surveillance (Accessed 17/1/2017).

http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

As with most cancers, also the risk of breast cancer increases with age^{7,11}. With respect to histology, some 70% of breast cancers are ductal carcinomas, and 15% lobular carcinomas with other more infrequent types accounting for the rest of the cases⁷. Breast cancer cannot thus be considered a single disease as it is very heterogeneous, both clinically and morphologically. The WHO classification of tumors of the breast recognizes over 20 different breast cancer subtypes. Generally, the prognosis is good if the disease is detected at an early stage.⁷ Although the stage and grade at diagnosis correlate with survival from breast cancer, patients with a similar cancer type may have a very different response to therapy or long-term outcome⁶.

6.2 BREAST CANCER IN FINLAND

There were 5008 incident breast cancers and 815 breast cancer deaths in Finland in 2014, as registered at the Finnish Cancer Registry (FCR)¹. Incidence increases significantly after 45 years of age, the average age at diagnosis being 60 years¹². Overall lifetime risk of breast cancer of a Finnish woman by the age of 75 years is about 10%⁸. In Finland, some 60% of breast cancers are localized (not metastasized) at diagnosis¹³. According to recent estimations, the 5-year relative survival of breast cancer patients was 90%^{1,14}. Figure 4 illustrates the time trends of breast cancer incidence and mortality in Finland in 1955-2014 as rates per 100 000 persons. The initiation of the nationwide organized breast cancer screening in 1987 can be seen as a steep rise in the incidence curve and correspondingly, a decrease in mortality in the late 1980s. The rationale and organization of the nationwide breast cancer screening program in Finland are explained in detail in Section 6.2.1.

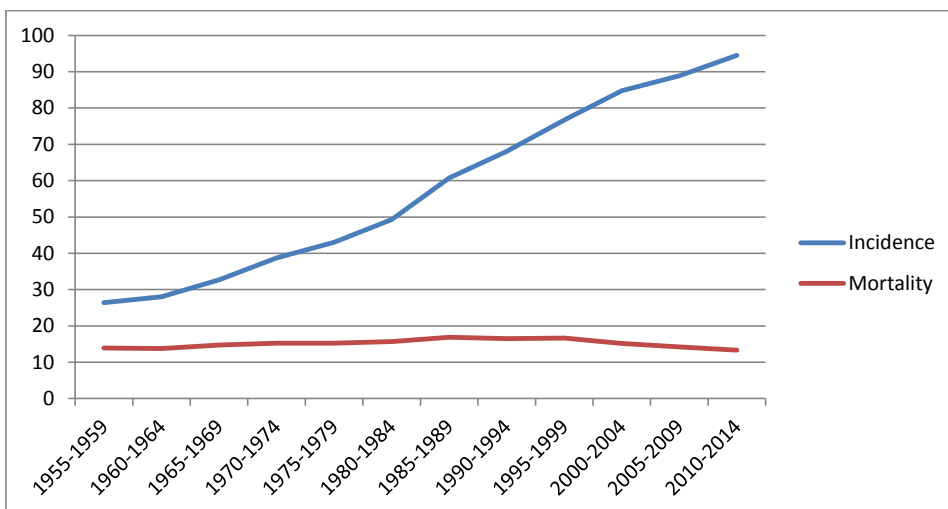


Figure 4. Time trends of breast cancer incidence and mortality in Finland in 1955-2014, age-standardized (World) rates per 100 000 persons.

Source: Finnish Cancer Registry Statistics, tilastot.syoparekisteri.fi. Information as of 16.11.2016, accessed 25.1.2017.

6.2.1 BREAST CANCER SCREENING

According to the early writings of Wilson and Jungner (1968), “*The object of screening for disease is to discover those among the apparently well who are in fact suffering from disease. They can then be placed under treatment and, if the disease is communicable, steps can be taken to prevent them from being a danger to their neighbours. In theory, therefore, screening is an admirable method of combating disease, since it should help detect it in its early stages and enable it to be treated adequately before it obtains a firm hold on the community.*”¹⁵.

Organized, population-based breast cancer screening has since proven effective in developed countries in terms of detecting cancers at a lower stage and subsequent decreased cancer-specific mortality¹⁶. The balance of harms and benefits of mammography breast cancer screening is, however, under continuous debate. Overdiagnosis and false-positive findings may lead to unnecessary examinations and treatment, doing more harm than good. Emotional and quality-of-life effects are also often discussed, although they are much more difficult to measure.^{17,18} Regardless of evidence concerning the harms of overdiagnosis, it is still considered that the benefits, namely reduced breast cancer mortality, of population-based organized breast cancer screening override the harms¹⁹. Organized breast cancer screenings were initiated in Europe in the late 1980s. By 2012, screening programs were running or being established in 24 countries in the European Union.⁶

In Finland, a national organized breast cancer screening program was launched in 1987. The program was initiated gradually; first cohorts of women born in even years were invited to screening and women born in odd years were used as controls. By 1992, all women aged 50–59 years received screening invitations every second year, and during the early years of organized screening the coverage was nearly 100%. By 2007, the upper age of invitations was set at 69 years and biennial screenings covered the whole country.^{20,21} Overall, the participation rate today is close to 85% and nearly one-third of all incident breast cancers in Finland are detected in the organized screening. More than half of the invasive cancers in women of screening age were detected by screening.²² According to the evaluation in 2008, breast cancer mortality was reduced by 22% in 1992–2003 among the screening invitees aged 50–69 years at death. Accordingly, among all women aged 60–79 years at death, the greatest reduction in breast cancer mortality, 28%, was estimated in municipalities inviting 50- to 69-year-old women to screening on a regular basis.²³ Organized screening has thus proved to be an efficient public health intervention and has contributed to timely diagnosis and improved breast cancer survival in Finland.

6.3 BREAST CANCER AS A PHENOMENON OF WESTERN SOCIETY

The World Health Organization (WHO) states that “*breast cancer is a disease of affluent societies that have acquired a “Western lifestyle”, characterized by high-calorie diet rich in animal fat and proteins, combined with lack of physical exercise.*” Such regions include e.g. Australia, North America and Northern Europe, where the plateau of incidence has already in part been reached. Conversely, countries that have only recently become industrialized and affluent show a marked increase in incidence and mortality, including countries such as India, Japan and the Republic of Korea.⁷

After the founding of the WHO in 1948, many international and cross-cultural health initiatives were launched and it was soon shown that several health-related issues and problems had as much a social and cultural aspect as a biological one. Social and cultural factors seemed to have a great impact on health behavior and consequently, health outcomes.²⁴ However, although cultural models are shared within a society by definition, considerable differences may exist between individuals in adherence to the models. Different levels of knowledge of a certain cultural domain, different social context of the occasion, and personal circumstances, e.g. economic or physical restraints, all play a role, enhancing the complex impact of social/cultural factors on health.²⁵

Some of the well-known factors contributing to the higher breast cancer incidence in Western societies than in less developed regions are low

birthrate, older age at first delivery, and obesity¹⁰. The ideal of a small nuclear family and higher age at first birth leads to a situation, where continuous contraception is needed for years, even decades. Additionally, there are likely to be other lifestyle-related factors that in part affect the higher breast cancer incidence in Western societies. Cultural norms related to appearance are ever-evolving and modifying one's looks by, for instance, hair dyeing is increasingly popular. Even if the idea of changing hair color is known all over the world, it is commonly considered a Western society phenomenon.

Multifaceted Western societies with schedule-oriented, demanding, and hectic lifestyles may also produce stress and anxiety. Many major life events are common worldwide, but coping mechanisms vary, also by cultural framework and background²⁶. There is naturally variation also in the types of events and the frequency at which they occur in different societies. Certain major life events have become less common in developed countries and others simultaneously more prevalent. Premature deaths of children and spouses have become rare, while e.g. divorces and problems related to work and employment are likely to be more common and may have profound effects on a person's life.

A question has been raised as to whether breast cancer in the Western world is in fact the same disease as it is in, for instance, Asian countries, where the increase in breast cancer incidence has lately been the greatest in the world. The incidence of breast cancer in Asia peaks at 40-50 years, whereas in Europe it does so at 60-70 years of age, although the prevalence of *BRCA1/2* mutations is assumed not to differ markedly.^{27,28} If distinct genetic backgrounds do not explain the variation in age at disease onset, the reason must be elsewhere. Leong et al. concluded that "*the observed differences are most likely attributable to different risk factors acting differentially on two (or more) different types of breast cancer*"²⁷. Estrogen receptor-negative breast cancers are more prevalent in developing countries, and it has been suggested that this may in part explain the higher breast cancer mortality in these regions. Also, the lack of population-based organized screenings may contribute to it, in addition to behavioral aspects.¹⁰ Although more attention has recently been directed to investigating disease risks within and between different social and ethnic groups, the cultural dimensions framing them and contributing to them are still not well understood²⁵.

When it was observed that the obvious changes in health behaviors, such as increased smoking prevalence or changes in diet only explained a small portion of the association between modernization and risk of certain diseases, the medical anthropologists focused their interest on the potential social stresses of culture change. The aim was to identify the socially and culturally relevant stressors affecting health. Already in the 1960s, Cassel and colleagues suggested that higher disease rates among migrants entering a new community may be a result of the experienced stress from "cultural

incongruity”, the high stress levels in turn resulting in poorer health³. The same phenomenon is likely to also apply to culture change within a society, regarding e.g. modernization in Western societies, when people need to adapt to a rapidly changing environment and mode of behavior. Also some biological anthropologists have suggested that disease occurrence can be seen as a marker for maladaptation to such changes²⁵.

6.4 KNOWN RISK FACTORS OF BREAST CANCER

Age is the most pronounced risk factor of breast cancer. The cumulative incidence among women in Europe is 2.7% by age 55, 5.0% by age 65, and 7.7% by age 75¹¹. After age, most of the contributing risk factors are assumed to be environmental. Studies of migrating populations have indicated that the breast cancer risk of the migrant population approaches that of the host country within one or two generations. This evidence together with the observed geographical variations and time trends suggest that environmental risk factors play a remarkable role in the etiology of breast cancer⁷. Many of the other known breast cancer risk factors are related to endogenous female hormones. Having more children, breastfeeding, and being young at first delivery decrease the risk, whereas young age at menarche and old age at menopause are known to increase the risk. All of these factors affect the number of lifetime menstrual cycles and the consequent cumulative exposure to ovary-modulated endogenous hormones stimulating cell growth in the mammary glands²⁹. Even though parity overall has protective effects against breast cancer, the risk is elevated during pregnancy and soon after, owing to the high levels of circulating hormones^{30,31}. Also, the beneficial effect of young age at first full-term pregnancy appears to be limited to hormone receptor-positive breast cancer^{32,33}.

Alcohol consumption and postmenopausal weight gain are known to increase the risk of breast cancer, with physical activity, by contrast, lowering it^{11,12}. The mechanism behind the carcinogenic effect of alcohol use is not fully understood, but it is assumed that at least part of it comes directly from the carcinogenicity of ethanol and its metabolites, the interactions with folate metabolism and the estrogen pathway possibly also being involved⁶. The adverse effect of postmenopausal weight gain, in turn, is likely to be directly related to increased levels of circulating estradiol. The influence of physical activity is, at least in part, through its benefits on weight control. It is, however, probable that it also acts independently of its effects on BMI, likely through hormonal changes.⁶

Use of hormone replacement therapy, most specifically combined estrogen-progestogen therapy is also known to be a risk factor for breast cancer through various, complex hormonal systems^{34,35}.

Certain occupational exposures, such as night shift work, have been suggested to be associated with elevated breast cancer risk by disrupting the

natural circadian rhythm, and the International Agency for Research on Cancer (IARC) has classified shiftwork as possibly carcinogenic to humans^{36,37}. A recent meta-analysis, however, questioned this association as the authors found no evidence of a relationship between night shift work and breast cancer incidence in the combined analysis³⁸.

