Turun yliopisto
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THE EFFECTS OF THE BREAST CANCER MAMMOGRAPHY SCREENING PROGRAMME IN WOMEN AGED 40 TO 84 YEARS IN TURKU, FINLAND (1987-2009)

Ilmo Parvinen

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University of Turku

Faculty of Medicine
Department of Clinical Oncology
Doctoral Programme of Clinical Investigation (CLIDP)

Supervised by

Docent Liisa Pylkkänen, M.D., Ph.D.
Department of Clinical Oncology
University of Turku, Finland and
Cancer Society of Finland, Helsinki

Docent Pekka J. Klemi, M.D., Ph.D.
Department of Pathology
University of Turku, Finland

Reviewed by

Professor Heikki Joensuu, M.D., Ph.D.
Department of Oncology
University of Helsinki, Finland

Docent and Professor (emeritus) Jarmo Virtamo, M.D., Ph.D.
Department of Public Health
University of Helsinki, Finland and
National Institute for Health and Welfare (THL)

Opponent

Professor Pekka Puska, M.D., Ph.D., M.Pol.Sc.
National Institute for Health and Welfare (THL)
Helsinki, Finland

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ABSTRACT

Ilmo Parvinen

The Effects of the Breast Cancer Mammography Screening Programme in Women aged 40 to 84 years in Turku, Finland (1987-2009)

Department of Clinical Oncology in co-operation with Department of Pathology, Turku University, Finland

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2014.

The objective of this thesis was to evaluate whether a more extensive mammography screening programme (TurkuMSP) conducted by the city of Turku, had an effect on breast cancer (BC) incidence, survival, or mortality in years 1987 to 2009. Despite the fact that some studies have suggested a 20 percent reduction in BC mortality due to mammography screening, there are findings of harm to subjects, which are claimed to negate the benefits of screening. Thus, the aims of this study are most pertinent.

A total of 176 908 screening examinations were performed in 36 000 women aged 40−74 during the years 1987−1997. In all, 685 primary BCs were found in the screened women, either screen-detected (n=531) or during screening intervals (n=154). Survival and BC recurrence rate of women with screen-detected BC was compared to 184 women with clinical BCs detected among individuals who did not take part in the screening. The invitation interval, which may influence the outcome, was studied in the age group 40 to 49 by inviting those born in even calendar years annually for mammography screening and those born in odd years, triennially.

In addition, BC incidence and mortality in the total female population of Turku aged 40 to 84 years was compared with the respective figures of Helsinki and the rest of Finland, both during the pre-screening era (1976-1986) and the screening era (1987-2009). The study was designed to compare women by age groups, because women aged 50 to 59 were generally screened in all of Finland, whereas only in Turku women aged 40 to 49 and 60 to 74 were screened in addition. Data regarding cancer recurrence were derived from the Finnish Cancer Registry and data on deaths were collected from Statistics Finland.

In survival analyses, screened women with invasive BC had a significantly higher survival rate than the women with clinical BC. The survival benefit started to appear already during the first follow-up years and was evident in all age groups. A marginal survival extension was also seen in screened women when BC had spread to ipsilateral axillary nodes already at diagnosis. Recurrence-free survival rate after BC treatment was significantly more favorable among the screened women compared with women with BC found clinically. The screening invitation interval did not significantly influence BC mortality in the subset of women aged 40 to 49 years.

There were no consistent differences in the changes of BC incidence between Turku and the comparison areas during the screening era. In Turku, the BC mortality incidence in women aged 55−69 years was significantly lower during the screening era (from 1987 to 1997) compared with the pre-screening era, whereas no such change was found in the city of Helsinki or Tampere. When comparing the changes in incidence-based BC mortality during years 1987 to 2009 in Turku to those of Helsinki and the rest of Finland, there was a suggestion of more than 20 percent lower mortality in Turku among oldest age group (75-84 years) compared with the reference residential areas, but the differences were not consistently significant.

Interpretation of the study results should be made with caution because there were no random control groups, and on the other hand, the number of cases in subgroups was fairly low to yield definite conclusions. Also due to the many statistical analyses, some of the findings may be due to chance. The results are, however, suggestive for a decrease of BC mortality in the elderly age groups due to wide mammography screening. This finding needs confirmation in further studies before recommending an expansion of mammography screening to women up to the age of 74 years

Key words: mammography; mass screening; service screening; breast cancer; incidence; incidence-based mortality; death-rate; survival; recurrence; invitation interval; population-based; female; aged 40-84; Finland/epidemiology; City of Turku; TurkuMSP study

TIIVISTELMÄ

Ilmo Parvinen

Turun Mammografiaseulontaohjelman vaikutukset 40-84 -vuotiaisiin turkulaisnaisiin (1987-2009)

Kliinisen syöpätautiopin yksikkö yhteistyössä Patologian yksikön kanssa, Turun yliopisto

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Tämän väitöskirjatyön tarkoituksena oli selvittää, voitiinko tavanomaista laajemmalla, Turussa toteutetulla mammografiaseulontaohjelmalla (TurunMSP-ohjelma) vaikuttaa rintasyövän ilmaantuvuuteen, eloonjäämiseen tai kuolleisuuteen vuosien 1987-2009 välisenä aikana. Vaikka jotkut tutkimukset ovat osoittaneet 20 %:n suuruusluokkaa olevia rintasyöpäkuolleisuuden vähenemiä mammografiaseulontojen tuloksena, on myös esitetty tutkimustuloksia, joissa seulontaohjelmiin liittyvät haitat kumoavat seulonnalla saadut hyödyt. Näin ollen tämän tutkimuksen tavoitteita voidaan pitää edelleen ajankohtaisina.

Kun 176 908 seulontatutkimusta tehtiin Turussa 36 000:lle 40-74-vuotiaalle naiselle vuosina 1987-1997, löydettiin heiltä 685 primaarisyöpää, joko seulonnan yhteydessä (n = 531) tai välisyöpinä (n = 154). Näiden tapausten eloonjäämistä ja rintasyövän uusiutumista verrattiin seulonnan ulkopuolella kliinisesti havaittuihin 184 rintasyöpään. Koska seulontakutsun aikaväli saattaa vaikuttaa seulonnan tuloksiin, tutkittiin tätä asiaa 40-49-vuotiaiden naisten ikäryhmässä, kutsumalla parillisina kalenterivuosina syntyneet naiset mammografiaseulontaan vuosittain ja parittomina vuosina syntyneet joka kolmas vuosi.

Tämän lisäksi Turun tuloksia verrattiin 40-84-vuotiaiden naisten osalta Helsingin ja muun Suomen tuloksiin sekä seulontaa edeltäneellä ajanjaksolla (1976-86) että seulontajaksolla (1987-2009). Tutkimus suoritettiin ikäryhmittäisenä vertailuna, koska Suomessa seulottiin tuolloin yleensä vain 50-59-vuotiaat naiset, kun sen sijaan vain Turussa myös 40-49-vuotiaat ja 60-74-vuotiaat. Syöpätapauksia koskevat tilastotiedot hankittiin Suomen Syöpärekisteristä ja kuolleisuustiedot Tilastokeskukselta.

Invasiivisten rintasyöpätapausten eloonjäämistulokset olivat seulotuilla naisilla merkitsevästi paremmat kuin kliinisesti diagnostisoiduilla naisilla. Eloonjäämishyötyä alkoi näkyä jo ensimmäisistä seurantavuosista alkaen, ja se näkyi kaikissa ikäryhmissä. Marginaalinen eloonjäämishyöty havaittiin myös niillä naisilla, joiden syöpä oli ehtinyt levitä kainalon seutuun diagnoosihetkellä. Myös taudin uusiutumiseen kuluva aika oli rintasyöpähoidon saamisen jälkeen merkitsevästi pidempi seulonnassa löytyneiden tautitapausten osalta verrattuna kliinisesti löytyneisiin tapauksiin. Kutsumistiheyden eroilla ei näyttänyt olevan vaikutusta (40-49-vuotiailla).

Turun naisten rintasyövän ilmaantuvuuden muutoksissa ei havaittu eroja vertailualueiden ilmaantuvuuden muutoksiin verrattuna mammografiaohjelman seulontajakson aikana. 55-69-vuotiaiden naisten rintasyöpäkuolleisuus oli Turussa merkittävästi pienempi seulontajaksolla (1987-1997) kuin sitä edeltäneellä jaksolla, jolloin seulontaohjelmat eivät vielä olleet käynnistyneet. Vastaavaa muutosta ei Helsingissä tai Tampereella havaittu. Kun vertailtiin puolestaan Turussa tapahtuneiden ilmaantuvuusperusteiseen rintasyöpäkuolleisuuden muutoksia vuosina 1987-2009 Helsingissä ja muualla Suomessa tapahtuneisiin muutoksiin, saatiin selviä viitteitä iäkkäimmän naisryhmän yli 20 % vertailualueita suuremmasta rintasyöpäkuolleisuuden pienentymisestä (75-84-vuotiaat), mutta tulokset eivät olleet kaikilta osin johdonmukaisesti merkitseviä.

Tämän tutkimuksen tulosten johtopäätökset on tehtävä varoen, sillä tutkimus ei toisaalta sisältänyt satunnaistettuja kokeita, ja toisaalta tapausten määrä oli joissakin alaryhmissä melko alhainen sitovien päätelmien tekemiseksi. Koska tutkimuskokonaisuuden aikana käytettiin useita erilaisia laskentamenetelmiä, jotkut tutkimuksen tulokset voivat myös johtua sattumasta. Tulokset kuitenkin viittaavat siihen, että varsinkin iäkkäimmissä naisryhmissä havaittu rintasyöpäkuolleisuuden lasku johtui laajasta mammografiaseulonnasta. Tämä havainto edellyttää kuitenkin vielä jatkotutkimusten kautta hankittavaa lisänäyttöä ennen kuin voidaan suositella seulontaohjelman laajentamista 74-vuoden ikään asti.

Avainsanat: mammografia; joukkoseulonta; rintasyöpä; ilmaantuvuus; ilmaantuvuuteen suhteutettu kuolleisuus; kuolleisuusluku; eloonjääntiluku; uusiminen; kutsuntatiheys; väestöpohjainen; naissukupuoli; ikäluokat 40-84: Suomi/epidemiologia; Turun kaupunki; Turun MSP tutkimus

CONTENTS

ABBREVIATIONS AND DEFINITIONS

BC	Breast cancer
BMI	Body mass index
CI	Confidence interval
CIS	Carcinoma *in situ*
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CISNET	Cancer Intervention and Surveillance Modelling Network
DCIS	Ductal carcinoma *in situ*
EBM	Evidence-based medicine
EPT	Estradiol-progestagen therapy
ER	Estrogen receptor
e.g.	*Exempli gratia*, for example
FCR	Finnish Cancer Registry
HCH	Hexachlorocyclohexane
HR	Hazard ratio
HRT	Hormone replacement therapy
HSR	Health service research
IBM	Incidence-based mortality
IDC	Invasive ductal carcinoma
i.e.	*Id est,* that is
ILC	Invasive lobular carcinoma
LCIS	Lobular carcinoma *in situ*
MRI	Magnetic resonance imaging
N.A.	Not available
NNS	Number needed to screen
NNS	Number needed to screen per life year gained
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
PR	Progesterone receptor
RoF	Rest of Finland
RR	Relative risk
SD	Standard deviation
SHBG	Sex hormone-binding globulin
THL	National Institute for Health and Welfare (Finland)
TurkuMSP	Turku mammography screening programme
TurkuMSP study	This thesis, Turku mammography screening programme study
UKCCCR	UK Coordinating Committee on Cancer Research
U.S.	The United States of America
QALY	Quality adjusted life years

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following articles, which are referred to, in the text, by Roman numerals.

I Klemi PJ, Parvinen I, Pylkkänen L, Kauhava L, Immonen-Räihä P, Räsänen O, Helenius H. Significant improvement in breast cancer survival through population-based mammography screening. Breast 2003;12:308-13.

II Immonen-Räihä P, Kauhava L, Parvinen I, Holli K, Kronqvist P, Pylkkänen L, Helenius H, Kaljonen A, Räsänen O, Klemi PJ. Mammographic screening reduces risk of breast carcinoma recurrence. Cancer 2005;103:474–82.

III Parvinen I, Helenius H, Pylkkänen L, Anttila A, Immonen-Räihä P, Kauhava L, Räsänen O and Klemi PJ. Service screening mammography reduces breast cancer mortality among elderly women in Turku. J Med Screen 2006;13:34-40.

IV Parvinen I, Chiu S, Pylkkänen L, Klemi PJ, Immonen-Räihä P, Kauhava L, Malila N, Hakama M. Effects of annual vs. triennial mammography interval on breast cancer incidence and mortality in ages 40–49 in Finland. Br J Cancer 2011;105:1388-91.

V Parvinen I, Heinävaara S, Anttila A, Helenius H, Klemi PJ, Pylkkänen L. Mammography screening in three Finnish residential areas: A comprehensive population based study of breast cancer incidence and incidence- based mortality from 1976 to 2009. (Submitted)

1. INTRODUCTION

Breast cancer (BC) is the most common malignant disease among women in many countries (in Finland, since 1961).[1] During the year 1986, an active discussion to start mammography screening in Finland was promoted at the national level (by the National Board of Health) and Finland was one of the first countries to begin a nationwide mammography screening programme. It targeted only women aged 50 to 59.[2] The decision to start this programme in Turku on a broader scope was based mainly on randomized study reports originating from the U.S.[3] and Sweden.[4]

However, the idea of implementing a mammography screening programme was voiced earlier. In the Finnish city of Tampere, the first Finnish mammography-based test-screenings were performed during 1974 to 1975 and a few years later in the Finnish city of Turku (1978-79).[5] In Southwest Finland, the initial interest stemmed from a non-governmental organization, the Cancer Society of Southwest Finland, and from the Department of Oncology and Radiotherapy at the Turku University Central Hospital.