Some benign breast diseases³⁹, higher breast density⁴⁰, and radiation treatment at a younger age^{41,42} have been found to increase breast cancer risk. Exposure to ionizing radiation in repeated mammography is also suggested to increase breast cancer risk^{43,44}, however the benefits of mammographic screening are considered to outweigh the consequential harms⁴⁵. Estimates of the magnitude of the associations are listed in Table 1, as summarized by Key et al.¹¹

In studies on the heritability of breast cancer, it is estimated that heritability explains about 30% of the variation in breast cancer risk, the remaining 70% being attributable to several environmental risk factors^{46,47}. Thus, approximately one-third of the variation in breast cancer risk in a population can be accounted for by interindividual genetic differences. As the authors highlight, this estimate includes both cancer-specific genetics and genetic contributions to some cancer risk factors, such as obesity, that have a genetic component.⁴⁶ Although genetic factors overall are presumed to play a rather small role in the etiology of breast cancer, mutations in *BRCA1* or *BRCA2* genes remarkably increase the risk of breast cancer, most specifically in early-onset disease. One affected first-degree relative doubles the risk and the risk increases further with more known affected relatives⁴⁸⁻⁵⁰. A mutation in either *BRCA1* or *BRCA2* gene increases a woman's lifetime breast cancer risk to some 50-65%^{51,52}. It has been estimated that germline mutations explain some 5-10% of all new breast cancer cases, mutations in *BRCA1/2* accounting for about 25-30% of these^{53,54}.

Table 1. *Estimated effects of some known breast cancer risk factors*

Risk factor	Estimated change in risk
Number of full-term pregnancies, ≥5 vs. none	-50%
Breastfeeding, ≥25 mo. vs. never	-33%
Physical activity, heavy exercise few hours/week vs. none	-30%
Parity vs. nulliparity	-25%
Menarche, each 1-year delay	-5%
Menopause, each 1-year delay	+3%
Alcohol, per each 10g unit per day	+10%
Combined oral contraceptives, current vs. never use	+25%
Hormonal therapy for menopause, 10 year use vs. never	+35%
Obesity, post-menopausal BMI >30	+50%
Ionizing radiation, 1 Gy vs none	+10-170%
Family history, yes vs. none	+100%
Benign breast disease (proliferative lesions) vs. none	+100-300%

Source: Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol. 2001 Mar;2(3):133–40.

Population attributable fraction describes the excess risk of the exposed in the study population in relation to the total risk of the disease in the whole population. Some population attributable fractions of environmental breast cancer risk factors are presented in Table 2, as estimated by Parkin et al. in a large study in the UK on the roles of different environmental exposures in the incidence of cancer⁵⁵. Another study on the population attributable risks for certain modifiable breast cancer risk factors estimated that the use of exogenous hormones accounts for some 19%, and physical inactivity for 13% of breast cancer risk. A set of non-modifiable breast cancer risk factors, including age at menarche and menopause, parity, family history of breast cancer, and a benign breast disease was estimated to account for 37% of all invasive breast cancers in the study.⁵⁶

Table 2. The percentages of incident breast cancers attributable to certain environmental risk factors.

Exposure (optimum exposure level))	% of breast cancers attributable to the specific risk factor exposure
Overweight and obesity (BMI \leq 25 kg/m ²)	8.7
Alcohol (none)	6.4
Occupational exposures (none)	4.6
Physical exercise (\geq 30 min 5 times per week)	3.4
Post-menopausal hormones (none)	3.2
Breastfeeding (minimum of 6 months)	3.1
Ionizing radiation (none)	0.9

Source: Parkin DM, Boyd L, Walker LC. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British Journal of Cancer*. 2011 Dec 6;105:S77–81.

6.5 LESS STUDIED LIFESTYLE-RELATED RISK FACTORS

Among others, the vast use of chemicals, the overall medicalization of the society, and health effects of different types of life events are less commonly studied potential risk modifiers of breast cancer. Related to the first, we investigated the effects of hormonal contraceptives and hair dye use on the risk of breast cancer. Regarding medicalization, also the prevalence of opportunistic mammography in Study III was considered a surrogate marker in an effort to examine the phenomenon in the Finnish society. Study IV focused on life stresses, but also investigated the potential beneficial effects of positive developments in life, which especially has been lacking scientific evidence.

6.5.1 CHEMICALS; HORMONES AND COSMETICS

Use of chemicals in modern societies is at an entirely different level than it was a century ago. Exposures to chemicals in our daily lives through food and water, cosmetics, detergents, pesticides, medicines, plastic goods, chemically-treated clothing, work-place exposures and so forth is likely to create a massive burden of exogenous chemicals in the body^{57,58}. Related to this, Studies I and II investigated the use of hormonal contraceptives and hair dyes and their possible relationships with the risk of breast cancer.

In the Western world, short-acting and reversible contraception methods are the most commonly used, in contrast to the long-acting, highly effective clinical methods used most in developing regions. Contraceptive pill is the

most commonly used method of contraception in Northern Europe, with some 21% overall usage among women of reproductive age. In developing countries overall, the predominant methods are female sterilization and intrauterine devices (IUD). This is especially the case in Asia - in Africa and Latin America, for example, the contraceptive pill is more popular than IUD. Worldwide, IUD is used by approximately 14% of women aged 15-49 years and living in a relationship. Contraceptive pill is the third most used method with a 9% overall share and the widest geographical distribution.^{59,60} Soini et al. estimated in their study on cancer risk in women using the levonorgestrel-releasing intrauterine system that up to 15% of fertile women used the system in Finland during their study period of 1994-2007⁶¹.

Regardless of extensive research, the scientific community still does not fully agree on the role of exogenous hormones in the etiology of breast cancer. A large prospective cohort study on the association of oral contraceptive use and breast cancer risk observed a positive association, as did a recent meta-analysis and a hospital-based case-control study⁶²⁻⁶⁴. Another population-based case-control study as well as a larger prospective cohort study found, however, no evidence of an association^{65,66}. Studies regarding the use of hormone-releasing intrauterine device (HR IUD) and breast cancer risk are more infrequent. A few studies have observed a significant increase in breast cancer risk among HR IUD users^{61,67,68}. There are, however, also studies where the association has not been observed, specifically in younger women^{69,70}.

According to the IARC, combined estrogen-progestogen contraceptives are carcinogenic to humans (Group 1 in overall evaluation). In the monograph, these substances were determined to cause cancer of the breast, in situ and invasive cancer of the uterine cervix, and cancer of the liver. Inverse associations are convincingly reported with respect to cancers of the endometrium, ovary, and colorectum.⁷¹ Regarding the use of progestogen-only contraceptives, the previous IARC monograph was published in 1999 and stated that there was inadequate evidence for a relationship between progestogen-only contraceptives and breast cancer⁷².

According to the estimation of the European Commission, some 60% of women and 5-10% of men in Europe use hair dyes on average 6 to 8 times per year⁷³. The history of hair dye use dates back to ancient Egypt, and today there are millions of people using cosmetic dyes⁷⁴. Before the 1980s, hair dyes contained aromatic amines, such as 4-methoxy-m-phenylenediamine (4-MMPD, 2,4-diaminoanisole), which was later found to cause cancer in animals⁷⁵. In some studies, use of such hair dyes was connected to increased cancer risk also in humans⁷⁶. As a result, manufacturers changed the formulation of hair dyes to remove some of these chemicals⁷⁷. Currently, P-phenylenediamine (PPD) is one of the most commonly used hair dye compounds. Its reactivity with air was discovered already in the 1860s and this was considered the starting point for development of synthetic, commercial hair dyes.⁷⁸ Also the safety of PPD has been questioned, either

through its own properties or as a mediator for such known carcinogens as 4-aminobiphenyl (4-ABP)⁷⁹.

Hair dyes can be divided into three basic groups by their mode of action. Permanent colors are oxidative and consist of colorless dye intermediates and dye “couplers”, which, in the presence of hydrogen peroxide, react with one another to form pigment molecules. These types of dyes are the most commonly used. Semi-permanent and temporary dyes are non-oxidative; they contain colored compounds that stain hair directly. Nowadays, however, also some semi-permanent dyes contain an oxidative agent⁸⁰.

Research on the association between hair dye use and risk of breast cancer has been relatively modest and the results somewhat contradictory. The studies of Nasca, Cook, and Petro-Nustas⁸¹⁻⁸³ observed positive associations between hair dye use and breast cancer risk, whereas the studies of Zheng, Mendelsohn, Green, and Koenig⁸⁴⁻⁸⁷ found no evidence of an association. A Nordic study on the occupational cancer risks (NOCCA) reported a 6% increased risk of breast cancer for a cohort of female hairdressers relative to the population overall⁸⁸. The previous IARC monograph on some aromatic amines, organic dyes, and related exposures from 2010 concluded that there was inadequate evidence for carcinogenicity of personal hair dye use and limited evidence in experimental animals for carcinogenicity of hair colorants, placing it in Group 3 in the overall evaluation (“*Not classifiable as to its carcinogenicity to humans*”)⁸⁹.

6.5.2 USE OF OPPORTUNISTIC MAMMOGRAPHY - A FORM OF MEDICALIZATION?

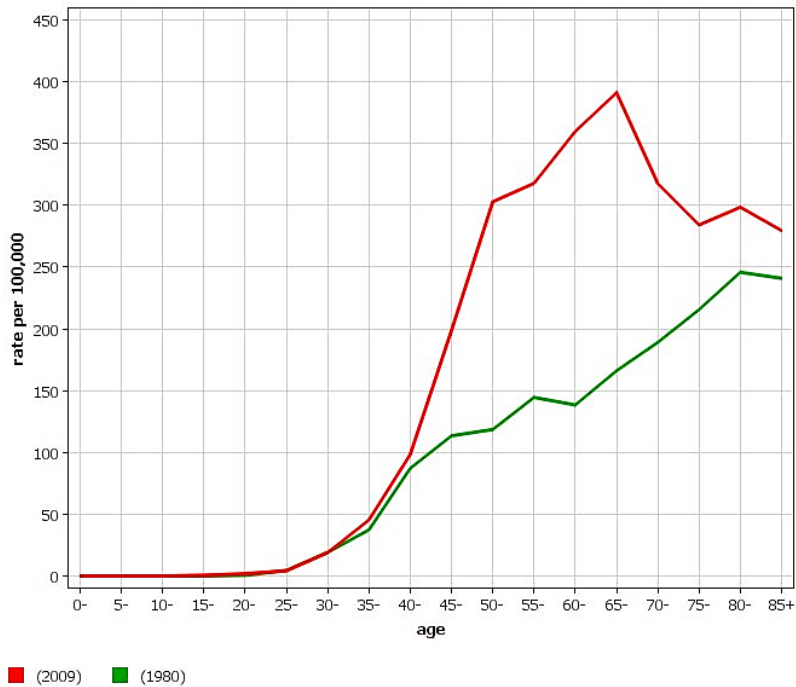
Maturo describes medicalization as a “*process by which some aspects of human life come to be considered as medical problems, whereas before they were not considered pathological.*”⁹⁰ Bell sees medicalization as a modern process and concept that is increasingly often perceived also as a patient/consumer-driven phenomenon and not alone boosted by medical authorities or the pharmaceutical industry⁹¹. Opportunistic mammography is an example of physician-initiated as well as consumer-initiated use of medicine, often unnecessarily. Easy access to mammography fulfills both a woman’s willingness to obtain certainty of healthiness and a physician’s need to confirm or reject a diagnosis.