A "kick-off" for the development of a comprehensive Turku city mammography programme occurred in June 1986 with the publication of a mammography-screening programme in the city of Turku (TurkuMSP) by Parvinen and Kauhava.[5] Their aim was to reduce mortality and improve survival by a mammography-screening programme. This was highly controversial, at the time, but the attitude in Turku was positive due to the good results of cervical cancer screening and the active role of the regional cancer society. The decision-making behind the Turku screening plan stemmed much from the female city council members. The Turku city mammography-screening programme was started in 1987 and covered the age of women from 40 to 74 years. During the same year, a nationwide Finnish mammography-screening programme began, which covered women 50-59 years of age.

The Turku city decision was founded on international study results from the U.S., Holland, and Sweden.[4 6 7 8 9 10] Finnish medical researchers were eager to monitor BC risk factors or screening effect assessments.[11 12 13 14] Based on the available evidence, the BC mortality reduction targets were assessed TurkuMSP in ten-year spans. In women aged 40 to 49, the anticipated target for reduction was 18 percent; in women aged 50 to 64: 42 percent; and in women aged 65-74: 43 percent. The reductions beyond 40 percent were ambitious because the results in published studies reported approximately 20 to 30 percent mortality reductions. However, the reduction target for the younger age group was the lowest due to the results from the initial randomized trials showing that this age group had about half of a reduction compared to the other age groups.[4] Hence, the TurkuMSP mortality reduction targets were fitted in line with these first scientific results.

The very initial plan to screen women in Turku consisted of diverse experts' opinions regarding the birth cohort coverage, invitation intensity, and the possibility to start randomized trials with a control group. This made the situation difficult for budget preparation and resulted in the first screening time span, in Turku, to cover only six years (1986-1991).[5] A randomized trial layout was not recommended for TurkuMSP

either by medical experts or by political decision makers due to reluctance to exclude any women's age group.

TurkuMSP received support from the National Board of Health, which enabled the follow-up of studies including a wide age perspective and giving special attention to the interval comparison among 40 to 49 year old women. Regardless of this, the state financial public authority (at that time the provincial government) did not pay any subsidiaries covering the age groups: 40 to 49 or 60 to 74, which meant that those expenses were solely covered from the budget of the city of Turku.

From the very beginning, the responsible Finnish BC screening executing organizations have committed to evaluative scientific follow-up responsibilities, which they have conducted.[15 16 17 18 19 20 21 22] This same commitment concerns an exceptional arrangement in Turku (TurkuMSP) and therefore a special study team was established. All this advancement happened globally, domestically, and at city level. This opened a gate to scientifically assess and evaluate the impact of mammography screening programmes conducted differently - based on age groups and an invitation base. By targeting the Turku city women population, research activities were started to determine if it influenced the mortality of younger women and elderly women, which was not possible using the standard Finnish screening schedule. These research activities led to the launch of this dissertation.

The objective of this TurkuMSP study alias this thesis was to determine if mammography screening was meeting its potential efficacy, and by that, the women of Turku were earning the benefits of this programme. Secondly, the effects of the screening programme on young and elderly women's BC incidence and mortality were determined.

2. REVIEW OF THE LITERATURE

In Finland, approximately one woman in 15 will get BC before the age of retirement and during their whole life span this becomes more than one in ten.[11] With an average lifetime risk to get BC of ten percent (*e.g.,* in the U.S. at 12.3 percent during the years 2006 to 2008)[23], BC is a common cancer that affects women predominantly in the Western world. Up to 15 percent of healthy women have at least one first degree relative with BC[24] and empirical data show that BC risk doubles in these "healthy" women.[25]

2.1. BC incidence

World

Based on the GLOBOCAN 2012 estimates, BC is the most frequently diagnosed new cancer cases accounting for 12 percent (1.68 million) of the total cancers (14.09 million) and 25 percent of all women cancers (6.66 million).[26]

In general, BC incidence rates are high in Western and Northern Europe, Australia/New Zealand, and North America. Increased incidence trends turned to rapid growth in many Western countries during the late 1980s and 1990s. This resulted in, for example, changes in reproductive factors (including the increased use of postmenopausal hormone therapy) as well as an increased screening intensity.[27] Due to the large array of known BC background risk factors, it is very reasonable that BC incidence levels vary around the globe but a global BC incidence increase has been a permanent trend for the last decades. In some countries like the U.S. and Canada, Australia, and some Nordic Countries,[28] this trend is has been plateauing (**Figure 1**), [26] but in many others still growing. Autier et al. has investigated this trend (2010)[29] but no comprehensive explanation exists. The relationship between the use of the HRT and BC is probably one of the most important explanatory factors.[30 31 32]

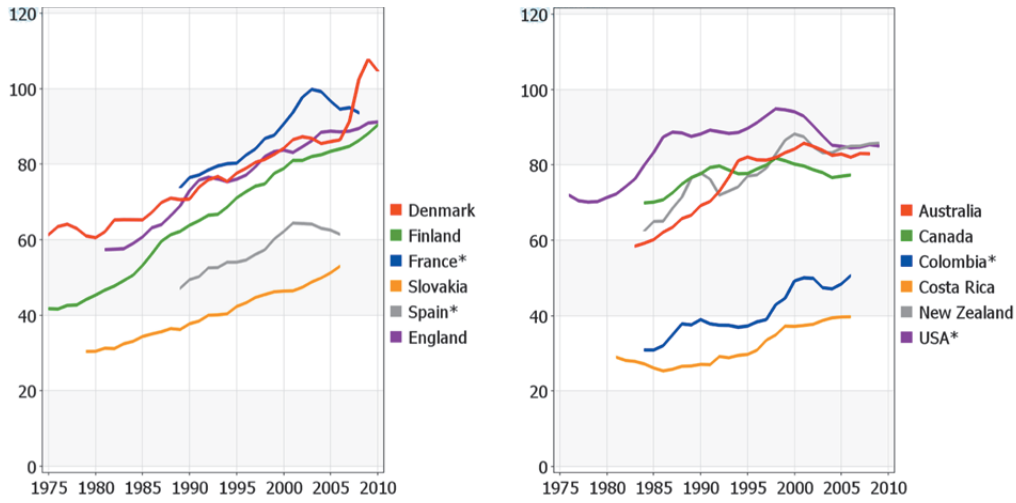

Figure 1. World-standardized BC incidence rates (per 100 000) and per year, 1975–2010, by country, for breast cancer in women[26][Countries marked with * are using regional samples for their report].

Nordic Countries

BC incidence and mortality statistics can be found from the NORDCAN database, which contains recent statistics of the cancer in the Nordic Countries (http://www-dep.iarc.fr/nordcan.htm), **Figure 2**.[33]

These differences may mirror differences in background factors;[34] *e.g.*, alcohol use[35] or smoking.[36]

In all the Nordic countries, almost 19 000 new BC cases emerge per year (during year 2007-11) and the estimated annual growth during latest 10-year period was 0.9 percent. The proportion of all cancers is 27.3 percent and the risk of getting BC, before the age of 75, is 9.6 percent.

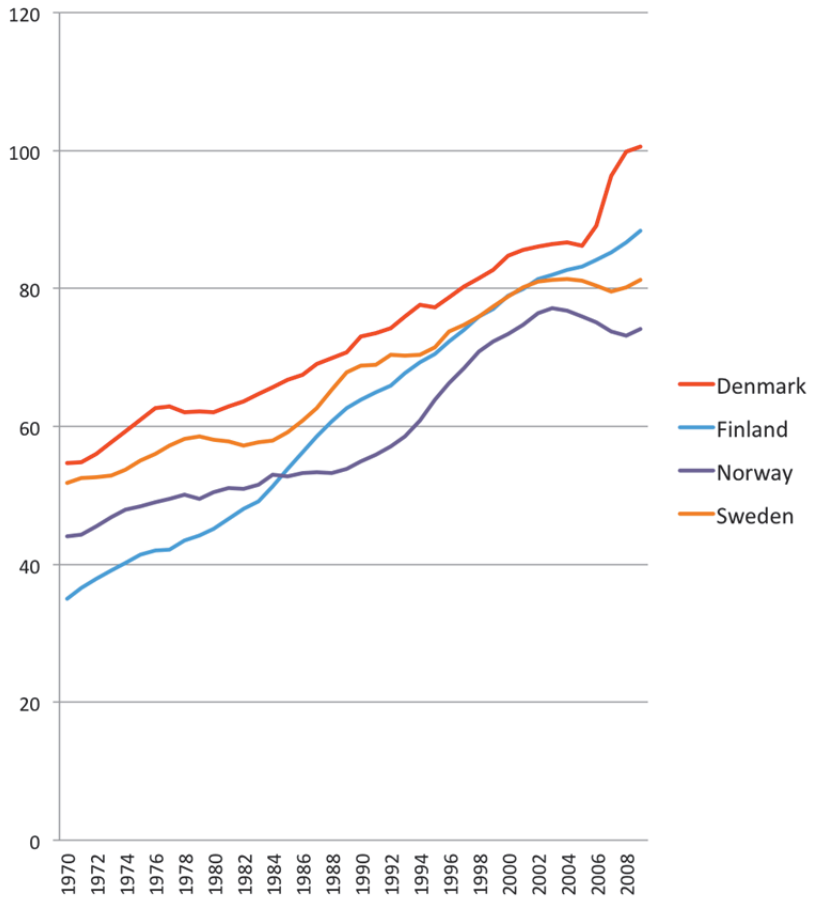

Figure 2. BC incidence rate in four Nordic Countries, during the years 1970-2009 [5 yrs. moving average]. The number of new cases per 100000 women per year standardized with the World Standard Population.[33]

Finland

In Finland, 4292 new invasive BC cases per year emerged (mean; years 2009-2011) and the estimated annual increase during the latest 10-year period was 1.3 percent. The

proportion of all cancers in women has been 31.2 percent and the risk of getting BC before age of 75 is 9.7 percent.[33] **Figure 3** shows the maps of the incidence of BC in Finland in four eight-year time periods (from 1953 to 2008) , both before starting the mammography-screening programme during years 1953 to 60 and 1977 to 1984 and after, from 1989 to 1994 and 2001 to 2008 are shown in **Figure 3**.[33] The most urbanized areas in South, South-Western, and Western Finland have, over time, had higher BC incidence level (particularly in cities such as Helsinki and Turku) compared with the remaining rural residential areas of the country.

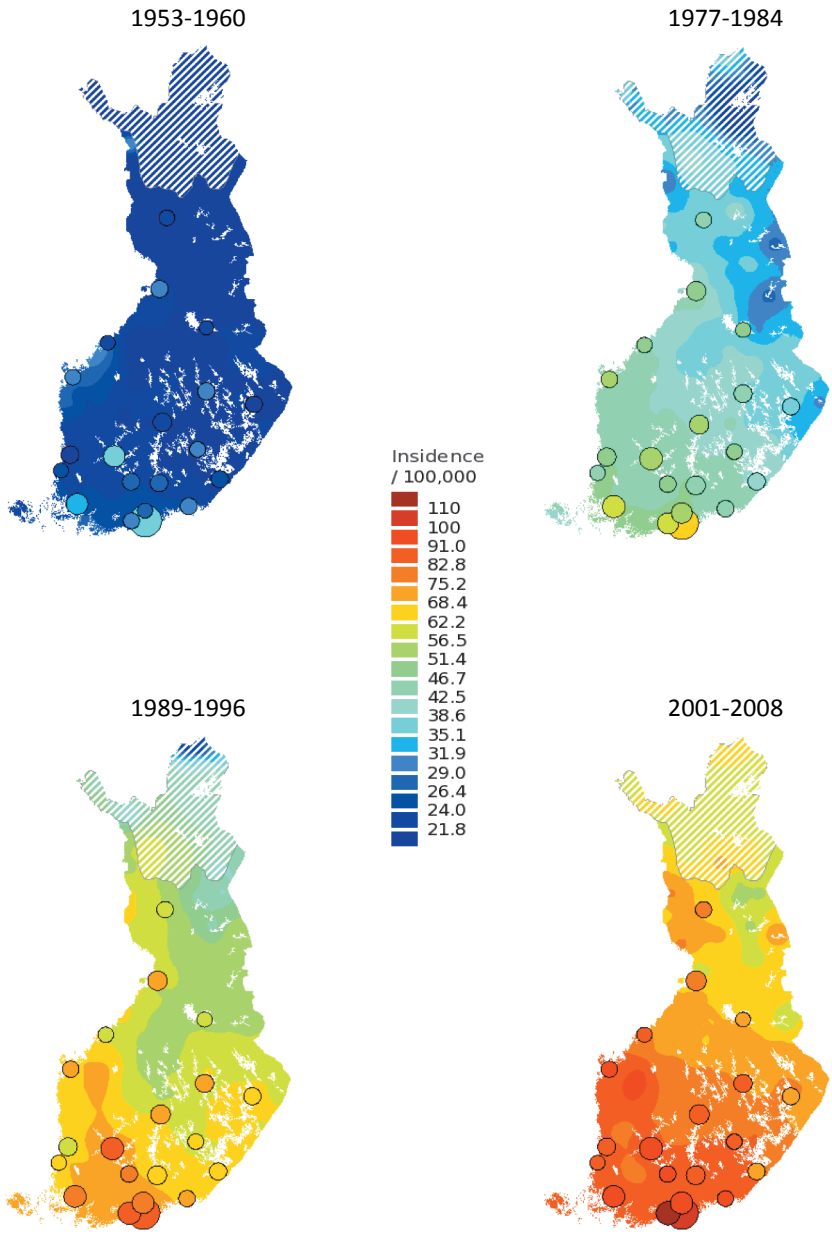

Figure 3. BC incidence in Finland, during four time periods (per 100000 women).[33]

Since the 1960's, in Finland, BC has remained the most prevalent cancer among women. The incidence is very low among women under 30 years of age but increases after 45 years of age. In 2011, 4869 new BC cases were diagnosed[37] of which approximately 1300 cancers were identified by the population-based screening programmes. The annual number of all cancer cases is predicted to increase by 3150 cases per year by 2020 and BC is responsible for one-third of this increase among women. Even if the amount of new BC cases has multiplied during the past decades, BC mortality has decreased due to improved treatments and an effective screening programmes. The success rate has continuously improved and now more than nine women out of ten women are surviving five years after diagnosis.[38]

2.2. Risk factors influencing BC incidence

The risk factors for BC may be categorized into family history, breast density, medical procedures, personal characteristics (race, ethnicity, BMI, physical activity, alcohol consumption, *etc.*) and hormonal factors.