As stated by Ouedraogo et al., organized breast cancer screening programs often coexist with easy access to opportunistic mammography in many developed countries. They define opportunistic mammography as a screening mammography performed based on a woman’s own initiative or following the advice of their physician. The system of opportunistic mammography is considered as decentralized and lacking systematic and reliable reporting, making the evaluation of its effectiveness difficult.⁹²

One of the main principles of cancer screenings is that the benefits must override the potential harms resulting from the screening procedure, e.g.

excess radiation or unnecessary invasive diagnostic procedures resulting from a false-positive result or harmless benign change. The fulfillment of this principle is well-studied and confirmed for population-based organized screening programs, but wild, opportunistic screenings bring an unknown element to the equation. Regarding breast cancer, a high prevalence of mammography outside the organized screening program may distort the balance of benefits and harms, as we may unnecessarily screen women too much with the coexisting, overlapping systems of organized and opportunistic screening.

Finland-Incidence
Breast: Female



NORDCAN © Association of the Nordic Cancer Registries (29.9.2016)

Figure 5. Breast cancer incidence in Finland in 1980 and 2009, rate per 100 000 persons.

The major change in the pattern of breast cancer incidence over the past decades can be seen in Figure 5, which presents breast cancer incidence in Finland in 1980 and 2009. The incidence curve in 1980 shows a relatively gradual increase in breast cancer incidence by age, whereas the 2009 curve shows a peak in the incidence at age 65 years and thereafter a downward

trend. Also, compared with the 1980 curve, the 2009 curve shows a steeper increase in the incidence from age 40 years, which may be related to a high number of mammography examinations already before the start of the organized screenings at the age of 50 years. Significantly higher breast cancer incidence of younger women in 2009 compared to that of 1980 is mostly a result of organized mammography screening started in 1987. Compared to clinical screening, invitation-based screening detects cancers earlier, with respect to both stage and age. Without the invited screening, it might have taken several more years for the cancer to become symptomatic.

6.5.3 STRESSFUL LIFE EVENTS

Major stressful life events have been shown to increase the risk of depression and anxiety⁹³⁻⁹⁵. In the Global Burden of Disease study in 2010, depression and anxiety disorders together accounted for over 50% of the overall disease burden measured in disability-adjusted life-years (DALYs)⁹⁶.

Brown & Harris carried out a classic study on the association between social and cultural factors and the onset of depression in women. They identified three major factors with an impact on the development of depression, with stressful life events, such as loss of mother, lack of a confiding relationship, and unemployment, being one of them.⁹⁷

Depression and anxiety have subsequently been shown to be associated with greater mortality in cancer patients. A meta-analysis by Pinquart et al. concluded this to apply to women expressing depressive symptoms either before or after cancer diagnosis⁹⁸. Satin and colleagues reached similar conclusions, estimating cancer mortality to be up to 39% higher in patients diagnosed with minor or major depression⁹⁹. There are, however, also studies with contradictory results¹⁰⁰. Psychological distress, including anxiety, was observed to be a predictor of cancer mortality overall¹⁰¹, and anxiety was also found to increase breast cancer-specific mortality¹⁰². One meta-analysis reported stressful life experiences to be associated with poorer all-cancer survival, and likewise, higher mortality. Site-specific analyses suggested that some psychosocial factors, such as depression, were also associated with poorer survival of breast cancer patients.¹⁰³ By contrast, however, Maunsell and colleagues did not find evidence of an association between stressful life events and breast cancer-specific or all-cause mortality¹⁰⁴.

Studies on the impact of positively experienced life events on breast cancer survival or breast cancer-specific mortality are few. Both Levy and Tominaga reported perceived joy and positive life events to be associated with longer survival or decreased breast cancer mortality^{105,106}. While Levy et al. found psychological expression of joy to be associated with longer survival with recurrent breast cancer, Tominaga and colleagues observed that having female children and hobbies affected the duration of survival in surgically treated breast cancer patients.

6.6 HISTORICAL TRENDS OF RISK FACTOR PREVALENCE

The surrounding society is changing at an accelerating pace. The prevalences of such relatively contemporary exposures as hair dyes and hormonal contraceptives are at markedly different levels today than they were a few decades ago. Accordingly, organized breast cancer screenings were initiated only in the 1980s, before which all mammograms were opportunistic, based either on symptoms or on a simple desire for reassurance of healthiness. These factors have considerably changed women's lifestyle and behavior and, at the same time, significantly altered the risk factor spectrum and risk burden in terms of breast cancer. Some historical perspectives regarding the exposures of interest of this study are summarized in Figure 6.

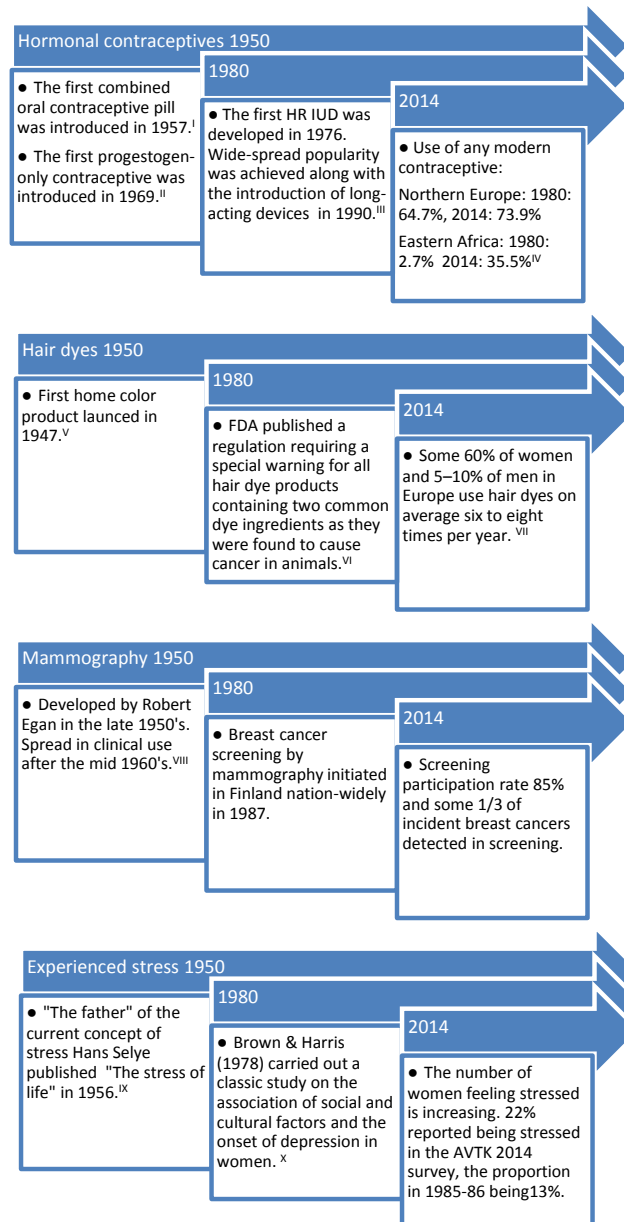


Figure 6. Historical turning points for the assessed life style factors related to breast cancer.

Sources:

ⁱJunod SW, Marks L. Women's trials: the approval of the first oral contraceptive pill in the United States and Great Britain. *J Hist Med Allied Sci.* 2002 Apr;57(2):117–60.¹⁰⁷

ⁱⁱLeary WE. U.S. approves injectable drug as birth control. *N Y Times Web.* 1992 Oct 30;A1,

A14.¹⁰⁸

^{III}Thiery, M. Intrauterine contraception: from silver ring to intrauterine implant. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2000: 90: 145–152.¹⁰⁹

^{IV}United Nations, Department of Economic and Social Affairs, Population Division (2016). *Model-based Estimates and Projections of Family Planning Indicators 2016*. New York: United Nations.¹¹⁰

^VSchwarzkopf: Milestones of success.

http://www.schwarzkopf.international/sk/en/home/schwarzkopf/about_us/history.html#id815629402 Retrieved 11.10.2016¹¹¹

^{VI}U.S. Food and Drug Administration: Cosmetics: Hair dyes.

<http://www.fda.gov/cosmetics/productsingredients/products/ucm143066.htm>. Retrieved 10.10.2016.¹¹²

^{VII}European Commission, Health and Consumers, Hair dye products. In European Commission; 2014 [cited 2014 Mar 24]. Available from:

http://ec.europa.eu/consumers/sectors/cosmetics/cosmetic-products/hair-dye-products/index_en.htm⁷³

^{VIII}Gold, R. H., Bassett, L. W., Widoff, B. E.: Highlights from the History of Mammography. *RadioGraphics*, 1990: 10(6), pp. 1111-1131.¹¹³

^{IX}Goldstein DS, Kopin IJ. Evolution of concepts of stress. *Stress*. 2007; 1;10(2):109–20.¹¹⁴

^XBrown, G.W. and Harris, T.O. (eds). 1978. *Social Origins of Depression: A study of psychiatric disorder in women*. London: Tavistock.⁹⁷

The prevalence of many known risk factors of breast cancer has increased tremendously over the past decades, shaping the landscape of breast cancer epidemiology. Table 3 presents estimated changes in the prevalence trends of certain risk factors from the mid-1900s to 2000s.

Table 3. Trends in the prevalence of breast cancer risk factors from the mid-1900s to 2000s.

Risk factor	Prevalence trend
Young age at menarche	↑
Nulliparity	↑
Small number of full-term pregnancies	↑
High age at first birth	↑
Breastfeeding	↑
Earlier age at menopause	↑
Ever use of combined oral contraceptives	↑
Ever use of intrauterine device	↑
Ever use of hormonal therapy for menopause	↓
Ever use of alcohol	↑
Obesity, BMI ≥ 30 kg/m ²	↑
Physical inactivity	↑
Amount of ionizing radiation from medical sources	↑
Opportunistic mammography	↑
Experienced stress	↑

Also the educational structure of the population has changed markedly in the recent decades. The proportion of highly educated women has increased, while the proportion of women with only basic education has majorly decreased. Figure 7 illustrates the changes in the educational level of women over 15 years old in Finland in 1970-2015.

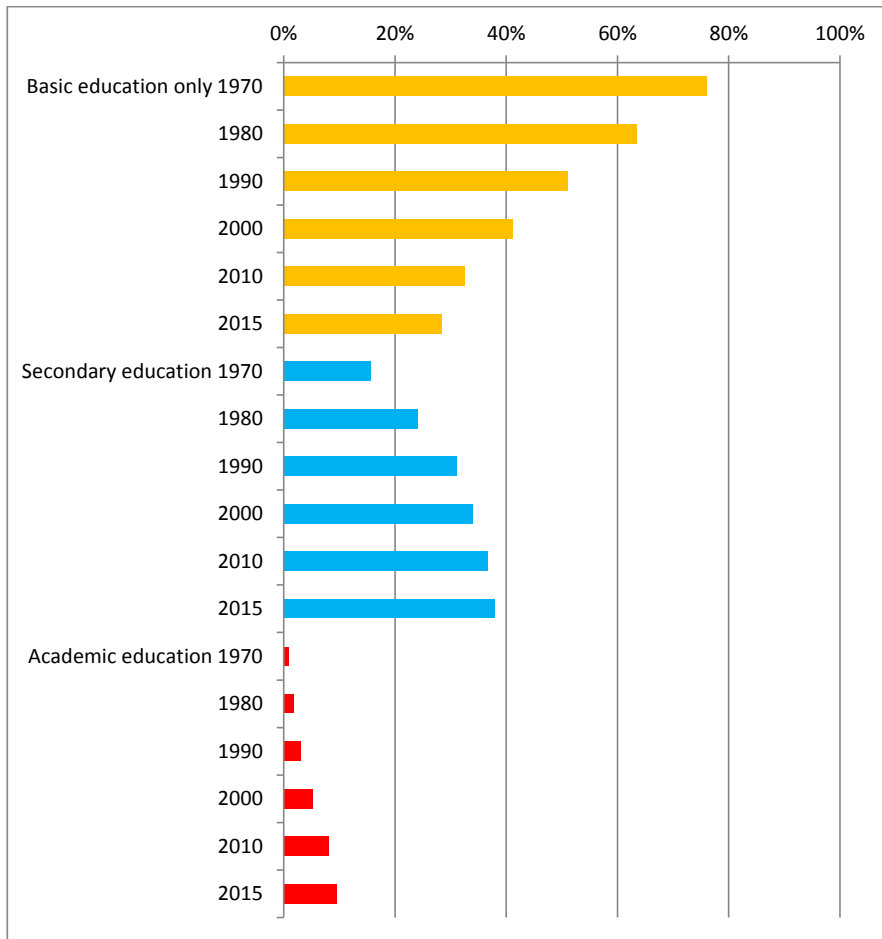


Figure 7. The percentages of women over 15 years old in Finland by educational level in 1970-2015.