Nelson et al. published a recent (2012) meta-analysis review assessing which factors increase the risk for BC in women aged 40 to 49 years and the magnitude of risk for each factor.[39] The factors were race and ethnicity, body mass index, physical activity, alcohol use, smoking, first and second degree relatives with BC, breast density, prior breast procedure, age at menarche, parity, number of births, age at first birth, breast feeding, oral contraceptive use, menopausal status and use of menopausal hormone replacement therapy (HRT). The results show that extremely dense breasts or first-degree relatives with BC cause a greater than two-fold increase. Prior breast biopsy, second-degree relatives with cancer, or heterogeneously dense breasts cause a 1.5 to 2.0-fold increase. Current oral contraceptive use, null parity, and being 30 years or older at first birth caused 1.0 to 1.5 fold increase, respectively.

2.2.1. Reproductive factors

Reproductive factors do have a significant background risk role in BC and may modify the BC incidence risk (*e.g.,* factors rise such as: early menarche, older age at first full time pregnancy, and high sex hormone levels in postmenopausal women). On the contrary, being younger at the first child delivery and higher parity as well as breast-feeding decrease the risk.[40 41 42 43]

The Collaborative Group collects these results in a report on Hormonal Factors in Breast Cancer (CGHFBC). This collaborative group collected very wide overviews of reproductive factors.[44 45]

These CGHFBC-meta-analyses have discovered that the effects of menarche and menopause on BC risk might not be acting merely by lengthening a women's total number of reproductive years but endogenous ovarian hormones are more active in inducing oestrogen and progesterone receptor-positive disease than for corresponding receptor-negative disease and also more for lobular than for ductal tumours. Thus, it is not surprising that hormonal factors seem to have a wider impact on BC.

2.2.2. Hormonal factors

Survival rates after BC detection were shown to be higher in postmenopausal users of HRT than in nonusers.[46 47] In a study (2002) involving postmenopausal women, long-term use of continuous combined hormone replacement therapy (HRT) was also associated with a higher risk of invasive lobular carcinoma (ILC) compared with sequential combined HRT.[48]

The overall effect of HRT on breast carcinoma mortality, in the general population, remained more or less uncertain for a long time,[49 50] but the Women's Health Initiative (WHI) reports (2002)[51] showed that the risk for increased BC mortality exists with a combined estrogen plus progestin therapy. The risk of developing various types of BC was increased two- to four-fold in HRT users as compared with never or past users in Europe [52] and with the average rate of incidence increasing by 142 percent in Denmark.[53]

Lyytinen et al. (2010) demonstrated that the use of combined estradiol-progestagen therapy (EPT) was associated with an elevated risk for BC, with less than 5 years of use, and the risk was greater for continuous EPT rather than for sequential EPT use. The use of levonorgestrel-releasing intrauterine system alone or as a complement to the estradiol sex-hormone binding globulin was associated with a higher risk for BC than sequential EPT use.[54]

These results stirred however controversy until the report from WHI investigators (2010) showed that estrogen plus progestin was associated with greater BC incidence, and the cancers were more commonly node-positive, BC mortality also appeared to be increased with combined use of estrogen plus progestin.[55 56] Due to these results the U.S. Preventive Services Task Force recommendations were updated (2012) stating that estrogen plus progestin combination increases the risk for BC, whereas estrogen alone may decrease that risk but increase the risk for uterine cancer.[57]

So postmenopausal HRT usage, based on HRT sales statistics, may predict BC incidence. However comparisons between screened and unscreened women may be susceptible to a selection bias if women receiving HRT are more likely to receive a mammography check.[54]

There was a 61 percent decline in sales in Sweden, 51 percent in Norway, 43 percent in Iceland, and 25 percent in Finland after the WHI report was released.[58]

2.2.3. Individual factors

Postmenopausal obesity

Elevated BMI is positively associated with the risk of estrogen and progesterone receptor negative (ER-PR) tumours among postmenopausal women who have never used HRT (Ritte et al., 2012).[59]

For hormone-receptor positive tumours, but not for hormone-receptor negative tumours, an inverse association of tumour risk with BMI, among young women of premenopausal age, exists. The World Cancer Research Fund Report (2010) concluded

that increased body mass protects against premenopausal BC but increased body mass is a cause of postmenopausal BC.[60] Sex hormones may have a role in the etiology of hormone-receptor negative tumours as concluded earlier from Endogenous Hormones Breast Cancer Collaborative Group.[61] Also Kawai et al. reported (2012) that there are inconsistencies in menopausal status, BMI, and survival between premenopausal and postmenopausal women. It is important to stratify patients based on menopausal status in order to adequately assess the relationship between BMI and mortality of BC patients.[62]

Parkin and Boyd assessed an estimated nine percent risk of female BCs in the UK are linked to excess body weight.[63]

Insulin resistance and SHBG

High circulating fasting glucose levels and insulin resistance, often related to obesity, appear to be associated with an increased risk of BC. Sieri et al. (2012) showed a significant increase in the diagnosis of BC after 55 years of age parallel to insulin resistance and decreased plasma sex-hormone binding globulin (SHBG) concentration in a case-cohort study.[64] This is in line with the earlier observation from the Netherlands (Bruning et al., 1992) that central body-fat distribution, promoted by a high dietary intake, and a sedentary lifestyle over many years, is related to elevated plasma triglycerides and free fatty acids, which lower plasma levels of SHBG. The resulting greater availability of estradiol, not bound to its plasma carrier, SHBG, could explain the high BC incidence occurring in Western industrialized countries.[65]

Physical activity

The World Cancer Research Fund Report (2010) concluded that there exists limited evidence in premenopausal women that physical activity protects against premenopausal BC but physical activity may protect against postmenopausal BC.[60] Friedenreich et al. (2010)[66] reported that BC risk could be around 25 percent lower in the most active women compared with the least active women. There also exists a report (Parkin, 2011) that investigated regular physical exercise protecting against the development of BC independently of reducing body weight.[67] Wu et al. showed with a recent meta-analysis, in turn (2013)[68] that BC risk decreases by five percent for every two hours per week increment in recreational activity (moderate and vigorous). Light-intensity activity, on the contrary, may be insufficient to reduce BC risk, as demonstrated in a case-control study by Kobayashi et al. (2013).[69]

Alcohol

The impact of alcohol consumption on BC risk depends on various factors. Concurrent alcohol use, hormonal status, and HRT have a substantial adverse impact on BC risk in the Women's Health Study report (2007) and higher alcohol consumption was associated with a modest increase in BC risk. An increased risk was limited to estrogen receptor and progesterone receptor positive tumours. The association was strongest among HRT users, but this was not significant.[70] An outcome from this prospective study suggests that moderate alcohol consumption with HRT use increases BC risk. The recent results of Horn-Ross et al. (2012) are in line with the results above. Their findings confirmed that concurrent exposure to HRT and alcohol had a substantial

adverse impact on BC risk. However, after HRT cessation, this risk was remarkably reduced.[71] Meta-analysis based results (2012) have shown that light drinkers (one drink per day) have a five percent higher BC risk compared with non-drinkers[72] and BC risk increases by around 10 percent per unit of alcohol per day.[73]

However, a study from Germany gives evidence that that consumption of alcohol before diagnosis is non-linearly associated with increased BC-specific mortality, but may be associated with decreased risk of mortality due to other causes.[74] Further, in a Boston University critique (nr 089)[75] (based on the Horn-Ross et al. results[71]), an expert's forum stated that while this study suggests that women who consume alcohol may have a decrease in risk for BC if they stop taking hormone replacement therapy, current understanding of factors affecting BC risk remains, now, quite inadequate. The complexity of different factors affecting the cancer risk arises from the disentangling connections between obesity, insulin bound effects, endogenous hormones, inflammatory markers, and their molecular interactions.[76]

Smoking

The association between smoking and BC is controversial but a study (Xue et al. 2011) showed that active smoking, especially smoking before the first birth, associates with a modest increase in the risk of BC.[77] Recent results demonstrate that smoking initiation before the first childbirth increases the risk of BC.[78] Braithwaite et al. (2012) found a two-fold higher rate of mortality from BC among current smokers but they found minimal evidence of an association between former smoking and BC mortality.[79]

Family history and genetic factors

Genetic factors from family background with one first-degree relative with BC around doubles the individual woman's risk compared with women with no first-degree relatives as shown (already 1997) by Pharoach et al.[80] and further by CGHFBC (2002).[81]

Women with *BRCA1* or *BRCA2* mutations have a 45 to 65 percent chance of developing BC by the age of 70.[82] Although these genetic defects cause only a few percent of all BC cases, they explain around 15 to 20 percent of the cases with a first-degree family history.[83] Recent studies are showing that three more high penetrance genes (*TP53, PALB2* and *PTEN*) and many moderate penetrance genes exist[84] and recent meta-analysis has identified 41 loci and suggest that over 1000 loci may be involved in BS disease susceptibility.[85]

Intensive research, for new susceptibility genes, is ongoing. This kind of research offers elements for new diagnostic and therapeutic approaches.[86]

2.2.4. Environmental factors

Epidemiological studies indicate that the involvement of environmental factors affect in the etiology of BC, but do not provide explanations about the pathophysiological mechanisms underpinning this disease.[87] Correlations between breast milk and PAH-compounds exist.[88] [89] [90] [91] Mussalo-Rauhamaa et al. (1990) did not find significant differences in BC occurrence with dietary intake of PAH compounds but the level of

beta-hexachlorocyclohexane (beta-HCH; an organochlorine compound) remained a significant risk factor of BC, due to the high residual levels in breast adipose tissue.[92] Associations with BC risk due to polychlorinated biphenyls (PCB; organochlorine) measured in breast adipose tissue[93] are evident and exposure to dioxin-like PCBs increases BC risk, but these results may be explained by differences in metabolic pathways involved in the biotransformation of both mono-ortho PCBs and oestrogens.[94] Raaschou-Nielsen et al. conducted a nested case-control study of 409 postmenopausal women who developed BC and an equal amount of selected controls. They reported (2005) that the results do not support the hypothesis that higher PCB body levels increase the risk of BC in postmenopausal women, whereas the interpretation of the inverse association for estrogen receptor-negative BC is currently unclear.[95] However, PCB levels, measured at the time of diagnosis, do not fully represent early-life exposures.[96] Nevertheless, it is interesting that, in the Canadian context, the urban-rural gradients of PAH-compounds and PCBs were high.

Environmental BC risk factors are unclear. However, these factors may give women, who live in urban areas, a greater BC incidence and mortality than the rural women. These differences in BC incidence between urban and rural areas are reported from Canada[97] and they are also seen in the Finnish follow-up maps since 1953 (Pukkala et al. 2010).[98] In conclusion, environmental factors may contribute to the differences in BC incidence, in addition to distinct lifestyles.

2.2.5. Other factors

Other factors contribute to BC-related mortality. Aro et al. found in 2001 that psychosocial factors play a role in BC risk because socially isolated; depressed and anxious women were less likely to comply with health recommendations and did not attend BC screenings.[99]

A nationwide, U.S. study supports the hypothesis that area-level socio-economic position is independently associated with mammography utilization.[100] However, this relationship is unclear. Results from Turku, Finland, showed (2001) that women, who had to pay for a mammography, attended less often than women who were entitled to free screening, irrespective of their socioeconomic status.[101]

After controlling for other factors, unexpected factors, such as the availability of mammography facilities and ethnicity influence the active participation in screening programmes. Mammography use was higher in neighbourhoods with a greater density of mammography facilities[102] and Meersman et al. (2009) also discovered that women with limited English proficiency, in Los Angeles and predominantly latinas were significantly more likely to have had a recent mammography than English-proficient women. Models of projecting individualized invasive BC risk in different women ethnicities have been developed in the U.S. (Gail Model, Breast Cancer Risk Assessment Tool, BCRAT and AABCS Model for Asian and Pacific Islander women).[103]

2.3. Risk factors in Finland

Regarding the impact of risk factors influencing the incidence of BC, Finland has not made any substantial improvements during the last decades compared with other Western European countries. Unfortunately, any total calculation as an equation to explain BC risk factors in Finland cannot be assembled, but examples from Finnish statistics give an understanding about how different factor elements contribute to the continuous increase of BC incidence during these last decades.