Age at menarche has been shown to become lower since the start of industrialization, initially due to improved health and nutrition and later at least partly due to increasing number of overweight children^{115,116}. In most developed countries, the decline in age at menarche has today somewhat levelled off¹¹⁷. There have also been suggestions that age at menopause in Europe may be shifting towards higher ages, although prevalence of many factors presumed to affect early menopause, such as smoking, nulliparity, and overweight, have become more common^{118,119}. In an American study, a 17-month increase in the mean age at menopause was observed for women born between 1915 and 1939 (49.1 vs. 50.5 years), after adjusting for potential confounders¹²⁰.

Many factors related to reproduction have also gone through major changes. The proportion of nulliparous women in Finland has increased over the past two decades. According to Official Statistics Finland (OSF), 13.8% of Finnish- or Swedish-speaking women aged 45-49 years were nulliparous in 1990, the corresponding percentage in 2014 being 18.7%. Parity has decreased most among women in the lowest educational class; 22% of 45 to 49-year-old women with only basic education were nulliparous in 2014, compared with 12% in 1990. Parity among highly educated women has in turn remained nearly the same, with 18.6% of women aged 45-49 years being nulliparous in 1990 and 18.9% in 2014.¹²¹

Also the number of children in families has decreased. While the total fertility rate in Finland in 1950 was 3.16, in 2014 it was 1.71, according to Statistics Finland. Even though there is still some post-war effect seen in the 1950 figure, the trend overall has been declining since 1910¹²². With respect to age at first birth, the average age at first delivery among women born in the 1950s was 25 years. Women born in the 1980s, by contrast, gave birth to their first child around the age of 30 years.¹²³ The trend, however, seems to have plateaued in recent years¹²².

As for breastfeeding, there was a marked downward trend from the 1930s to the 1970s in the proportion of children breastfed for at least 6 months. Since then, the trend has been upwards, the respective percentage being 60% in 2005. Still, exclusive breastfeeding until the age of 6 months is very rare in Finland, around 1%, compared with e.g. Sweden, where about 15% of babies are exclusively breastfed until 6 months of age.¹²⁴ Overall, breastfeeding is more prevalent in poor than rich countries. While the prevalence of breastfeeding for at least 12 months is below 20% in most high-income countries, it is close to 100% in many African countries, South Asia, and parts of Latin America.¹²⁵

As a result of the altered reproduction behavior and modern innovations, contraceptive patterns have also changed significantly over the past 50 years. The first combined oral contraceptive pill was introduced in 1957 and the first progestogen-only contraceptive in 1969, and according to the IARC, there were approximately 100 million women worldwide in the year 2000 using combined hormonal contraceptives¹²⁶. The shift from traditional to modern contraceptive methods has been vast.

Use of hormone therapy for menopausal symptoms increased tremendously since the introduction of the first preparations in the 1940s, but the usage has been declining since studies such as the Women's Health Initiative in 2002, convincingly showing their adverse effects with respect to the risk of breast cancer and some other diseases. The peak usage was in 1999, when some 20 million women in developed countries used combined hormonal therapy. Since 2002, the use has declined by more than 50%.³⁵

The use of radiation in medical applications has increased markedly, especially in industrialized countries in the recent decades. Radiation in medicine accounts for some 98% of all ionizing radiation exposure obtained

from artificial sources, and it is responsible for nearly 20% of the total burden of ionizing radiation. In developed countries, where the vast majority, about two-thirds, of all radiological operations occurs, up to 50% of the annual average effective dose of ionizing radiation comes from medical use. Continuing modernization will lead to further increases in population doses of ionizing radiation due to medical exposure. According to UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), the annual number of medical radiological operations worldwide was some 3.6 billion in 1997-2007, while the corresponding figure in 1991-1996 was 2.5 billion.¹²⁷ It was also reported that there were ca. 38 X-ray generated mammography equipment per 1 million population in Finland in 2008. The corresponding number in e.g. Sweden and Australia was 20 per 1 million population. France, Germany, and Greece held the top positions with Finland, all with some 40 equipment per 1 million population.

As shown by the Health Behaviour and Health among the Finnish Adult Population (AVTK) survey, the proportion of Finnish women reporting themselves as being stressed has been increasing over the past decades. In 1978-1982, on average 13% of women reported experiencing stress, the corresponding percentage in the 2009-survey being 20% and in 2014-survey about 22%.¹²⁸ Accordingly, while 17% of respondents reported depressive symptoms in the past month in the 1985-1986 survey, 20% reported the same in the 1998-1999 survey¹²⁹.

Women's alcohol use in Finland has been increasing since the 1960s, relatively more than men's. In 1968, some 40% of women reported never using alcohol, while at the beginning of the 2000s about 90% of women reported using alcohol within the last 12 months. Women are also consuming an increasingly large proportion, 25%, of all alcohol consumed in Finland. In 1968, women accounted for approximately 10% of the total consumption.^{130,131}

In 2012, 77% of Finnish women aged 25-64 years reported being physically active during their leisure time, and correspondingly, 18% reported being physically active while commuting. Leisure-time activity has increased over the past four decades; the increase has, however, levelled off since its peak in the 1970s and 1980s. Physical activity while commuting has decreased until 1992, after which it has remained more or less constant. Physical activity or strain at work has accordingly decreased steadily since the 1970s, in part contributing to the decrease in overall activity of the population.¹³² The BMI of Finnish women has increased since the 1980s, currently, however, at a plateau. In 2012, around 46% of Finnish women were overweight and 19% obese. Although the proportion of overweight women is no longer increasing (at least not greatly), the proportion of obese (BMI: ≥ 30 kg/m²) women continue to rise.¹³³

7 AIMS OF THE STUDY

The main aim of this study was to empirically evaluate the roles of currently common but controversial factors that are highly dependent on culturally related behavior and potentially impact breast cancer outcomes. The aim was also to gain an overall view of the etiology of breast cancer in modern Western society from an epidemiological perspective, considering also changes over time.

7.1 SPECIFIC AIMS

Regarding breast cancer risk factors, studies examining the roles of hormonal contraceptive use and hair dye use in the etiology of breast cancer were carried out.

The proportion of women who had an opportunistic mammography before the age of 50 years was estimated and the roles of breast cancer family history and educational level in having an opportunistic mammography were also assessed.

Finally, the impact of pre- and post-diagnostic negatively or positively experienced major life events in breast cancer-specific mortality was investigated.

8 MATERIAL AND METHODS

8.1 CANCER INFORMATION

Information on the outcomes of interest, namely breast cancer diagnosis and breast cancer-specific deaths, was retrieved from the FCR. The FCR is a population-based, nationwide registry that covers about 99% of solid tumors¹³⁴. Nationwide cancer registration was started in Finland in 1953, and with unique personal identity numbers and regular linkages and updates for deaths and immigration, there are basically no losses to follow-up. Information on causes of death is updated to the FCR from Statistics Finland annually, information on immigration is obtained from the Population Registry Centre (PRC). Data used in the studies include details on topography, histology, morphology, and cancer stage, as well as the primary cause of death. Breast cancer was defined as the person's first in situ or invasive breast cancer registered at the FCR at the end of 2008. All morphologies of breast cancer were included.

8.2 WOMEN'S HEALTH AND USE OF HORMONES (WHH) SURVEY

The primary source of exposure information was the survey "Women's Health and Use of Hormones" (WHH), conducted in 2009 (Figure 8). The WHH survey was initially developed to address the association between use of hormones and risk of breast cancer⁶⁹. Additionally, the survey mapped out several other known or suspected factors impacting the risk of breast cancer or survival from it, such as family history of breast cancer, age at menarche, smoking, alcohol use, BMI, physical activity, use of hair dyes, mammography, and stressful life events.

The survey was aimed at women diagnosed with breast cancer in Finland in 2000-2007 and aged 18-60 years at diagnosis. The survey was mailed to study subjects and it was self-administered and identical for cases and controls. The filled and returned survey was considered as an informed written consent. Breast cancer cases were identified from the FCR in December 2008. Age-matched controls were randomly sampled from the PRC.

Initially, 14 815 women with breast cancer were considered eligible for the survey. After excluding women who had died or emigrated, who had had a previous malignancy, or who had been erroneously sampled, 9 537 cancer cases remained, 6 567 (67%) of whom responded to the questionnaire. After two rounds of control samplings, 41 978 control women remained in the sample, out of the 64 353 originally identified. Of these, 23 114 responded to

the survey (55%). After excluding controls reporting previous malignancies (N=1 516), 21 598 controls were left in the analytical data set.

8.3 BREAST CANCER SCREENING, LIFESTYLE AND QUALITY OF LIFE (EET) SURVEY

In Study III, the survey "Breast Cancer Screening, Lifestyle and Quality of Life" (EET) was also utilized for information on opportunistic mammography. In 2012 and 2013, the EET survey was sent to 5 000 women born in 1963 and 1964, respectively (a total of 10 000 women aged 49 years at survey), randomly sampled from the PRC. In addition to the questions on lifestyle and quality of life, the EET surveys covered information on the family history of breast cancer, education, and opportunistic mammography. Any mammography was considered opportunistic, as the respondents were still below the age of organized screening, which starts at the age of 50 years.

8.4 EXPOSURES IN SUB STUDIES

Questions on hormonal contraception use were covered in the WHH survey. The use of HR IUD was asked as never- vs. ever-use. Use of other hormonal contraceptives (oral contraceptive pills, contraceptive patches, contraceptive implant, or contraceptive injection) was defined as never- vs. ever-use and the total duration of use was also queried.

Hair dye use as an exposure was defined as personal hair dye use reported in the WHH survey. The different dye types were defined as follows: 'Temporary' = a color that rinses off at first wash, 'Semi-permanent' = a color that rinses off after several washes, 'Permanent' = a color that does not wash off, 'Bleach' = hair was bleached before coloring, and 'Partial' = hair was only partially dyed. The frequency of dye episodes in each of the above-mentioned categories was classified as 'Often', 'Quite often', 'Rarely', or 'Never'. The responders were also asked to estimate the cumulative number of hair dye episodes during life as well as the age at first dye.

Opportunistic mammography in Study III was defined as mammography examinations carried out before the national screening-age of 50 years. In the WHH survey, the responders was asked whether she had had a mammography and to specify the age at first mammography. In the EET survey, the responder was simply asked whether she had ever had a mammography. In both surveys, mammography may refer to either purely opportunistic, self-initiated mammography executed for reassurance of one's healthiness in the private sector or symptom-induced, physician-initiated mammography in private or public health-care. Family history of breast cancer was used as either the primary exposure or it was treated as a confounding variable in the statistical analyses. A person was considered to have a family history of breast cancer if she had reported at least one first-degree relative being affected with breast cancer.

In the WHH survey, the responders were given a list of 22 negative and 8 positive life events and were asked to indicate if the specific event had been experienced and if so, when. The responders were also asked to rate the experienced negative event according to its perceived impact as “Not very hard,” “Hard” or “Extremely hard”.

Level of education was considered in all sub studies. Information on the educational level of the WHH survey responders in Studies I, II, and III was based on self-reporting, in Study IV, the educational level was obtained from Statistics Finland. Educational level of the EET survey responders utilized in Study III was also retrieved from Statistics Finland. Educational categories in the studies were based on the number of school years; women with a maximum of 12 years of education falling into the category of low education and those with more than 12 years of education categorized as having high education.