The average age of menarche, in Finland, was 12.7 years in 2000, which was two years less than 50 years earlier,[104] whereas menopausal age was 50 years in 1997 and 51 years in 2007.[105] The average age at delivery of the first child delivery was 25 years in 1982 and 28.5 years in 2010, an increase of 3.5 years.[106] However, the total fertility rate was, in the year 2010, 1.38 in Helsinki but 35.5 percent higher in the whole country (1.87).[107] This is one example to explain the urban and rural differences found in the results from this study.

HRT use increased five-fold during the time period of 1976 to 1989, which may have caused BC burden.[108] Salmi and her co-workers showed, already in 2004, that HRT use declined in Finland.[109] However, the use of HRT in Finland increased steadily until 2003. In 2002, approximately 22 percent of all women, older than 45 years were users (in Helsinki 27% and in Turku 25%, respectively), with a peak in usage rates at ages 55 to 56 years. This may be one notable factor when evaluating the incidence of BC during the time period before and after the turn of the century.

The prevalence of being overweight has steadily been increasing among Finnish women. During the year 1978, the percentage of overweight women (BMI $\geq$30 kg/m^2), aged 30 to 59, was 9 percent, but after gradual increases, during the year 2010, it doubled to 18 percent.[110] The proportion of overweight among women aged 55 to 74 years in 2010 was 22.4 percent in Turku and 20.2 percent in the whole country.[111]

The consumption of alcohol was, in Finland, until the end of 1960's, almost exclusively a male habit. Approximately 40 percent of women, aged 15 to 69, in 1968, were absolutists. Gradually, the proportion of alcohol drinking in women has increased. In 2009, approximately 90 percent of women have consumed alcohol during the last 12 months. In 1968, women consumed approximately 10 percent of total alcohol while, in 2009; women consumed a quarter of all alcohol.[112]

The facts above do show that much has been changed in the risk-estimation field, since Irma Soini (1977) published her study report,[12] which showed the risk of BC to be in Finland, at that time, low (40.1/100 000) compared to the other Nordic countries. This case-control study was carried out on 122 cases of BC and 534 controls between the ages of 41 and 60. Nowadays, our knowledge is very much more versatile and identification of risk factors may be useful also in the future for personalized mammography screening planning.

Unfortunately, this TurkuMSP study could not focus on these BC predisposing background factors because systematic Finnish research results or database entries did not exist for that.

2.4. BC mortality

2.4.1. BC mortality level decline

World

Based on the GLOBOCAN 2012 estimates, BC ranks as the fifth cause of death from cancer overall (522 000 deaths) and while it is the most frequent cause of cancer death in women in less developed regions (14.3% of total), it is now the second cause of cancer death in more developed regions (15.4%) after lung cancer.[26] BC mortality reduction is a common trend, which began in the middle of the 1980's in many industrialized countries (**Figure 4**).[26] In many African and Asian countries, including Uganda, South Korea, and India however, BC incidence and mortality rates are rising.[26 113] In the U.S., the turning point appeared to be the year 1990[23] and in the U.K., 1990 (for the age group 35-69) [114] and 1991 (for the age group 70+), respectively.[115]

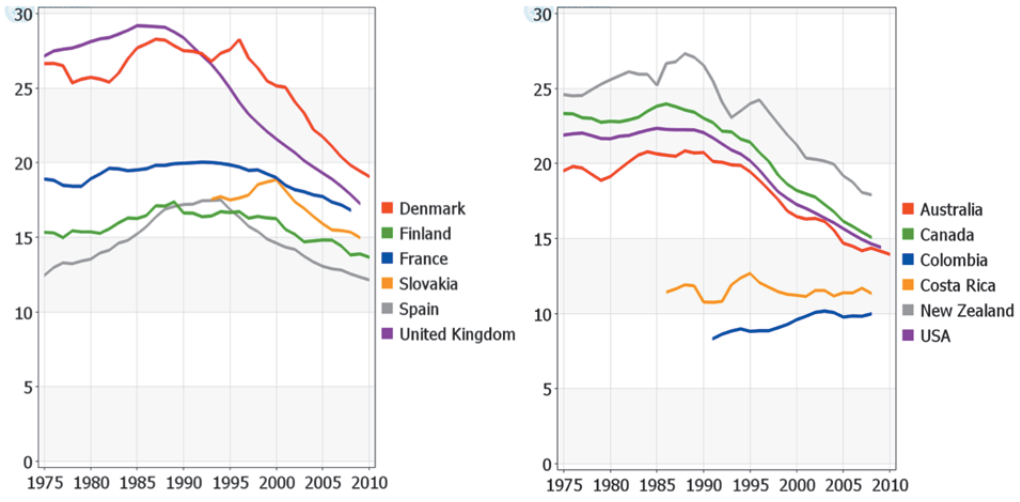

Figure 4. World-standardized BC mortality rates (per 100 000) and per year, 1975–2010, by country, for breast cancer in women.[26]

Nordic Countries

According to the NORDCAN database,[33] the decline of women BC mortality (age standardized by world population age structure) started in Sweden already in 1974, in Finland 1991, in Norway 1995, and in Denmark 1989. The year 1997 showed the greatest decline in BC mortality rate (**Figure 5).**

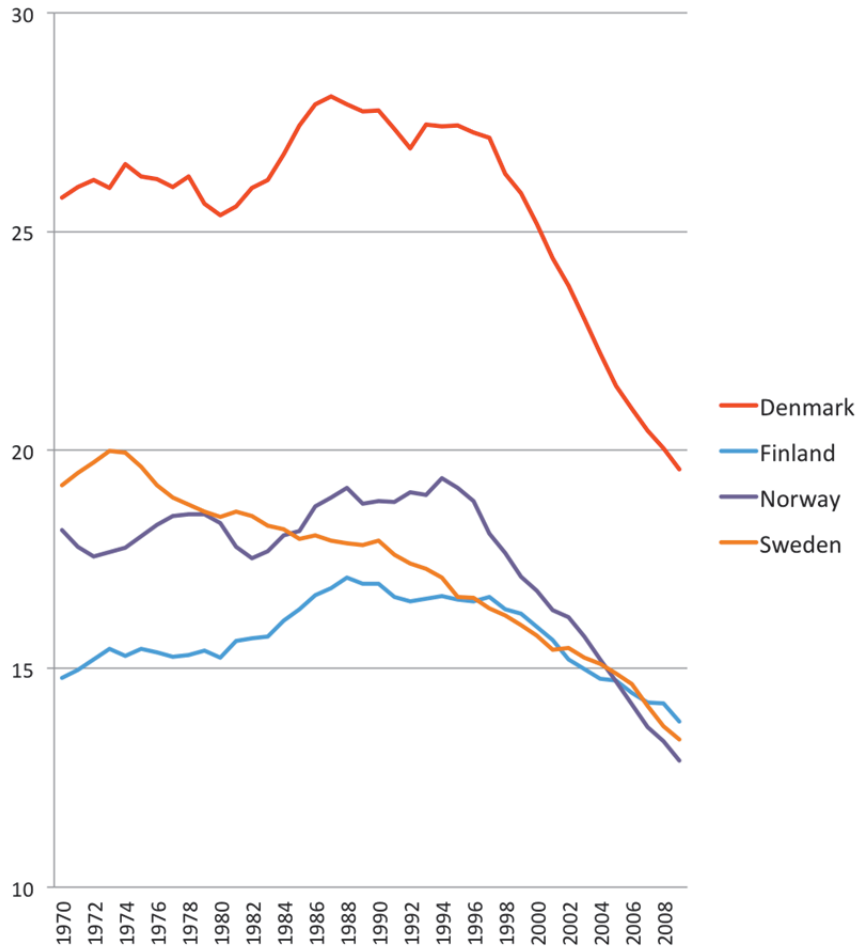

Figure 5. BC mortality rate in four Nordic Countries, during the years 1970-2009 [5 yrs. moving average]. The number of new cases per 100000 women per year standardized with the World Standard Population.[33]

Finland

The most recent BC mortality statistics, in Finland, show positive changes with a declining mortality. The age-standardized BC death rate per 100000 women per year, during the year 2011, was 13 whereas during 2000 to 2004, it was 15.2 and ten years earlier, from 1990 to 1994, it was 16.5.[37]

2.4.2. BC mortality in Turku before screening

In the city of Turku, BC was, before the time of mass-screenings, a target of interest. Joensuu and Toikkanen (1991) reported the age adjusted incidence and mortality from a very long perspective starting already at the year 1953 (**Figure 6**).[116]

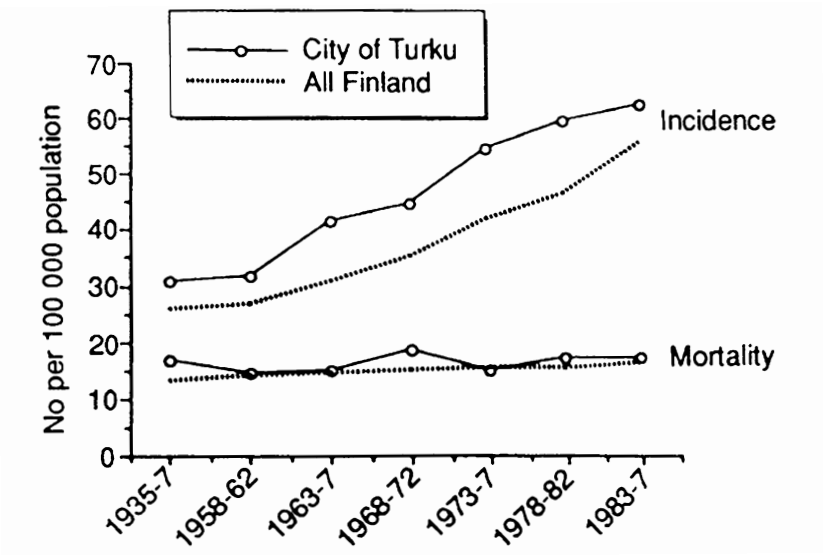

Figure 6. Age adjusted incidence of BC and mortality from BC statistics in Finland. Data supplied by Finnish Cancer Registry (*note: 1935 should be 1953, error is in journal*).[116]

2.4.3. Causes that affect mortality

As stated by Autier et al. (2010), there are four factors which may explain the considerable variations in BC mortality: (1) the mortality levels years previously, (2) the BC incidence level, (3) BC size at detection, and (4) adoption of process favouring early detection and treatment. Sweden is an example of a country that obtained BC mortality reductions, since 1972, and the causes for these reductions were within screening, treatments, and system efficiency.[29] In practice, mass screenings and treatment processes must be organized properly according to high quality standards and assessments to achieve BC mortality reductions.

Risk factors

Avoiding the risk factors discussed above (in Chapter 2.2) should be the most efficient methods to reduce incidence and as a result also mortality, but unfortunately an individual woman cannot affect some of the concrete factors such as dense breasts or hereditary family history. However, *e.g.,* oral contraceptives or HRT use, alcohol drinking and smoking are their own choices. Proper education improves their possibilities to design a life-style, which can prevent BC.

Early detection of BC

As Robert A Smith stated (2011) the benefit of early BC detection is the foundation for programmes around the globe to reduce morbidity and mortality related to BC. Until recently, the emphasis on early BC detection was limited to mammography, but the steady rise in incidence and mortality in low and medium developed countries, where mammography may be unaffordable, has led to a renewal in emphasizing the incremental value of downsizing palpable tumours through physical exams.[117] This was the case also in Finland during the years 1972 to 1986 when palpation-based screenings were conducted either by self-identification or by educated nurses.[118] This

kind of screening programmes were reported [119] to yield a lower than expected BC mortality rate ratio (0.75) in Finland, but the authors state that selection bias, inherent in any observational study of screening, may be an alternative explanation to these findings. In Turku the palpation-based screenings were conducted by educated nurses and supplemented with breast self-examination (BSE) teaching.

In Shanghai 5-year randomized BSE trial (with one demonstration at start and two reinforcement sessions during the subsequent 4 years including video shows) could not reduce mortality rate of BC, but more and smaller benign lumps could be detected[120] and in Canada Miller and Baines stated (2011) that in technically advanced countries where adequate treatment is given, no screening modality is likely to be sufficiently beneficial to outweigh the harms of screening, especially false positives and overdiagnosis.[121]

Robert Egan was the first American radiologist who published an evaluation study with an adequate follow-up using 1000 mammography examinations in Texas (1960).[122] Egan hypothesized that mammography screening enhances population-based early detection of BC and reduces BC mortality. This notion supports this thesis's hypothesis.