8.5 STUDY POPULATIONS AND DATA COLLECTION PROCESSES

Study I on the relationship between hormone use and breast cancer risk utilized the WHH survey as the source of information on exposures and the FCR as the source of data on the cancer outcomes. Additionally, aggregated data from the OSF and from two Finnish nationwide surveys; the Health Behavior and Health among the Finnish Adult Population in 2010 (AVTK, 1 583 female responders) and the national FINRISK study from 2007 (3 346 female responders) were used for data validation. For comparability with the referent surveys, WHH responders born before 1 945 (640 cases, 1965 controls) were omitted from the study to have equal age cohorts in all surveys.

The source of exposure data in Study II, which examined the effects of hair dye use, was the WHH survey with 6 567 cases and 21 598 controls aged 22-60 years. Information on the cancers was retrieved from the FCR.

Study III on the use of opportunistic mammography utilized both the WHH survey and the EET survey as data sources and included 9 845 women without cancer in total. From the WHH survey, breast cancer cases were not included in the analysis, but controls aged 45-49 years at the time of the survey formed the analytical dataset (N= 4 666). From the EET survey, 5 179 women aged 49 years were included in the analysis.

Study IV on the impact of major life events utilized WHH survey data from the responded breast cancer cases as the source of exposure information. As matching with the control population was not needed, all responding breast cancer cases could be included in the analysis (N=8 364). Outcome data (death due to breast cancer) were retrieved from the FCR.

8.6 VALIDATION AND STATISTICAL METHODS

Validity assessment of the WHH survey data was also conducted. The exposure prevalences retrieved from the WHH survey were compared with corresponding data from OSF as well as AVTK and FINRISK-studies with simple cross-tabulation and by estimating the differences in prevalences in percentage points. Data from OSF were available regarding education, parity, and marital status. Additionally, AVTK and FINRISK -studies provided information on alcohol use, smoking, BMI, and use of hormonal contraceptives, including HR IUD.

The AVTK and FINRISK studies by the National Institute of Health and Welfare were used as reference data because of their established nature as routine nationwide health surveys and because they have been validated and conform to the guidelines of the European Health Risk Monitoring project. The OSF, in turn, offers statistical aggregation of authority-based data, providing virtually complete data on the variables of interest.

Study I utilized conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The obtained results were compared with those reported in earlier large-scale studies on breast cancer risk factors. Analyses were stratified by age: women aged 50 years or less at survey and those aged 51 years or over. Univariate results were adjusted for birth year; multivariate analysis included the following covariates: use of HR IUD, use of other hormonal contraceptives, use of hormone replacement therapy, age at menarche, parity, family history of breast cancer, BMI, education, smoking, and alcohol use.

In Study II, ORs, with 95% CIs were reported from the conditional logistic regression model applied to a frequency-matched study design. Potential confounding factors, such as parity and family history of breast cancer, were included in the multivariate adjusted model, as suggested by the step wise model search. Dose-response trend according to the number of hair dye episodes and the odds of breast cancer was tested by treating the number of episodes as a continuous variable in the logistic regression. The attributable fraction in exposed subjects was calculated with the formula $((OR-1)/OR) \times 100$. This represents the magnitude of the role of hair dye use in breast cancer risk in the exposed subjects.

Due to study populations of different ages and with different types of variable categorization, the percentages of women having had at least one mammography before the age of 50 years were estimated differently from the WHH and EET surveys. From the WHH survey, the percentages were estimated by the Kaplan-Meier method, as there were several categories given for the age at first mammography. From the EET, all reported mammographies were considered opportunistic as all respondents were under 50 years of age, and the percentages could be directly drawn from these figures. Ratios of percentages for opportunistic mammography in women with or without family history of breast cancer and with different

levels of education were estimated by Poisson regression with log-link function and profile likelihood based on 95% confidence intervals.

Regarding the primary exposures in Study IV, each negative life event was given a score (0-3) based on the reported impact of the event; score 0 was given if the person had not reported the event. Total stress score of the negative life events was formed by adding all event-specific scores together, the total stress score ranging from 0-66. Information on the experienced impact with respect to positive life events was not asked in the survey, and these events were considered individually as such without impact weights.

Different Cox models were used to estimate breast cancer-specific mortality hazard ratios (MRs) and their 95% confidence intervals for the different exposures. The patients were followed up until the end of 2013, the primary end point in all Cox models being death due to breast cancer. The observed survival times were effectively conditioned on surviving up to the survey, all estimated Cox models thus allowing for delayed entry. Age groups of 0-54, 55-59, and 60+ years were used in the analyses. Parity, BMI, alcohol use, physical activity, cancer stage, cancer type, and cancer behavior were included as controlling variables in all models.

9 RESULTS

9.1 BASIC CHARACTERISTICS FROM THE WHH SURVEY

With respect to morphology of the cancers of the WHH case-responders, 5 248 (80%) were ductal carcinomas, 4 758 (91%) of which were invasive, whereas 1 022 (16%) were lobular carcinomas, 1 002 (98%) of which invasive. The remaining 4% (N= 297) included cases of medullary, mucinous, tubular, and other more infrequent types of breast cancer, or cases where morphology could not be clearly specified. These morphological distributions correspond to the estimated population-level figures⁷.

Regarding the diagnostic ages of the cases who responded to the survey compared with those who did not, no major differences were observed, median age being 52 years in both responders and non-responders. Median age at the time of the survey was 57.5 years among both cases and controls. Cases had a response rate of 69% and controls 55%. With respect to different age groups, the response figures varied from 52% to 69%, being the lowest in controls aged 35-44 years (52%) and the highest in cases aged 35-44 years and 55-64 years (both 69%).

9.2 PREVALENCE OF PRIMARY EXPOSURES

The overall prevalences of the primary exposures are presented in Table 4.

Exclusive ever-use of HR IUD was reported by 7% of both breast cancer cases and controls aged 50 years or less. Of the responders aged 51 years or over, 15% of the cases reported exclusive ever-use of HR IUD, whereas only 1% of the controls reported the same. With respect to use of other hormonal contraceptives, 89% of the breast cancer cases aged \leq 50 years reported ever-usage, compared with 86% of same-aged controls. Within the age group of \geq 51 years, 72% of cases reported ever using other hormonal contraceptives, the corresponding figure among the controls being 71%.

The prevalence of hair dye use varied over time. While 84% of the WHH - responders born before 1950 reported ever using hair dyes, of the women born in or after 1960 already 92% reported ever-use. Some 19% (4 752 of the total of 24 479) of the ever-users of hair dye reported using dyes 90 times or more in their life time. Regarding differences between breast cancer cases and controls, ever-use of hair dyes was slightly more common among cases, with 88.2% of cases reporting ever-use vs. 86.5% of controls. No difference emerged in age at first dye between cases and controls, 62% of women reporting the first dye episode at an age of less than 30 years.

The most commonly reported negative pre-diagnostic life events in the WHH survey were death of a parent or other close relative, divorce or separation, serious illness of a family member, miscarriage, and financial difficulties. Of the events occurring post-diagnostically, illness causing work disablement, death of a close relative, serious illness of a family member, retirement, death of a close friend, and relationship problems with spouse were most often encountered. With respect to positive life events, falling in love and positive developments in living conditions and in family relationships were the most common pre-diagnostically experienced events. Post-diagnostically, positive developments in family or personal relationships and in hobbies were most commonly reported.

Overall, some 13% of responders in the WHH survey reported having a family history of breast cancer. Of the breast cancer cases, 17% reportedly had at least one first-degree relative affected with breast cancer, and as for the controls, the figure was 9%. In the EET survey, the corresponding percentage among women without cancer was 10%.

Regarding the level of education, 49% of the women in the WHH survey reported a higher level of education (> 12 years). The corresponding figure in the EET survey, where the information was retrieved from Statistics Finland, was 55%. These figures concern women aged less than 50 years at the time of the survey. The proportion of highly educated women was lower among the older responders; some 35% of the WHH-responders aged more than 50 years had a high education.

Table 4. Prevalence of primary exposures in each sub study

Exposure	% of respondent cases in the WHH	% of respondent controls in the WHH	% of respondents in the EET
Use of hormonal intrauterine device (Study I)			
<i>Ever</i>	22	8	-
<i>Never</i>	78	92	-
Use of other hormonal contraceptives (Study I)			
<i>Ever</i>	75	74	-
<i>Never</i>	24	25	-
Hair dye use (Study II)			
<i>Ever</i>	88	87	-
<i>Never</i>	12	14	-
Pre-diagnostic negative life events¹ (Study IV)		-	-
<i>Death of a parent</i>	39		
<i>Death of other close relative</i>	16		
<i>Divorce or separation</i>	11		
<i>Serious illness of a family member</i>	10		
<i>Miscarriage</i>	8		
<i>Financial problems</i>	8		
Post-diagnostic negative life events (Study IV)			
<i>Illness causing work disablement</i>	27		
<i>Death of a close relative</i>	21		
<i>Serious illness of a family member</i>	17		
<i>Retirement</i>	16		
<i>Death of a close friend</i>	13		
<i>Relationship problems with spouse</i>	11		
Pre-diagnostic positive life events² (Study IV)			
<i>Falling in love</i>	20		
<i>Positive development in living conditions</i>	13		
<i>Positive developments in family matters</i>	11		

Table 4. Continued.			
Post-diagnostic positive life events (Study IV)			
<i>Positive developments in family matters</i>	39		
<i>Positive developments in personal relationships</i>	30		
<i>Positive developments in hobbies</i>	29		
Family history of breast cancer³			
Yes	17	10	10
No	83	88	90
Level of education⁴			
≤12 years	61	63	45
>12 years	38	36	55

¹Six most commonly reported life events listed.

²Three most commonly reported life events listed.

³Reportedly at least one first-degree relative affected with breast cancer, based on WHH results in Study I, EET results in Study III.

⁴As self-reported in the WHH survey for Studies I, II and III, and from Statistics Finland for Study IV. For the EET survey information retrieved from the Statistics Finland (Study III).

9.3 RESULTS FROM STUDY I - HORMONE USE AND RISK OF BREAST CANCER

Exclusive use of HR IUD was associated with increased breast cancer risk among post-menopausal women (OR 1.52, 95% CI: 1.14-2.02) when comparing ever-users with those using or having exclusively used a copper-releasing intrauterine device. An effect of similar magnitude (OR 1.48, 95% CI: 1.10-1.99) was observed also when comparing post-menopausal, exclusive HR IUD-users with never-users of any hormonal contraceptive and including only cases who reported using HR IUD before breast cancer diagnosis.

As for use of other hormonal contraceptives, ever-usage increased breast cancer risk by 32% (OR 1.32, 95% CI: 1.08-1.61) in pre-menopausal women and by 8% (OR 1.08, 95% CI: 1.01-1.16) in post-menopausal women, compared with never-users of other hormonal contraceptives. When restricting the analysis to the more recently (2004-2007) diagnosed cases, we obtained an OR of 1.14 (95% CI: 1.02-1.29). By contrast, an OR of 0.91 (95% CI: 0.80-1.03) was observed for those diagnosed in 2000-2001. Significant associations were also observed with respect to the duration of other hormonal contraceptives use in both pre- and post-menopausal women

(OR 1.37, 95% CI: 1.12-1.68 and OR 1.11, 95% CI: 1.03-1.20, respectively), when comparing usage of ≥ 2 years with never-users.

9.4 RESULTS FROM STUDY II - HAIR DYE USE AND RISK OF BREAST CANCER

When comparing ever-users of hair dyes with never-users, we observed a significant association with increased risk of breast cancer in the multivariate analysis including a set of confounders (OR 1.23, 95% CI: 1.11-1.36). Regarding different age groups, the odds of breast cancer were most increased in women born before 1950 (OR 1.28, 95% CI: 1.10-1.48, ever- vs. never-use of hair dyes). In comparison, an OR of 1.14 (0.85–1.54) was obtained for women born in 1960 or later.

With respect to cumulative number of life time hair dye episodes, we obtained OR 1.07 (95% CI: 0.88-1.29) for 1-2 dye episodes in total and OR 1.31 (95% CI: 1.14-1.51) for 35-89 dye episodes. A significant trend for dose-response was also observed ($P= 0.005$).

When estimating the role of age at first hair dye episode, a significant association between earlier starting age and breast cancer risk was observed (OR 1.14, 95% CI: 1.05-1.25) when comparing women reportedly starting to dye their hair at age 20-29 years with women starting at 40 years of age or later. It should be noted, however, that no association was seen when comparing women with first hair dye under the age of 20 years and those started at ≥ 40 years of age (OR 1.06, 95% CI: 0.96–1.16). With pooled age groups (first hair dye at age <30 years vs. ≥ 30 years), the odds of breast cancer was 1.07 (95% CI: 1.01-1.14) for women first using hair dyes before the age of 30 years.

9.5 RESULTS FROM STUDY III - OPPORTUNISTIC MAMMOGRAPHY BEFORE ORGANIZED SCREENING

Of the responders aged 45-49 years in the WHH survey, 66.7% had reportedly had their first mammography, the corresponding figure drawn from the EET survey being 60.4%. When comparing women with breast cancer family history with women without a family history of breast cancer, the percentage ratio (PR) for having an opportunistic mammography was 1.06 (95% CI: 0.98-1.15), as estimated from the WHH survey, and 1.17 (95% CI: 1.09-1.26), as estimated from the EET data.

Education of more than 12 years was associated with an increased proportion of opportunistic mammography, relative to schooling of 12 years

or less. PR for women with longer education from the WHH data was 1.05 (95% CI: 1.00-1.10) and from the EET 1.17 (95% CI: 1.09-1.26).

9.6 RESULTS FROM STUDY IV - MAJOR LIFE EVENTS AND BREAST CANCER-SPECIFIC MORTALITY

Regarding the total stress score of the reported negative life events and their experienced impact, the average score was 14, with an observed range from 0 to 51. The 25%, 50%, and 75% quantiles were 9, 13, and 18, respectively. While there was no association between high total stress score from pre-diagnostic negative life events and breast cancer-specific mortality, women with total stress score of 9-12 from post-diagnostic negative life events had significantly higher breast cancer-specific mortality (MR 1.81, 95% CI: 1.23-2.67), when compared with women with a maximum score of 8. No relationship was observed with respect to the two highest total stress score groups (13-17 and 18-66). None of the individual pre-diagnostic negative life events was associated with breast cancer-specific mortality, while e.g. post-diagnostic retirement (MR 1.87, 95% CI: 1.59-2.19), illness causing work disablement (MR 1.29, 95% CI: 1.16-1.44), and unemployment of spouse (MR 1.28, 95% CI: 1.02-1.61) increased breast cancer-specific mortality. Positive associations were also observed with respect to post-diagnostic relationship problems with spouse (MR 1.23, 95% CI: 1.08-1.41) and death of a close friend (MR 1.19, 95% CI: 1.04-1.36).

Out of the surveyed positive life events, falling in love and hobbies stood out in the analysis. Falling in love pre-diagnostically and post-diagnostic positive development in hobbies had a favorable impact on breast cancer-specific mortality, decreasing mortality by 33% (MR 0.67, 95% CI: 0.49-0.92) and 26% (MR 0.74, 95% CI: 0.57-0.96), respectively.

Estimated attributable fractions of the use of HR IUD (calculated from OR 0.79, 95% CI: 0.54-1.17 and OR 1.48, 95% CI: 1.10-1.99, comparing exclusive users of HR IUD into never-users of any hormonal contraceptive) were -26.58 (95% CI: -85.19 – 14.53) for women in the age group 25-50 years and 32.43 (95% CI: 9.09 – 49.75) for women aged 51-64 years at survey. With respect to use of other hormonal contraceptives, the attributable fractions were calculated from the odds ratios comparing ever-users of other hormonal contraceptives to never-users (1.32, 95% CI: 1.08–1.61 in age group 25-50 years and 1.08, 95% CI: 1.01–1.16 in age group 51-64 years). The obtained attributable fraction in the younger age group was 24.24 (95% CI: 7.41-37.89) and in the older age group 7.41 (95% CI: 0.99-13.79). Total stress score derived from the reported impact of negative life events that occurred before the breast cancer diagnosis did not appear to affect breast cancer-specific mortality. In contrast, some 4% of the breast cancer deaths were estimated to be attributable to post-diagnostic negative life events (3.85, 95% CI: 0.99 – 6.54).

Measures of the associations between primary exposures and breast cancer outcomes as considered in the sub studies are presented in Table 5, and attributable fractions of hair dye use and IUD use in the risk of breast cancer and of life events in breast cancer-specific mortality are shown in Table 6.

Table 5. Measures of the associations between primary exposures and the defined outcomes used in the sub-studies.

Exposure/Association		Effect estimate used	WHH respondents		EET respondents
			Age at survey 25-50 years	Age at survey 51-64 years	
Use of HR IUD	Ever	Odds ratio ^{1b}	0.79 (0.54-1.17)	1.48 (1.10-1.99)	-
	Never ^{1a}		1.0	1.0	
Use of other hormonal contraceptives	Ever	Odds ratio ^{1b}	1.32 (1.08-1.61)	1.08 (1.01-1.16)	-
	Never		1.0	1.0	
Use of hair dyes	Ever	Odds ratio ^{2b}	All respondents		-
	Never ^{2a}		1.23 (1.11-1.36)	1.0	
Opportunistic mammography before organized screening	Breast cancer family history	Percentage ratio ^{3b}	Age at survey < 50 years		1.17(1.09-1.26)
			Yes ^{3a}	1.06(0.98-1.15)	
	No		1.0	1.0	
Educational level, school years	≤12 years	1.0	1.0	1.0	1.0
	>12 years	1.05 (1.00-1.10)	1.17 (1.09-1.26)		
Major life events and breast cancer mortality					
Pre-diagnostic life events	Total stress score ^{4a}	Mortality hazard ratio ^{4b}	1.00(0.97-1.02)		-
	Death of father		1.07(0.93-1.22)		
	Death of mother		1.11(0.98-1.26)		
	Death of other close relative		1.03(0.88-1.21)		
	Divorce or separation		1.13(0.99-1.30)		
	Serious illness of a family member		1.02(0.88-1.18)		
	Miscarriage		1.10(0.93-1.31)		
	Financial problems		0.96(0.80-1.14)		

Table 5. Continued.			
Post-diagnostic life events	Total stress score ^{4a}	1.04(1.01-1.07)	
	Illness causing work disablement	1.29(1.16-1.44)	
	Death of other close relative	0.94(0.81-1.09)	
	Serious illness of a family member	1.05(0.93-1.19)	
	Retirement	1.87(1.59-2.19)	
	Death of a close friend	1.19(1.04-1.36)	
	Relationship problems with spouse	1.23(1.08-1.41)	
	Positive developments (pre-diagnostically) in	Family	0.89(0.60-1.33)
Work		0.83(0.55-1.26)	
Personal relationships		0.85(0.57-1.28)	
Spiritual life		0.71(0.40-1.25)	
Financial situation		0.74(0.47-1.16)	
Living conditions		0.92(0.65-1.30)	
Hobbies		0.90(0.58-1.39)	
Falling in love		0.67(0.49-0.92)	
Positive developments (post-diagnostically) in	Family	0.85(0.62-1.17)	
	Work	0.96(0.73-1.26)	
	Personal relationships	1.09(0.83-1.44)	
	Spiritual life	1.22(0.89-1.67)	
	Financial situation	0.94(0.73-1.22)	
	Living conditions	0.88(0.65-1.19)	
	Hobbies	0.74(0.57-0.96)	
	Falling in love	1.01(0.69-1.47)	

^{1a} Never-users of any hormonal contraceptive, ^{1b}Odds ratios with 95% confidence interval, multivariate model adjusted for either HC or HR IUD use, education, family history of breast cancer, age at menarche, parity, body mass index, smoking and alcohol use, ^{2a}Reported never using hair dyes, ^{2b}Odds ratios with 95% confidence interval, multivariate model adjusted for birth year, parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, body mass index and level of education, ^{3a}Reported at least one first degree relative affected with breast cancer, ^{3b}Univariate ratios of percentages with 95% confidence interval, ^{4a} Total stress score as a continuous variable, ^{4b}Breast cancer-specific mortality ratio from a multivariate model, adjusted for parity, body mass index, alcohol use, physical activity, cancer stage, cancer type, and cancer behavior.

Table 6. *Attributable fractions of hair dye use and use of hormonal contraceptives in the risk of breast cancer and of life events in breast cancer-specific mortality.*

Exposure	OR (95% CI) from which calculated	Attributable fraction % (95% CI) in breast cancer risk
Use of HR IUD, age group 25-50	0.79 (0.54-1.17)	-26,58 (-85,19-14,53)
Use of HR IUD, age group 51-64	1.48 (1.10-1.99)	32,43 (9,09-49,75)
Use of other HC, age group 25-50	1.32 (1.08–1.61)	24,24 (7,41-37,89)
Use of other HC, age group 51-64	1.08 (1.01–1.16)	7,41 (0,99-13,79)
Use of hair dyes	1.23 (1.11–1.36)	18,70 (9,91-26,47)
	MR (95% CI) from which calculated	Attributable fraction in breast cancer-specific mortality (95% CI)
Pre-diagnostic negative life events	1.00 (0.97-1.02)	0 (-3,09 – 1,96)
Post-diagnostic negative life events	1.04 (1.01-1.07)	3,85 (0,99 – 6,54)
Pre-diagnostic falling in love	0.67 (0.49-0.92)	-49,25 (-104,08 - -8,70)
Post-diagnostic hobbies	0.74 (0.57-0.96)	-35,14 (-75,44 - -4,17)

9.7 RESULTS FROM VALIDITY ASSESSMENT

Compared with AVTK, FINRISK, and OSF, the WHH survey responders were more often highly educated and parous, and this effect was more pronounced in the younger study participants. On average, the control responders in the WHH reported 8 percentage points (pp) more academic education than the figures retrieved from the OSF. The difference was the largest in the 25 to 34-year-old responders (+16pp) and smallest in the 45 to 54-year-olds (+4pp). With respect to parity, the controls in the WHH reported on average 9pp more often being parous relative to the data collected from the OSF. Again, the largest difference was observed in the youngest age group (25-34 years), with a +18pp difference. The smallest difference occurred in the age group of 55-64 years, with a +5pp difference.

On average, 24% of the FINRISK participants and 15% of the cases and 17% of the controls in the WHH reported never having used hormonal contraceptives (excluding intrauterine devices in the WHH). Regarding the use of HR IUD, there were on average 7pp more reported ever-users among WHH controls than in the FINRISK, the difference being the largest in the youngest age group (+11pp), whereas the user-proportions in the age group 55-64 years differed by only +1pp.

Reporting of certain lifestyle factors, such as smoking, was surprisingly consistent between the examined surveys. Responders of all three surveys reported highly similar smoking prevalences, differing on average by only 2-

3pp among both cases and controls in the WHH. While 11-12% of women in the AVTK and FINRISK studies reported never using alcohol, the corresponding average percentage was 7% in cases and 8% in controls of the WHH survey. WHH controls reported on average 6pp lower BMIs than AVTK and FINRISK participants.

10 DISCUSSION

A significant positive association was observed between the use of HR IUD and the risk of breast cancer among post-menopausal women. Regarding the use of other hormonal contraceptives, the users' risk of breast cancer was increased most in the younger women. As for the duration of use of other hormonal contraceptives, a significant association for longer usage (≥ 2 years vs. < 2 years) and breast cancer risk was observed in both analyzed age groups.