Mammography's gradual transformation from a test for women with suspected BC to a test for healthy women to reduce mortality was culminated in the Breast Cancer Detection Demonstration Project (BCDDP) between 1973 and 1980 with 280 000 voluntary participating women reporting follow-up results from this project, with success.[123] [124] These results were the basis of confirming the hypothesis above. This hypothesis is continuously supported also by recent results (2012) by Hendrick and Helvie. They calculated, using CISNET modelling results, that eighty-four women need to be screened (NNS) annually between 40 and 84 years to save one life from BC and 5.3 need to be screened annually to gain one life-year from BC (NNS/LYG).[125]

Results of randomized controlled trials show a reduction in BC mortality, in association with mammography screening, led to the launching of population-based service screening programmes in several countries in the late 1980´s and early 1990´s. BC is a long-term disease, and several years of follow-up are needed to determine the effectiveness of BC mammography screening. However, currently available reports suggest a reduction in BC mortality in conjunction with service mammography screening.[126] [127] [128] [129] [130] In published reports, the reduction of mortality is assessed by comparing mortality rates before and after the initialization of screening,[117] by comparing invited with never-invited women during the screening period,[131] or even comparing incidence and mortality changes among women exposed to mammography screening gradually over the years. Otto et al. (2012) reported the findings of the largest Dutch case–control study (with cases matched to five controls) of mammography screening data (1995-2003) and showed that the OR of BC mortality for screened women compared with never screened, in all ages (49–75 years), was 0.51 (95% CI; 0.40–0.66). They concluded that these results give overwhelming support for the beneficial effect of screening in reducing the risk of BC mortality among women invited and participated in national mammography screening programme.[132]

2.5. Survival

The International Cancer Benchmarking Partnership indicates that BC survival rates, which can be reached countrywide with existing means, have reached their zenith. For example, in Sweden, survival is greater than 95 percent at one year and near 90 percent after five years.[28]

The first worldwide study (CONCORD) did show wide international differences in age-standardized survival. Population-based data were collected at diagnosis at baseline and characteristics like diagnostic procedures, treatment, and follow-up for about 2000 women diagnosed with BC aged 15 to 99 years during 1996 to 1998 in seven U.S. states and 12 European countries. Age-standardization, net survival, and the excess hazard of death up to five years after diagnosis were estimated by jurisdiction (registry, country, European region), age and stage with flexible parametric models. BCs were generally less severe in the U.S. than in Europe. The stage also varied less between the U.S. states than between European districts. Early, node-negative tumours were more frequent in the U.S. (39%) than in Europe (32%), while locally advanced tumours were twice as frequent in Europe (8%), and metastatic tumours of similar frequency (5-6%). Net survival in Northern, Western and Southern Europe (82-85%) was similar to that in the U.S. (84%), but lower in Eastern Europe (72%). For the first three years after diagnosis, the mean excess hazard was higher in Eastern Europe than elsewhere. The difference was most marked for women aged 70 to 99 years, and mainly confined to women with locally advanced or metastatic tumours. Differences in BC survival between Europe and the U.S., in the late 1990s, were mainly explained by lower survival in Eastern Europe, where low healthcare expenditure may have constrained the quality of treatment.[133]

In the city of Turku, a significant improvement in survival (from 44% to 69% after ten years) was observed when patients were diagnosed from years 1980 to 1984 if compared with those diagnosed during years 1953 and 65.[116]

2.6. Recurrence

Philpotts et al. reported (1996) that after conservative treatment of BC, the majority of recurrent tumours appear to be mammographically similar to primary tumours and it is prudent to review preoperative mammograms during follow-up of patients after lumpectomy and radiation therapy.[134] Since then the characteristics of recurrent cases versus primary cases have received attention. Chang et al. showed (2003) that biologic features of primary tumours were correlated independently with outcome after first recurrence in patients with metastatic breast carcinoma and may be used as indicators of prognosis in the metastatic setting.[135]

Absence of BC metastases in the axillary lymph nodes, low histologic grade and small tumour size are known significant prognostic variables of both overall and recurrence-free survival for patients with breast carcinoma[136 137], but also cancer p53 and Ki-67 expression results are associated with the risk of recurrence (Song et al., 2012).[138]

Therefore they recommend that patients with poor prognostic variables need to be properly treated and should be closely followed up.

Günhan-Bilgen and Oktay (2007) found that the majority of recurrent tumours appear to be mammographically similar to primary tumours. Therefore, it is important to review preoperative mammograms during follow-up of these patients. Although the study population is small, the investigators could conclude that a mass with spiculated contour is associated with a lower risk for local recurrence.[139]

However, Roselli Del Turco et al. demonstrated (already at 1994) that intensive follow-up allows earlier detection of distant metastases in recurrent cases, but earlier diagnosis of metastatic disease appears to be the only effect of intensive follow-up with no impact on prognosis is evident after five years of follow-up.[140]

2.7. Mammography as a mass screening method

2.7.1. Principles of screening

The mammography method was developed simultaneously in a few countries to be the method of choice for early detection of BC. The aim of a population-based screening programme is the reduction of the mortality caused by BC. Tumours should be found early, detectable preferably at the preclinical phase, when the curative treatment is still possible. During the early phases, BC is usually symptomless and not palpable.[38]

BC screening is performed by mammography at special BC screening units. Mammography is an X-ray examination with X-rays taken on both breasts at different angles. If the first mammogram is unclear or any abnormality is detected, the woman will be called for further assessment. This may include an additional mammogram, ultrasonography and a core needle biopsy, and sometimes MRI-scan, galactography or pneumo-cystography. If the possibility of cancer cannot be excluded, a biopsy, with open surgery, is performed.

The screening programme detects an early phase cancer if it is detectable by mammography, but not yet palpable. If the cancer has a long preclinical phase, it is growing slowly and its prognosis may be favourable. It is likely that the impact of screening on the reduction of mortality is due to early detection of these not very fast growing cancers. Early detection designates that the primary tumour should be, in optimal detection, 2-cm or less in its greatest dimension (=T1), have no palpable homolateral axillary lymph nodes (=N0), and have no evidence of distant metastases (=M0). The stage and TNM-classification were formulated during late fifties and have been revised several times during the past decades.[141] In addition to stage, all other important prognostic variables need to be taken into account.[142] First and foremost, a mass-screening programme can only reach its full potential and effectiveness through high participation willingness from women.

2.7.2. Practices in Finland

The population-based screening programme for BC in Finland was introduced in 1987. It is currently based on the Government Decree on Screenings (1339/2006). According to this decree, municipalities organize a free of charge screening for women, aged between 50 and 69 years. At its inception (1987-2006), the programme covered only women aged 50 to 59. The decree was renewed so that municipalities could gradually add age cohorts from age group 60 to 69 (2007-April 2011). After the beginning of May 2011, the programme started to cover all cohorts from age 50 to 69 (new Decree on Screenings 339/2011).

Women are invited to screening biannually and they receive their first invitation at the age of 50. The written invitation letter is posted personally as are the results of the mammography screening. Over 1 800 000 women have been invited to the screening since the year 2000 and this covers 68.4 percent of the current target population in Finland.

The Mass Screening Registry provides information about the name and address of women to be invited for the screening centres several times per year. Information is gathered from the Finnish Cancer Registry and it is based on the information the screening units have received from the municipalities about the age groups (age-cohorts) that are included in the screening programme each calendar year.[37]

During the 2000s, the coverage of the target population has improved by about 10 percent but the attendance rate has dropped from 87 percent to 84 percent.[38]

2.7.3. Controlled randomized studies

Randomized studies allow a straightforward interpretation of cause and effect, while observational studies are just that - observational. Randomized studies are conducted based on the randomization procedure that implements exchangeability between compared groups.[143] The Health Insurance Plan (HIP) of Greater New York, during the years 1963 to 1966, demonstrated that a reduction of BC mortality was achieved through BC mammography screening,[3] subsequent randomized controlled trials in the 1970s and 1980s (plus the UK Age trial, started 1991) further investigated the effect into BC mortality among women invited to participate in the mammography screening. Interpretation of these trial results is incoherent and divisive. Because of this situation, an Independent UK Panel of Breast Cancer Screening was established. Their report attempts to clarify the results of these randomized studies.[144]

The UK Panel interpreted the relative risk of BC mortality in women who received screening invitations. Randomized trials collected from Cochrane Review[145] and other publications[146] [147] were used in their analysis. Altogether eight trial reports were included. Malmö II was excluded because the follow-up data after 13 years was not available, and the Swedish Two County (Kopparberg and Östergötland) and Canada I and II trials were split into their component parts. The Edinburgh trial was also excluded because of imbalances existed in randomized groups. The overall result of the

Panel was that the relative risk of BC mortality for women invited to screening compared with controls was 0.80 (95% CI: 0.73–0.89), which favoured screening.

Since research indicated a strong evidence of benefit from modern mammography screening, Smith (2014) stated that it is time to move beyond the randomized controlled trial estimates of benefit and to consider policy decisions. These policy decisions should rely on calculations of the benefits and harms extrapolated from the results of current screening programmes.[148] This opinion is in line with other recent statements.[149] [150] However, the seemingly endless considerable debate continues as to which randomized controlled trials are valid and which ones are not. A recent example is an article published by Canadian researchers[151] with numerous conflicting opinions.

2.7.4. Population-based service screenings

Twenty-two countries implemented BC screening programmes after the positive results obtained from the randomized controlled trials. Since the late 1980s and early 1990s, these programmes have been in use for women aged 40 to 74.[152]

In Sweden, population-based service screening began in some counties in 1986. A 20 percent lower mortality rate from BC was evident among women who attended screening in these counties than in women who lived in counties where the screening was initiated later (Jonsson et al 2001).[153] The mean follow-up time in this study was 8.4 years.

In Finland, a nationwide population-based BC screening for women aged 50 to 59 was introduced gradually between 1987 and 1991. Randomized trials were not conducted in Finland, but mortality from BC was in line with the results obtained for other countries: 24 percent lower among the women offered screening, and 33 percent lower among those who were actually screened than in non-screened women (Hakama et al, 1997).[16] According to research conducted in the Mass Screening Registry later on, during the beginning of 2000s, the screening was still of high quality and BC mortality decreased about 20 percent among women who were invited and 28 percent among those who attended in screening.[21]

Mortality was expected to fall as a result of screening after 10 years also in the Netherlands and the United Kingdom, being 29 percent and 24 percent, respectively.[154]

2.7.5. Invitation intervals

In the Canadian guidelines review,[155] screening intervals of women aged 50 to 74 years were collected from seven studies [147] [156] [157] [158] [159] [160] [161] ranging from 12 to 33 months (median was 22 months). The Canadian reviewers concluded that the optimal frequency of screening could not be determined because the only randomized trial comparing different screening intervals (established by the UK Coordinating Committee on Cancer Research; UKCCCR-group) was not adequately powered to detect a small benefit of more frequent screening. The UKCCCR-group concluded that shortening the screening interval in this age group (50-74) is predicted to have a relatively small effect on BC mortality. Improvements in the screening programme

could be better obtained in areas other than the screening interval, such as improving the screening quality.[162]

Already in 1987, Tabár and his co-workers investigated the relationship between the screening interval and BC detection.[163] They showed that more interval cancers were found among women aged 40 to 49 than in women over 50 years of age. However, because of varying methodology and inconclusive results from previous studies, there are no consistent guidelines for mammography screening in women who are aged 40 to 49 years and hence, there is no consensus on the screening interval for this age group. Finland started a biannual nationwide BC screening programme for women aged 50 to 59 in 1987 and extended the screening to women, aged 60 to 69, in 2007. However, the city of Turku, in Southwest Finland, with a population of about 170000, advanced the screening further already in 1987 by also inviting women aged 40 to 49 years annually (even year-of-birth cohorts) or triennially (odd birth-year cohorts) (**Article I**).

2.7.6. Age specific results and limits

Even though BC screening in women aged over 50 years is a well-accepted practice in many countries and controlled randomized trials show a mortality reduction in BC of about 25 percent (IARC Handbook of Cancer Prevention, 2002) in women aged 50 to 69 years, there is still debate concerning screening this age group.[144] In Finland, the results of the mammography screening programme were in line with those of other countries with an effect of approximately 24 to 28 percent on BC mortality (Hakama et al. 1997[16]; Sarkeala et al. 2008).[20]

In women, younger than 50 years, the benefit of mammography screening is considered to be less apparent. Even though a meta-analysis of previous randomized trials showed a 15 to 18 percent BC mortality reduction in women invited at age 40 to 49 years at entry by Hendrick et al. (1997)[164] and Smith et al. (2004)[165], this finding could be due in part to the screening of these women after the age of 50 years. Further, an article from the Netherlands showed evidence of the effectiveness of biennial mammography screening in women aged 40 to 49,[166] but the value of screening in women younger than 50 years of age remained unclear. The Age Trial in England, Wales, and Scotland, with a total of 160 921 women under 50 years of age, randomly assigned in the ratio of 1:2 to an intervention group of annual mammography or to a control group, showed a 24 percent reduction in mortality (RR=0.76; 95% CI: 0.51–1.01) in women actually screened with a mean follow-up of 10.7 years, which was not significant (Moss et al, 2006). [161] An analysis of the WHO database of BC mortality trends in 30 European countries showed a 19 percent reduction in age-adjusted BC mortality in Europe from 1989 to 2006 (Autier et al. 2010). The greatest mortality reduction, 37 percent, was observed among women under 50 years of age, and it occurred also in countries where screening at that age is uncommon. The main contributors to this observed BC mortality reduction are considered to be treatment, screening, and system efficiency.[29]In various studies, the benefit of screening in women aged 70 to 74 is indirectly shown. The most outstanding result was published from Netherlands - the ORs (95% CIs) between screened and never screened women aged 70 to 75 years, RR=0.16 (0.09-0.29).[132]

At present, there are still no consistent global guidelines for mammography screening of women aged 40 to 49 or 70 to 74.