Hormonal carcinogenesis is likely to be attributable to hormone receptor-mediated responses. Progestogens are suggested to have the ability to stimulate cell proliferation in human breast cells, the magnitude of the effect being different in different synthetic progestogens. The presence of estrogen has been speculated to be essential for this progestogen-mediated cell proliferation, which does not support the hypothesis regarding the carcinogenic effect of hormonal contraception including only a progestogen component, such as the HR IUDs discussed here.⁷¹ Still, there is also evidence of genotoxic effects of progestogen and many progestogens have been shown to have estrogenic activity, which may play a role in the potential effect as well⁷².

That the association between HR IUD use and increased risk of breast cancer was only observed in post-menopausal women is likely to reflect a latent phase before the onset of breast cancer. However, the possibility of selection bias cannot entirely be ruled out, as HR IUD may be a preferred method of contraception or used as part of hormone replacement therapy (HRT) among women with e.g. increased familial breast cancer risk. Regardless of the efforts made to control for both family history of breast cancer and use of HRT in the models, there is a possibility of residual confounding.

The observed association between HR IUD use and risk of breast cancer among post-menopausal women supports the findings of the register-based study by Lyytinen et al. that suggested an increased risk of breast cancer in post-menopausal women using HR IUD⁶⁷. It should be noted though that opposite results have also been reported in, for instance, the large questionnaire-based post-marketing study of *Mirena*® levonorgestrel-releasing intrauterine system use and the risk of breast cancer⁷⁰. However, the follow-up of that study was rather short, a maximum of 10 years, therefore, not necessarily allowing an adequate induction period.

The observed increase in breast cancer risk among recent HC users probably arises from the fact that the recent users are younger women in need of contraception. This finding is of special interest, considering the vast popularity of the use of contraceptive pills and findings also of null-associations^{65,66}. Our findings are still mostly in line with previous research

on the association between HC use and risk of breast cancer. A prospective study by Hunter et al. reported estimations of an increased breast cancer risk among younger (24-43 years) users of hormonal oral contraceptives⁶², and Rosenberg and colleagues concluded in their case-control study that the risk of breast cancer was elevated in women currently using HC⁶⁴. Also Gierisch¹³⁵ and Beaber et al.¹³⁶ reported significant associations between recent HC use and increased breast cancer risk.

With respect to hair dye use and its association with the risk of breast cancer, the risk was 23% higher in ever-users of hair dye than in never-users. We also observed a significant association between earlier age at first hair dye and increased breast cancer risk when comparing two age groups (women who started at age 20-29 years and women who started at age 40 years or over) and with pooled age groups. The fact that no association was seen in those with first dye episode before the age of 20 years compared with women who started at ≥ 40 years of age (OR 1.06, 95% CI 0.96-1.16) implies, however, that age at first dye as such does not have an impact on the risk of breast cancer. The mechanism behind the potential association between hair dye use and breast cancer is unknown. 4-ABP has been suggested to have an ability to cause mutations in the genome⁸⁹. Also, the potential estrogenic activity of 4-ABP may have a role in the chain of events¹³⁷.

Earlier studies on the potential role of hair dye use in the risk of breast cancer have concluded with mixed results. While the research groups of Mendelsohn⁸⁵, Green⁸⁶, and Koenig⁸⁷ reported null-associations, the results obtained in our study are mainly in line with the studies by Nasca⁸¹, Petro-Nustas⁸³ and Cook⁸², all of which reported increased breast cancer risk estimates for hair dye users.

Some two-thirds of the women in both WHH and EET surveys had reportedly had a mammography before the start of organized screening at the age of 50 years. Having an opportunistic mammography was even more common among women who reported a family history of breast cancer and longer education.

The estimates of the proportion of women having had an opportunistic mammography in our study were surprisingly high (>60%), although few previous studies exist with which to compare results. Earlier studies on use of opportunistic mammography in settings where organized and opportunistic screening systems co-exist are sparse, and the results vary greatly, with estimates ranging from e.g. 4% in Denmark¹³⁸ to 64% in Spain¹³⁹.

It should be taken into account that self-reporting of screening attendance may overestimate true proportions, as suggested by Cronin et al., who observed a 16 percentage point higher uptake of mammography in Vermont women aged 40-49 years, when comparing self-reported figures with register-based data¹⁴⁰. The setting in which the above-mentioned study was performed obviously differs from the Finnish setting, as there is no population-based screening program in Vermont, but the estimate may be somewhat generalizable to Finnish women of the specific age group. Also a

meta-analysis on the accuracy of self-reported cancer screening concluded with a similar magnitude of overreporting of mammography attendance¹⁴¹. However, considering Study III, the proportion of women under 50 years of age with a history of mammography would still be unexpectedly high, even if one-fifth were removed from the estimate.

Certain negative life events were associated with increased breast cancer-specific mortality, while some positive events decreased the mortality. The effect was not seen with all specific events, but none showed effects against preliminary expectations of negative events having negative effects and positive events having good implications. Overall, the total stress score of the post-diagnostic negative life events increased breast cancer-specific mortality only slightly (by 4% per increment), but significantly. Meaningful associations regarding individual negative events were obtained for unemployment of spouse, relationship problems with spouse, and death of a close friend.

The apparent associations between breast cancer-specific mortality and retirement and illness causing work disablement most likely only reflect the consequence of becoming a breast cancer case as the diagnosis could have led to early retirement or a period of sick leave. This assumption is supported by an observation in the further analysis, where the impact of retirement disappeared after age-group stratification – no effect was seen among women having reached the actual retirement age. Also, pre-diagnostic retirement did not have an effect on breast cancer-specific mortality.

Earlier research on the effects of stressful life events on cancer survival or mortality is diverse with various methods. A large meta-analysis of the associations between stress and cancer determined that stress-related psychosocial factors were associated with poorer survival in cancer patients in 330 studies and 53 studies reported higher cancer mortality¹⁰³. The results of Study IV suggested only post-diagnostic life events as having an impact on breast cancer-specific mortality; none of the pre-diagnostic negative life events appeared to have an effect. This latter finding supports the conclusion of Maunsell and colleagues that stressful life events experienced before the breast cancer diagnosis have no impact on breast cancer-specific mortality¹⁰⁴. The observed positive association between post-diagnostic negative events and higher breast cancer-specific mortality, on the other hand, supplement the field of diverse research findings on the topic and second the conclusions reached by Chida et al. in the aforementioned meta-analysis¹⁰³.

As for positive life events, falling in love before the diagnosis and positive developments in hobbies after the diagnosis were found to be associated with lower breast cancer-specific mortality. Regarding the beneficial effect of having hobbies, our finding is in line with the study by Tominaga et al.¹⁰⁶, where having a hobby and also a greater number of hobbies were associated with better survival of breast cancer patients.

Changing levels of the body's stress-related hormones are assumed to impact the essential immune functions, thereby also affecting the course of

the disease. For instance, natural killer cells (NK cells) are suggested to play a major role in many diseases by various mechanisms, including the immune surveillance of tumors. Certain stress hormones, including cortisol, adrenaline, catecholamine and epinephrine, have been hypothesized to impair the immune system by lowering the cytotoxicity of NK cells¹⁴²⁻¹⁴⁴. The effect of NK cells on the initiation of cancer and accelerated tumor growth is rather well documented and NK cells are currently used in many new and experimental immunotherapeutic cancer treatments^{145,146}. A potential mechanism underlying the relationship between stress and cancer could be increased DNA damage caused by stress hormones¹⁴⁷⁻¹⁴⁹. The causality between stress and cancer is not, however, straightforward. Some studies suggest that certain levels of stress may even suppress tumor progression^{150,151} and that the effect is greatly dependent on stress-coping mechanisms¹⁵².

10.1 ESTIMATIONS OF THE ATTRIBUTABLE FRACTIONS OF NOVEL EXPOSURES

Use of HR IUD did not seem to impact the risk of breast cancer of women in the age group of 25-50 years. Use of other hormonal contraceptives, by contrast, was estimated to account for 24% of the risk. In women aged 51-64 years at survey, use of HR IUD was estimated to account for 32% of the breast cancer risk if exposed, some 7% being attributable to use of other hormonal contraceptives. Combining these two, we end up with a 20% attributable fraction for use of exogenous hormones, which is very close to that reported by Barnes et al.⁵⁶.

Hair dye use was estimated to account for 19% of the breast cancer risk. While pre-diagnostic negative life events did not affect breast cancer-specific mortality, some 4% of breast cancer deaths were estimated to be attributable to negative events occurring after breast cancer diagnosis.

10.2 STRENGTHS OF THE SUB STUDIES

Population-based study design with a large sample size, and extensive, high-quality cancer information are the most evident strengths of all of the sub studies in this work. Cancer data were not self-reported, data were collected nationwide, and there were basically no losses to follow up. An extensive set of questions in the WHH survey also provided good possibilities for adjusting for many potential confounders in the analysis. Owing to the high-quality registries and statistics in Finland, it was also possible to perform a validity assessment for the WHH survey. Based on this assessment, data from the WHH survey appeared to serve well, especially regarding use of hormonal

contraceptives and with respect to most of the background variables and potential confounders queried at the survey.

10.3 POTENTIAL SOURCES OF BIAS

Risk of bias in the WHH survey was likely to be greatest due to differences in response activity between breast cancer cases and controls. Socioeconomic status is also a potential modifying variable in many etiological studies, and thus, must be taken into account. Level of education is often used as a surrogate to estimate socioeconomic status, as in all sub studies here. Biased distribution of educational level of the survey responders naturally complicates assessment of the roles of factors commonly affected by the socioeconomic status, and accordingly, may reduce representativeness of the results. Also, information on responders' occupation was missing, thus not allowing the assessment of potential occupational exposures and risks.

As suggested earlier, women participating in health-related studies are likely to be more health-conscious and prone to a healthy lifestyle overall^{153,154}. This is a problem concerning most survey-based studies and probably also affected this study. This should be taken into account when considering generalizability of the obtained results. However, surveys continue to be valuable sources of information on many potential risk factors and exposures related to lifestyle and behavior in general.

Overall, recall bias is often identified as a likely source of bias in studies based on self-reported data. Naturally, magnitude and direction of bias are greatly dependent on the nature of the survey questions. Risk of recall bias is relatively large regarding, for example, questions on hair dye use in Study II. It might have been difficult for the responders to estimate lifetime hair dye episodes or to determine the different dye types used. Women with breast cancer may also be prone to overestimate their hair dye use if they saw it as a potential causal component of their disease. Reporting ever- vs. never-use of hair dyes is, however, not likely to be as susceptible to bias, as it is easier to remember and the chance of cases and controls reporting usage differently is lower. A similar type of recall bias might also have affected Study IV. Some life events may have been difficult to assign to a certain time period. This may have consequently affected categorization of the events as pre- or post-diagnostic. Also, it should be noted that existing depression might influence the way of perception when encountering other life stresses. Usually mildly experienced events may then be overwhelming or in the other extremity, become ignored. Either way, it may severely impact the experience and thus also bias reporting of it.

Recall bias was not a major concern in Study III, which investigated the prevalence of opportunistic mammography, as women probably remembered the somewhat painful procedure. Overall in Study III, the possibility of selection bias was likely to be greater in the WHH survey due to study design.

There, the WHH study population was formed from the controls of breast cancer cases. Still, the observed effect estimates did not differ much between the WHH and EET surveys, suggesting that role of selection bias was not very big.

It should also be noted that there is major variation in times between cases' diagnosis and the survey and this may affect the recall of the events and their timings in Study IV. While the minimum time between breast cancer diagnosis and the WHH survey was 1 year, the maximum was 9.5 years. The median interval was 5.5 years. The retrospective nature of the WHH survey also creates potential for selection bias, as we inevitably miss the most aggressive types of cancers. It is also possible that a person recently diagnosed with the disease in question is more devoted and motivated to participate in a study concerning one's disease, and possibly also more prone to over-reporting exposures that may be considered to have an impact on the disease onset. This may especially apply to Study I, where the title of the WHH survey may have led responders to strongly associate hormone use with breast cancer, hence affecting their survey responses on the topic.

Bias concerning case-control ascertainment was considered to be insignificant, as FCR coverage is nearly complete¹³⁴.

10.4 BREAST CANCER – IS IT A PHENOMENON OF WESTERN SOCIETY?

Attempts to modify people's beliefs regarding risk avoidance and preferred behavioral patterns as well as to overcome ignorance are among the most essential public health objectives. It is assumed that a person changes his/her behavior once he/she is made aware of the potential dangers or benefits of a certain type of behavior. The success of the resulting behavior change is uncertain. It is likely that the intentions of more healthy behavior are often defeated by busy everyday life, and it should be remembered that people have priorities in life beyond pursuing good health⁵. It is thus argued that health interventions should focus on the recognized pressure points that generate health behaviors. An example of such a pressure point could be found in the statutes and more importantly in the informal practices and work-place sub cultures that regulate working times and lunch, and other breaks. The demanding, performance-oriented culture of today's working life is apt to foster unhealthy diet and sedentary behavior, which over time become normalized and also routine in other areas of life. Targeted, well-grounded policy measures in, for instance, work time legislation may have a marked effect on overall behavioral patterns with respect to eating, among other things, as discussed by Dixon.⁵ Dixon also states that "*if cultural norms are contributing to the rise in health risks such as obesity and the persistence of smoking, then it follows that cultural forces need to be unleashed to counteract their present trajectories*". Governments, religious

institutions, the commercial sector, etc., all influence the ideas and practices comprising the cultural framework, and thus, also have the ability to induce or contribute to cultural changes, and through these, behavioral changes.⁵

Olsen states that a multidisciplinary, mixed-method approach in health research would be key to a more nuanced understanding of human behavior and disease patterns¹⁵⁵. Medical anthropologists argue that current epidemiology is merely focused on isolated disease risk factors, separated from broader context, disregarding the societal determinants of disease^{25,155}. The aim of the following paragraphs is to place the main findings of the sub studies into the cultural and societal context of today's Finland.

Use of HR IUD is especially common in Finland, which may in part be related to the history of first such device being invented in Finland, and thus being in a spotlight. While oral contraceptives hold their first place position in hormonal contraceptive use, intrauterine devices come second¹⁵⁶. Increased use of hormonal contraceptives in Western countries is naturally related to the need for longer periods of contraception, as increasingly fewer children are had at an increasingly older age. Reasons for this are diverse. Education for a profession takes longer than before, as university-level education has become "the norm" for many people, and it is customary for both parents to work. People enter work life at a later age than a few decades ago, and childbearing is often delayed until an established position in work life and financial security have been obtained. Also, social pressure of getting married and having children – created traditionally by parents and other relatives - perhaps no longer exists in Western societies to the same degree as before. The patent of the world-leading HR IUD brand *Mirena*® expired at the end of 2015, and it remains to be seen how the markets react; will there be more competition with new less expensive products, potentially leading to increasing numbers of HR IUD users. The Annual Report 2015 of the *Mirena*® manufacturer Bayer indicates that the sales of *Mirena*® have been increasing in the USA, ranking among their bestselling pharmaceutical products¹⁵⁷. Reliable information on the long-term effects of HR IUD use is crucial.

Use of hair dyes, on the other hand, is among the most stereotypic features of Westernization and falls into the same category as other ideals related to the concept of beauty and appearance, including fashion diets and a constant flow of new methods and products for beauty care and make-up. Western culture idealizes youth, beauty and vitality and many related products and modes of behavior in pursuit of these ideals cannot unambiguously be deemed safe. Results obtained in Study II suggest that the role of hair dye use may be substantial in etiology of breast cancer. Taking the popularity of hair dye use into account, the impact in public health could also be considerable, even if the increase in risk of breast cancer attributed to hair dye use is small at the individual level.

A large proportion of women having had an opportunistic mammography before organized breast cancer screening age is probably one the most recent

effects of modernization and a manifestation of a medicalized welfare society. Access to public health-care, occupational health care and private gynecologists is easy and affordable for many women. In a comparative study on performance of organized and opportunistic breast cancer screening, Bihmann and colleagues reported significantly higher sensitivity of organized breast cancer screening compared with opportunistic screening, specificity being relatively similar in both. Considering this, they recommended implementation of population-based breast screening programs, as also recommended in the European guidelines.¹⁵⁸ The problem in many developed countries, however, is the mixed model of two co-existing systems, and a starting point for the overall benefit-harm evaluation of breast cancer screenings would be better reporting systems for opportunistic mammography. This would be highly useful also in Finland.

Research on the effects of stress in health and disease has increased over the past years. Regardless of the already rather convincing evidence of the negative impact of stress on health, efficient and long-ranging public health interventions are lacking. This may be due to the non-measurable nature of the exposure or simply the lack of concrete intervention methods. Of all the investigated exposures in this study, stress probably has the most significant role in terms of overall health. Actions and structures of society have become immensely complex and diverse, and it is likely that the human body and mind cannot fully keep track of the changes and adapt to the ever-changing environment.

The high incidence of breast cancer in Western countries may reflect physical maladaptation to immense, continuous cultural change. As societies are becoming more and more complex and multidimensional, it is increasingly difficult to identify factors affecting disease outcomes. Many contributing environmental and behavioral factors regarding breast cancer have, however, been identified, and alongside the ongoing preventive public health measures initiated in Western societies, more efforts should be directed to public health in developing countries. The effects of modernization in these countries are just starting to become apparent, and timing would be right for efficient health interventions.

Our studies suggested significant associations between use of both hair dyes and hormonal contraceptives and an elevated risk of breast cancer. Such exposures are ideal examples of modernization and the Western lifestyle and the accompanying downsides. The effects of certain major life events on breast cancer-specific mortality, on the other hand, exemplify the fact that while great strides have been made in breast cancer treatment, uncontrollable factors also play a role. The key is to identify such factors and if they are not modifiable, they can at least be taken into account in recognizing potential risk groups and in planning treatment.

11 SUMMARY AND CONCLUSIONS

The purpose of this study was to investigate modern, less known Western society lifestyle-related factors affecting breast cancer outcomes. A secondary aim was to explore the change in the overall breast cancer risk factor spectrum and to evaluate it as part of a larger cultural and societal framework.

The observed increase in breast cancer burden in Finland and elsewhere is undoubtedly greatly influenced by modernization and modes of behavior related to changes in the Western culture. Women entering work force and its implications for reproduction patterns, excessive use of chemicals, a demanding stressful society, increased use of alcohol, and overall sedentary lifestyle are all reflective of Western lifestyle. In addition to the evident differences in behavioral patterns between Western and non-Western cultures producing most of the variation in global breast cancer incidence and mortality, there are likely to be other factors contributing to the differences seen in the known epidemiology of breast cancer.

The current landscape of breast cancer risk factors of Finnish women is constructed of the well-known, classical factors detected also in the sub studies here and more novel exposures. Later age at first delivery, low birth rate, sedentary life style, increasing alcohol use and overweight may be considered established risk factors and these are, as suggested by the findings of the sub studies, more and more often complemented by the effects produced by the directly measurable factors like use of exogenous hormones and cosmetics such as hair dyes. Other complex factors, including stressful daily life, add to the burden. The surprisingly popular opportunistic mammography may also impact breast cancer susceptibility by increasing radiation body burden, when added to all other medical sources of radiation. The latter two were not evaluated in the framework of this thesis, but are intriguing topics for future analysis.

When looking at the big picture of the etiology of breast cancer, we can see many changes in the contributing risk factors over time. According to current knowledge, prevalence of many known breast cancer risk factors has increased markedly over the past few decades. Some of these are directly modifiable, such as physical activity, overweight, and alcohol and hormone use, while others, e.g. reproduction behavior, are more complex. Promotion of a healthy lifestyle, specifically regarding physical activity, overweight, and alcohol use, should receive more attention and there should be a clear message of its importance also in breast cancer prevention – at present, the focus tends to be on other diseases, e.g. other cancers, cardiovascular diseases, or mental health. In contrast, it is more difficult to make recommendations on reproduction behavior. Women can, and should, however, be made aware of the modes of behavior resulting in an increased

risk of breast cancer so that they can make informed choices in family planning. Use of hormonal contraceptives is tightly linked to this and women ought to be more comprehensively informed of the risks related to their usage. While the evidence for use of combined oral contraceptives in increased risk of breast cancer is strong, research on the association between HR IUD use and breast cancer risk is still sparse – our study clearly suggesting a need for this. Further studies with other populations and a prospective study design are strongly recommended, taking into consideration the increasing use of HR IUD. Also, longer exclusive breastfeeding would be of benefit considering the risk of breast cancer and this should be more efficiently promoted – as mentioned, exclusive breastfeeding up to the recommended age of 6 months is very rare in Finland. Not only would this benefit the child, but it would also lower the mother's risk of breast cancer.

Use of chemicals, including cosmetics, increases the body burden of potentially toxic and carcinogenic substances. Caution is warranted in use of all chemicals and there is a need for stricter control of sales and use of personal hair dye products. Usage is currently not recommended for those aged under 16 years in the EU, but monitoring is insufficient. More responsibility should also be directed to regulatory authorities on the safety of these products, as more research on their accumulation in the body and long-term effects is needed. Risk evaluation of hair dye substances should be carried out by an organization independent from the manufacturing industry.

With respect to opportunistic mammography, it would be important to guide and restrict the wide use of non-organized activity in healthy women without clinical indications or significant familial cancer burden. It would be useful to start registering the examinations in order to be able to take these into account when evaluating the organized breast cancer screening program. High usage of opportunistic mammography may undermine the organized screening program and complicate proper assessments of its functions and effectiveness. It should also be noted that women may be unaware of the risks of excessive use of mammography in terms of accumulating radiation burden. The negative aspects of false-positive findings should also be disclosed. Likewise, it is important to increase women's knowledge of when there is reason to suspect a true familial risk of breast cancer, as opposed to sporadic breast cancer cases in the family, which warrant no additional worry or preventive measures.

In addition, there are biological factors, including age at menarche and menopause, where the change is a result from long-term societal evolution and cannot be directly modified by an individual. A hectic, stressful lifestyle is also so tightly bound to the surrounding societal norms and modernization that it may prove difficult to make drastic changes to it. Better understanding by health professionals of the possible adverse effects of stressful life events – and the potential positive impact of positive events - would provide a starting

point for more holistic health-care planning, disease prevention, and efficient, personalized treatment. It is well-known that there is an excess risk of death even 15 years after breast cancer diagnosis, and the follow up should be extended beyond the routine mammography, including also mental well-being and recovery.

It should be noted, however, that modernization and its implications can also be looked at from a different perspective and it cannot be considered as resulting only in emergence of new potential risk factors. There has been great improvements in women's position in a Finnish society overall and it is evident that some of the elements discussed here have also resulted in remarkable positive developments in women's life. As mentioned, for instance matters of reproduction are complex and making steady recommendations on them may be considered inappropriate or unconventional. As discussed earlier, people often have priorities in life other than solely pursuing good health and they may be willing to make choices that are known to possess additional risks on certain health outcomes. It is of health professionals' responsibility to make sure they are informed choices.

From the epidemiological point of view, while in the mid-1900s breast cancer in Finland was a rare disease and its etiology was likely based on fewer risk factors, today it is a rapidly increasing disease of women from all walks of life, and with much larger variation in the risk factor spectrum. This study provides new information concerning some less studied factors affecting breast cancer risk and survival from it. These findings combined with known factors should improve prevention efforts. The primary target of breast cancer prevention from the epidemiological perspective is to provide new research-based information for both women and policy makers to advocate healthier choices in life.

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