2.7.7. Harms and benefits

The U.S. National Cancer Institute (NCI) has declared in their fact sheets concerning the potential harms of mammography screening: false-negative results, false-positive results, overdiagnosis, overtreatment, and radiation exposure.[167]

False-positive results

In the U.S. Elmore et al. reported (1998) that the rate of false positive BC screening tests was 6.5 percent in the mammography group and 3.7 percent in the clinical breast examination group. This leads to the conclusions that over 10 years, one third of women screened had an abnormal test result that required additional evaluation, even though no breast cancer was present. Techniques are needed to decrease false positive results while maintaining high sensitivity. Physicians should educate women about the risk of a false positive result from a screening test for breast cancer. [168] Fletcher assessed further (1999) [169] that fewer than 10 percent of mammogram readings should be false positive[170], but the false-positive rates (and the numbers of unnecessary biopsies) in mammography units vary substantially across the U.S.[171]

In Europe the estimates of false-positive results are reported (2014) to be at the range from 8 percent to 21 percent, with a pooled estimate of 17 percent without invasive assessment and 3 percent with invasive assessment.[161] As stated in a recent report (Tosteson et al., 2014)[149] there is a growing literature on how women view false-positive screening mammograms and what are the harms in societal cost-effectiveness analyses. However, they conclude that the anxiety associated with false-positive findings increases in short-term but not long-term, and there was no measurable total health utility decrement. False-positive mammograms increased women's intention to undergo future breast cancer screening and did not increase their stated willingness to travel to avoid a false-positive result.

Risk of radiation carcinogenesis

Another harm that has received relatively much attention is the potential risk of radiation carcinogenesis. During the early years mammography screening equipment were relatively undeveloped and all the devices in use were recording on film. Since then the radiation doses per screening have continuously and considerably reduced, and digital technology has been introduced. Mettler et al. calculated (1996)[172] that for a woman beginning annual mammography screening at the age of 50 and continuing until the age of 75, the benefit of screening exceeds the radiation risk by a factor of almost 100. Even for a woman who begins annual screening at the age of 35 and continues until the age of 75, the benefit of reduced mortality is projected to exceed the radiation risk by factor of more than 25. However Moss et al. claimed (1997) that these estimations could be potentially misleading due to the calculation methods; in particular the conclusions regarding screening at younger ages might be overly optimistic.[173]

Due to the technical development the situation has changed further. The recent Norwegian results (2013)[174] show that the risk of radiation-induced BC and BC death due to mammography screening is minimal. The total lifetime risk of radiation-induced BCs per 100 000 women was 10, if the women were followed from the ages of 50 to 85 years. After receiving a cumulative dose of 2.5 mGy, and the number of radiation-induced BC death was 1. The assumed number of lives saved was approximately 350.

Influence of age on the harm-benefit ratio

As shown in the above examples, some risk estimations apply only for women aged 50 years of age or older (postmenopausal women). This concerns also the implementation of digital mammography.[175] For every 1000 women screened biennially from age 50 to 74 years, switching to digital from film yielded a median within-model improvement of 2 life-years, 0.27 additional deaths averted, 220 additional false-positive results, and $ 0.35 million more in costs. Extending biennial digital screening to women aged 40 to 49 years would increase the annual screening costs to $ 5.26 million per 1000 women, in part because of higher numbers of screens and false positives, and were not efficient or cost-effective. In another study[176] women aged 40 to 49 years with an estimated 2-fold increased risk of BC had similar harm-benefit ratios with biennial screening mammography as average-risk women aged 50 to 74 years.

The difference between the results of the premenopausal and postmenopausal women has impacted also on screening recommendations: the NCI recommends women aged 40 and above to have screening mammography every one to two years. In addition, the quality of life parameters should be assessed. Also, the renewed American Cancer Society Guidelines recommend beginning annual mammography screening at the age of 40 years.[177] Since 2009, the U.S. Preventive Services Task Force (USPSTF) suggests a more restrictive definition for women younger than 50: The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. According to this definition, more generally, women should start regular biennial screening until the age of 50.[178]

Overdiagnosis

When interpreting results, one should consider factors that may affect BC mortality and survival, such as age and changes in treatment modalities over the years.[132] A controversial issue is the overdiagnosis of BC. This is defined as the diagnosis of BC that will not affect life expectancy or quality of life.[179] Also, an overdiagnosis bias may exist if screen-detected lesions being labelled as a cancer would not have progressed to a clinical cancer, in other words, the possibility of finding an increasing number of cancers that would not harm the subjects should also be considered when interpreting results.[125]

Gøtzsche and his co-workers have drawn attention to their critical opinions regarding mammography screening activities for over a ten years span. In their recent article, they conclude that screening leads to serious harms in healthy women through overdiagnosis with subsequent overtreatment and false-positive mammograms and that the observed decline in BC mortality in many countries seems to be caused by

improved adjuvant therapy and BC awareness, not screening. They also believe that it is more important to reduce the incidence of cancer than to detect it "early." And they argue that, by avoiding getting screening, the risk of becoming a BC patient is reduced by one-third. They suggest that policy-makers should urgently reassess the rationale for breast screening.[180] Welch and Frankel (2011) concluded that most women with screen-detected BC have not had their life saved by screening. They are instead either diagnosed early (with no effect on their mortality) or overdiagnosed.[181]

Canadian guidelines report that outcomes of screening for BC, such as tumour detection and mortality, must be put into context of the harms and costs of false-positive results, overdiagnosis, and overtreatment. Consideration of benefits, harms, and costs is complicated by variations in risk factors and in the types and stages of cancer. Any positive result from screening has emotional costs such as anxiety and worry for patients and their families, and financial costs to both the patient and the health care system as a result of additional and potentially unnecessary diagnostic tests. According to their report, no primary studies looked at the risk among women who are aged 40 to 49 years but studies involving older women have estimated, according these reports that the frequency of overdiagnosis ranges from 30 percent to 52 percent.[155]

The debate of overdiagnosis was also a fundamental part of the work of Independent UK Panel. In their report, overdiagnosis is nominated to be the major harm. The Panel could not get a unanimous answer to the overdiagnosis question and they focused on two estimates, which included both invasive and intraductal cancers, and the estimates varied with a range of zero to 36 percent.[144]

Additional aspects

Controversy exists regarding the value of BC screening in terms of the modest benefit of screening and the numerous negative outcomes.[182] [183] The debate about the relevancy of screening is the focus of negative discussions, as shown in the extraordinarily high amount of attention paid to recent papers claiming minor effects of screening, which may ignore five decades of research.[184] [185] Mandelblatt et al. described (2009) the benefits of mammography screening programmes.[186] They conclude that biennial screening achieves most of the benefit of annual screening with less harm.

Raftery and Chorozoglou (2011) combine the life years saved with the quality of life losses in quality adjusted life years (QALYs).[187] Their study combined the benefits and harms into a single measure. The net QALYs from screening were negative for the early years after the introduction of screening, after which, net positive QALYs accumulated but by much less than predicted by Forrest report (the initial report for the U.K. BC screening programme).[188] This has led to the proposed review of BC screening programmes in the United Kingdom.[189] Further clarification and reflection are required also in Australia to the question of the mortality benefits of screening mammography compared with the harms of overdiagnosis and unnecessary treatment.[190]

This controversy will not be resolved in the near future. This is demonstrated by the recently released disputing reports[191] [192] [193] [194] [195]. Different views on the methodology

used in screening research will maintain this discourse [158 159 196] and currently it is not possible for either the woman or her doctor to know whether a screen detected cancer is an "overdiagnosed" case or not. In particular DCIS does not inevitably equate to overdiagnosis.[144]

Discussion and consideration of the optimal mammography-screening method and how to organize the counselling women at high risk for BC is still on the agenda. In addition to providing information about her risk and assessing each woman's perception of risk, the emotional issues must also be addressed.[197]

3. THE AIM OF THIS STUDY

In the 1980's, there was a worldwide consensus of the beneficial effect of mammography BC screening of women aged 50 to 59 and Finland started a nationwide BC mammography screening for women aged 50 to 59 in 1987. However, the city of Turku decided to screen also younger women aged 40 to 49 and elderly women aged 60 to 74. This decision made it possible to evaluate the effect of BC screening in women outside of range of the organized national mammography screening programme.

The overall objective of this study was to evaluate how different mammography screening invitation programmes impact BC incidence and mortality in different age groups and to investigate which kind of factors (in these programmes) were significant by using BC mortality difference and its surrogate results as impact measures. The research span was started before the screening (pre-screening era) and covered the actual screening during the years 1987 to 2009 (screening era).

The specific aims of the study were to investigate (articles in parenthesis):

1. The prognostic variables that affected the survival of women after 10 years from the beginning the screening **(Article I)**;
2. The impact of the screening participation on the recurrence of BC **(Article II)**;
3. The impact of screening on the reduction of BC mortality among elderly women in Turku, Helsinki, and Tampere **(Article III)**;
4. The effects of screening on the BC incidence and mortality in women, aged 40-49, who were screened annually or triennially **(Article IV)**;
5. The differences in the incidence-based BC mortality among women by age group (40-49, 50-59, 60-74, and 75-84) during long-term follow-up in three residential areas (Turku, Helsinki, and the rest of Finland) as a result of the Finnish mammography screening programme by invitation **(Article V)**.

4. MATERIAL AND METHODS

4.1. Mammography screening programme in the city of Turku (TurkuMSP)

In Finland, public healthcare services offer screening mammography and treatment for breast diseases. Nationwide population-based breast carcinoma screening was introduced in Finland in 1987, and this national programme covers women aged 50–59 years. Nationwide, women, who are younger than 50 and older than 59, were not systematically covered in this free of charge screening programme until the year 2007 (see Chapter 2.7.2 and **Article V**).

In the city of Turku, in Southwest Finland, population-based mammography screenings were mainly free of charge for all women, aged 40 to 74 years since 1987 that makes BC screening in Turku unique compared with other municipalities from the policy point of view.

Two-view, double-read mammograms were taken at one screening center in Turku, where altogether eight radiologists were involved in the diagnostic process throughout the study period. The screening procedures are described in detail elsewhere.[198] The independent, double reading of results was performed at the Cancer Society of Southwest Finland Breast Examination Centre in cooperation with the city of Turku. No other mammography screening took place concomitantly with this public screening programme.

However, mammography examinations for clinical purposes were available both at public and private health care for all women with symptoms or signs of breast disease after referral by a physician.

The data on BC cases and deaths were further validated (see details in the articles). For women included in the TurkuMSP, all primary invasive BCs diagnosed during the study period were crosschecked case-by-case between the Finnish Cancer Registry (FCR) and the Turku BC database. All discrepant cases were resolved by means of reviewing patient medical record information.

4.2. Determinants of the study

The key determinants of the five original publications that comprise this thesis are shown in **Table 1.**

The five publications (**Articles I to V**) of this study were generated during a long time span: the first was published in 2003 and the last was submitted in 2014. The first article of this thesis was published 16 years after the start of TurkuMSP – and the last article 27 years later. This is related to the interest that some of BCs will recur many years after its diagnosis.

The study supervision started during the first years by an expert advisory group (with participation mainly from the city of Turku and the Turku University Hospital authorities). To secure a long-term process and progress, a permanent scientific

steering committee was established. This committee prepared the research plans, obtained the authorization of an ethics committee (Ethics Committee of the Hospital District of Southwest Finland) and of the Ministry of Social Affairs and Health. The scientific steering committee has also continuously collaborated with National Institute for Health and Welfare and with the Cancer Organizations.

Table 1. The key determinants for the original articles

	ARTICLE				
	I	**II**	**III**	**IV**	**V**
STUDY VARIABLES					
Age Groups	40-49, 50-59, 60-74	40-49, 50-59, 60-69, 70-74	55-59, 60-64, 65-69	40-49	40-49, 50-59, 60-74, 75-84
BC Incidence			X	X	X
BC Recurrence		X			
Mortality			X	X	X
Survival	X	X			
Treatment		X			
Prognostic indicators	X	X			
Comparison	Screened *vs.* unscreened	Screened *vs.* unscreened	Turku *vs.* Helsinki or Tampere	Invitation interval	Turku *vs.* Helsinki or RoF

4.3. Subjects and methods

As mentioned above, the screening invitation programme in city of Turku was an exception compared to other municipalities. The screening programme in Turku was extended to cover the age groups of 40 to 74 years. Women of age 50 to 74 years were invited every second year to the screening. Only in Turku, women aged 40 to 49 years, were invited to screening starting at year 1987 and ending year 2009. The invitation programme in Turku, for women aged 40-49 followed modified invitation intervals compared to a general invitation programme: women born during even years were invited annually and those born during odd years, triennially.

In Turku, 176 908 screening examinations were performed in 36 000 women aged 40-74 during years 1987-1997. The average participation rate was about 85 percent, with small non-systematic variations by residence, calendar time and age group.

The different screening programmes by residence and age groups elsewhere in Finland as also the non-screening calendar period from year 1976-1987 served a fertile opportunity to study the possible screening effects from different points of view.

The focus in **Articles I** and **II** was the comparison between screened and non-screened cases (BC found through mammography screening *vs.* clinically found BC among

women invited but not attending the screening). In **Article IV**, the objective was to study the importance of the screening invitation interval, *i.e.*, screening annually or triennially. To achieve an overall view, in **Article III** the research approach changed to an inter-city comparison (Turku *vs.* Helsinki or Tampere) and in **Article V** to all Finland comparison (Turku *vs.* Helsinki or the Rest of Finland (RoF).

Table 2 presents the number of incident BCs and deaths, and lengths of follow-ups in the **Articles I-V.**

Table 2. Quantitative features of the study.

	BC CASES	BC DEATHS	DATA SOURCE SIZE	DATA COLLEC-TION TIME PERIOD	FOLLOW-UP FOR SURVIVAL OR BC MORTALITY
Article I	913 invasive 84 CIS 2 Paget diseases	121 (total)	Approx. mean women pop. aged 40 to 74 years = 36 000. 176 908 two-view mammography examinations.	1987-1997	1987-1999
Article II	562 invasive 41 CIS	52 (screening), 22 (outside of screening)	Approx. mean women pop. aged 40 to 74 years = 36 000.	1987-1993	1987-2001 10.0 yrs. (screened mean), 12.4 yrs. (unscreened mean)
Article III	2 029 invasive (study), 1 631 invasive (reference)	483 (study), 532 (reference)	680 335 women years in the study population (in 1987-97), 726 256 women years in reference population (in 1976-86)	1987-1997	1987-2001
Article IV	111 invasive (triennial), 96 invasive (annual)	18 (triennial), 18 (annual)	77 083 women years (triennial) 68 018 women years (annual)	1985-2007	1985-2007 10 yrs. +3 additional yrs., 12.8 yrs. (overall mean for incidence-based BC mortality)
Article V	83 497 invasive (total): 3 387 in Turku, 11 478 in Helsinki, 68 632 in RoF	17 508 (total): 614 in Turku, 2 400 in Helsinki, 14 494 in RoF	40.7 million women years (total) from three study periods (1976-1986, 1987-1997, and 1998-2009)	1976-2009	1976-2009 (until death or the age of 85)

Data on BC during years 1976-2009 among all Finnish women aged 40-84 were obtained from the nationwide Finnish Cancer Registry (FCR) that has registered all the Finnish cancer diagnoses and cancer deaths since the year 1953. This study deals only with invasive BCs, except for **Article** V, in which some analysis was done also for in situ cancers.

The deaths and mortality data in one-year age groups and one-year calendar periods for municipalities from year 1976 to 2009 were obtained from Statistics Finland as well as the census data. Census data of municipalities in one-year calendar periods and for one-year age groups was not available until 1976 onwards.

The formulation of calendar periods and age groups depended on the focus of the specific study question. For the analyses, the material was divided into sub-categories according to: the residence of the women, the age group at BC diagnosis, the calendar time of diagnosis, age group of BC death and the calendar time of BC death.

Statistical methods

In **Article I,** the differences in the characteristics between the screened and unscreened BC cases were tested by Pearson's chi-square test. The Kaplan–Meier method produced survival curves and Cox proportional hazard models were used to estimate HR with 95% CIs for survival analysis.

In **Article II**, the differences in patient characteristics were assessed using the Fisher exact test. Differences in recurrence-free rates, recurrence rates, and survival rates were evaluated using survival analysis methods. Survival curves were generated using the Kaplan–Meier method, and tested using the log-rank test or (in Cox proportional hazards analysis) the Wald test. HR calculations with 95% CIs were performed using the Cox proportional hazards model.

Relative risks were computed using Poisson regression analysis for BC incidence and mortality rate in **Article III**.

In **Article IV** for analysis of BC mortality between women invited annually and triennially, a Poisson regression model was applied to estimate the relative rate and its 95% CI.

In **Article V**, BC incidence and IBM were analysed using Poisson regression. The differences in IBM changes between the residential areas were tested using Wald's test.

5. RESULTS

5.1. Incidence

The overall cumulative BC incidence over all three different study periods that consisted of the pre-screening era: 1976-1986 and during the two screening era periods: 1987-1997 and 1998-2009 is described in **Article V**.

Between the first and last follow-up periods, there existed two trends. Firstly, the cumulative overall incidence of BC continued to grow. During the years 1998 to 2009 (compared to 1976-1986), the number of new BC cases was much higher in all residential areas. Secondly, the order of magnitude stayed unchanged: BC incidence remained the highest in Helsinki and lowest in RoF, whereas Turku fell intermediate **(**see **Figure 7)**. Helsinki, in our study, represented the most urbanized and populated area in Finland.

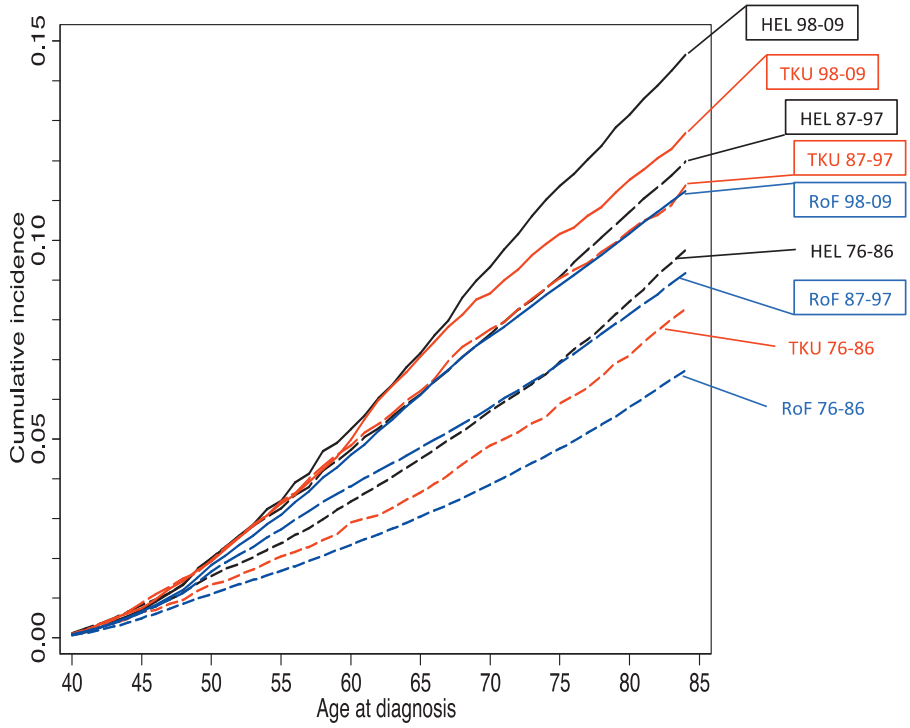

Figure 7. Cumulative BC incidences (per 100 000) until the age of 84 before initiation of the BC screening programme (1976-86, short dotting, unframed labels) and after the implementation (1987-97, longer dotting, framed labels) and (1998-2009, solid lines, framed labels). Helsinki (HEL) = black, Turku (TKU) = red, and the rest of Finland (RoF) = blue.

The incidence growth occurred most prominently in the two younger age groups in Turku, so that the level of Helsinki was reached and, for a short period of time Turku even exceeded Helsinki (in the age groups of 40-49 and 50-59), (**Figure 8).**

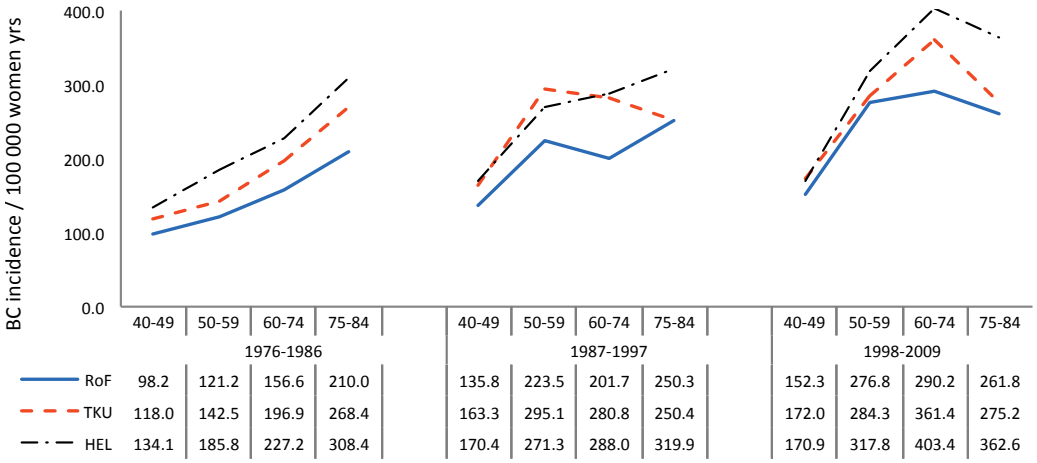

Figure 8. BC incidence by age group before the start of the mammography screening programme (1976-86) and after the start during the follow-up periods (1987-1997 and 1998-2009).

In contrast, the incidence increase growth was very moderate in the oldest post-screening age group (75-84 years old) in Turku. This deviated from the incidence changes in Helsinki and fell close to the level compared to the RoF. The incidence in RoF was lowest in all age groups.

A clearly detectable change occurred (in **Figure 8**) in the incidence distribution of the three age groups after the start of screening (during 1987-1998) compared to the situation prior to screening.

5.1.1. Women aged 55 to 74 years

As reported in **Article V**, the incidence level growth was very similar during 23 years of follow-up in different residential areas (150% in Helsinki, 167% in rest of Finland, and 154% in Turku) with no order changes.

A more detailed analysis (**Article III**) from the age 55 to 69 showed no change either in the order of magnitude between Helsinki, Tampere, and Turku by comparing the before screening period with the after screening period. The increase of incidence levels also corresponded in these two studies.

The period for analysis for BC incidence (the screening period) was 11 years (years 1987–1997) and the studied pre-screening period was selected to be equally long (years 1976–1986). During this 22-year period, in the three reference cities, 3 660 new invasive BC cases were diagnosed.

Breast carcinoma incidence increased significantly between the two periods in the three cities by 31 to 38 percent in the whole study population, and no marked differences in the rate of incidence occurred between the cities **(Figure 9).**

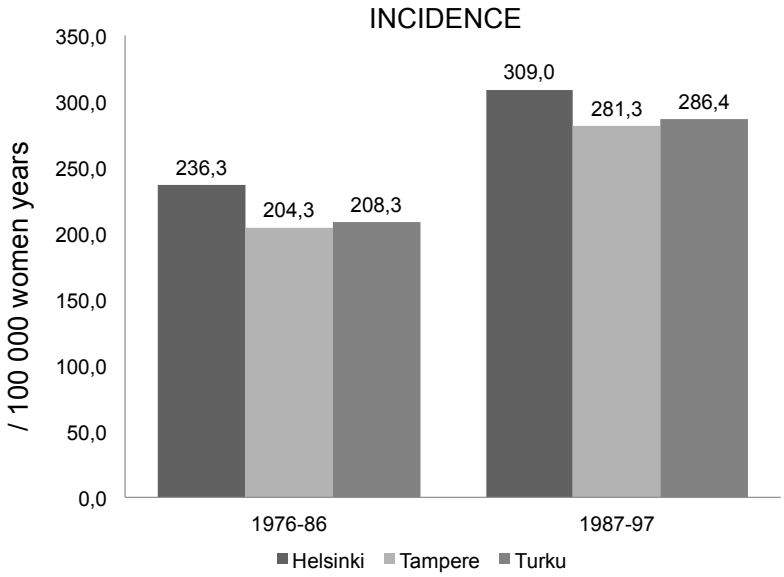

Figure 9. BC incidence in three cities in women aged 55-69.

A significant increase in breast carcinoma incidence was observed during the screening period as compared with the pre-screening period in all age cohorts and in all cities with two exceptions: non-significant trends were observed among women aged 60 to 64 years at entry in Tampere and among women aged 65 to 69 years at entry in Turku. The most prominent increases in incidences were observed among women aged 55 to 59 years at entry in Tampere (RR 1.56; 95% CI: 1.20–2.02 [p=0.001]), and among women aged 60 to 64 years at entry in Turku (RR 1.58; 95% CI: 1.21–2.05 [p>0.001]). Compared with Helsinki, there were significant differences in the other two cities regarding the change of incidence rates.

5.1.2. Women aged 40 to 49 years

The incidence was the highest in Turku in this age group (in the entire residential area comparisons) among the reference areas (during the period 1998-2009). It was at that time 172.0/100 000 women years, compared with Helsinki 170.9, and the RoF 152.4 (**Article V**).

The incidence growth was significant in all three residential areas (from the pre-screening era of 1976-1986 to the second period of screening era of 1998-2009) but was the most rapid in the RoF (RR=1.55; 95% CI 1.48-1.63) and relatively stable in Turku (RR=1.46; 95% CI 1.18-1.81) and in Helsinki (RR=1.27; 95% CI 1.14-1.43). However, calculated from the incidence of 145 101 women years (**Article IV**) (including all incident BCs in the study material) of 40 to 49 aged women with an invitation interval of three years (triennial) or one year (annual), the incidence levels were 144.0 and 141.1 (per 100 000 women years), respectively, with no difference (RR=0.98; 95% CI 0.75-1.29).

5.1.3. Women aged 50 to 59 years

The second period when the incidence was highest in Turku (compared with reference residential areas) occurred during the first screening era period of 1987 to 1997. The incidence figures were, respectively: Turku: 295.1, Helsinki: 271.3 and the RoF: 223.5. This time growth was greatest in Turku: RR=2.07; 95% CI 1.71-2.50 (RoF: RR=1.84; 95% CI 1.77-1.93 and Helsinki: RR=1.46; 95% CI 1.32-1.62). During the second screening era period, the situation was, however, changed. The incidence growth was the most rapid in the RoF: RR=2.28; 95% CI 2.20-2-2.38 (Turku: RR=1.99; 95% CI 1.67-2.39 and Helsinki: RR=1.71; 95% CI 1.56-1.88).

Conclusion
BC incidence was in accordance with the urbanization of residential areas and the order of magnitude and the incidence growth between these relationships remained unchanged. Two non-significant exceptions took place in the two youngest age groups, which were indicative of accelerated diagnostics. (see Figure 8).

5.2. BC Mortality

5.2.1. Cumulative mortality

In Turku, the cumulative BC mortality rate of women aged 40 to 84 was 0.0262 deaths per year per 100 000 women years during the last screening period (1998-2009) and 0.0310 deaths per year per 100 000 women years during the pre-screening period (1976-1986), and the risk ratio (RR) between the periods was 0.85 (95% CI 0.71-1.00; p=0.055). In Helsinki and in the RoF, the rates during the screening period were at the same level than during the pre-screening period. The rates in Helsinki were 0.0365 and 0.0356, RR=1.01 (95% CI 0.92-1.10; p=0.89) and in RoF 0.0265 and 0.0268, RR=0.99 (95% CI 0.95-1.02; p=0.51), during the screening period and pre-screening period, respectively. Cumulative BC mortality rates are shown in **Figure 10**.

Because long-term evaluation showed that cumulative BC mortality decreased in Turku, but in Helsinki and in the rest of Finland, it stayed at the previous level, additional detailed analyses were needed to explain the differences observed by age groups. For this reason, more detailed incidence-based mortality calculations were performed (in **Article V)**.

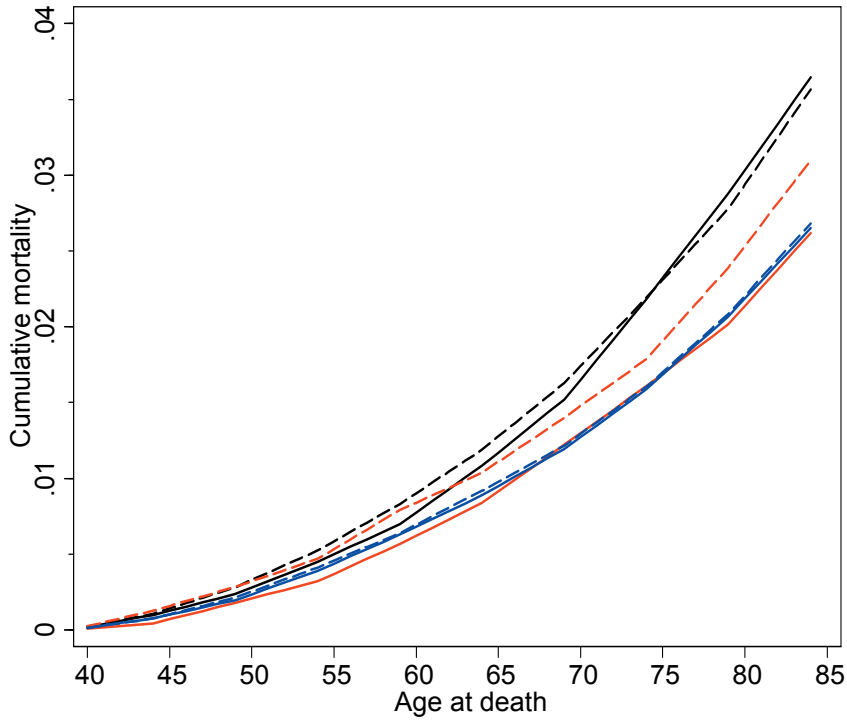

Figure 10. Cumulative BC mortality of women aged 40 to 84 in Helsinki, Turku, and the rest of Finland during the pre-screening period of 1976-1986 [dashed] and during the last screening period: 1998-2009 [solid]. Helsinki (HEL) = black, Turku (TKU) = red, and the rest of Finland (RoF) = blue.

5.2.2. Incidence-based mortality

Incidence-based mortality (IBM) was calculated for the age group at the time of diagnosis, as well as at the time of death. Prior to the start of screening, there was one noteworthy IBM difference in at death calculation at the pre-screening period: Turku had an exceptionally low mortality in the age group 60 to 74. This may be due to the very intensive palpation screening programme of Turku, just targeting this age group before the start of mammography[5] (see **Figure 11**).

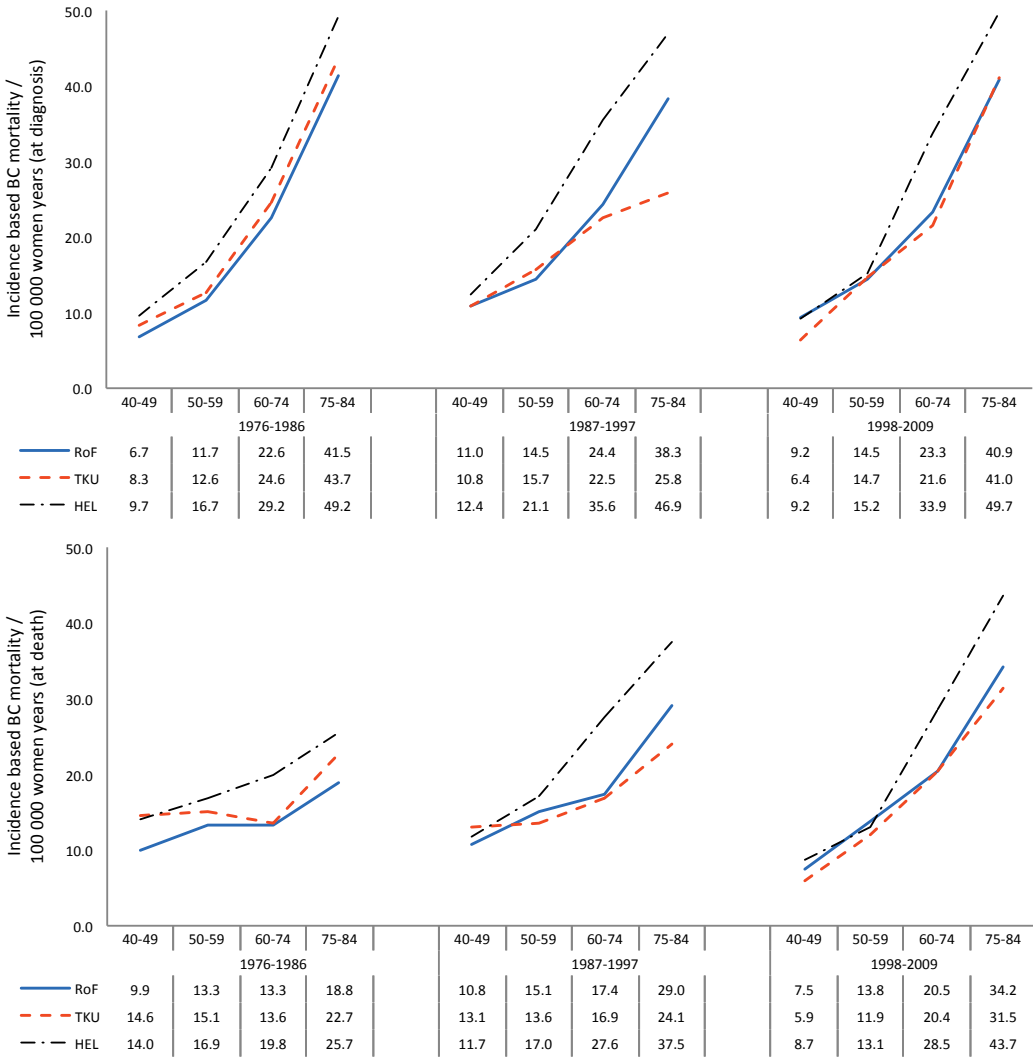

Figure 11. Incidence-based BC mortality per 100 000 women years in three Finnish residential areas, four age groups, and three calendar periods during 1976-2009, calculated by the at diagnosis and at death principle (the explanations are in Figure 10).

As seen from **Figure 11**, substantial changes happened in Turku especially during the first screening period (1987-1997) in the oldest age groups compared with Helsinki and the RoF. These changes were no longer as clear during the last screening period (1998-2009) in these age groups. In contrast, the youngest age group in Turku scored their best BC IBM results during this last period. However, in Turku, a significantly larger relative decrease in BC IBM occurred, during the entire screening period of 1987 to 2009, in the age group of 60 to 74 at diagnosis compared with Helsinki (RR=0.75; CI 95% 0.57-1.00, p=0.049) and in the age group of 75 to 84 at death compared with the RoF (RR=0.72; 95% CI 0.53-0.96, p=0.028), respectively.

When IBM with time and within each residential area were studied using 10-year follow-up, IBM decreased during the first screening period (1987-1997) compared with the pre-screening period and resulted in a significant difference compared with other residential areas (p=0.037) as women died at the age of 75 to 84 years. This decline in Turku was 44 percent (RR=0.56; 95% CI 0.38-0.83).

5.2.3. Women aged 55 to 74 years

In line with these results above, the BC mortality changes of 55 to 69 aged women (**Article III**) are shown in **Figure 12**. In this case, instead of the RoF, Tampere was chosen for comparison. Tampere is a city that has the same size and background risk factors as the City of Turku. The results here simply mark the refined mortality differences in the women group aged 55 to 69 years.

In Turku, a significant BC mortality reduction of 36 percent was observed during the screening period in the whole Turku study population (ratio of RR=0.64; 95% CI 0.47–0.88, p=0.007). In Helsinki, a non-significant increase in mortality of 11 percent was observed during the screening periods compared to the pre-screening period in the whole study population, whereas a non-significant mortality reduction by 14 percent was observed in Tampere. Turku remained the only city with a significant change.

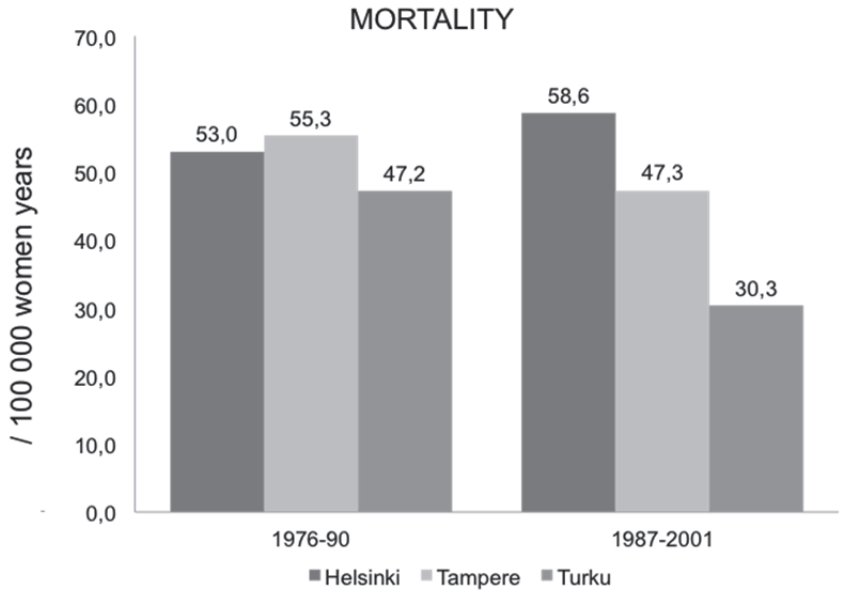

Figure 12. BC mortality in three cities in women aged 55-69 years (mortality follow-up of 15 years).

The change in the BC refined mortality rate in Turku compared with Helsinki was significantly lower by 42 percent (ratio of RR= 0.58; 95% CI 0.41–0.83, p=0.003) in the whole study population **(Figure 13)**.

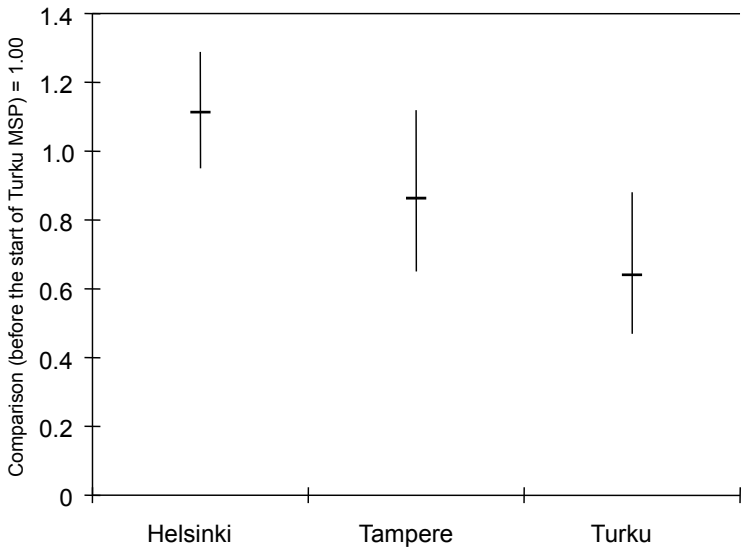

Figure 13. BC mortality changes in three cities in women aged 55-69 (at entry).

Compared to Helsinki, Tampere had a 23 percent lower refined mortality rate, but the result was not statistically significant. Compared to Tampere, the change in the mortality rate in Turku was 25 percent lower, but the difference was not significant, either. The most prominent result of BC mortality was discovered when comparing Turku with Helsinki among the oldest women cohort **(Article III)** - women aged 65 to 69 years at entry (ratio of RR=0.42; 95% CI 0.21–0.84, p=0.014). When compared with Tampere, the decrease in BC mortality was numerically higher in Turku in the two oldest birth cohorts, but those differences were not statistically significant among women aged 60–64 at entry, the ratio of RR was 0.69 and among women aged 65 to 69 years at entry 0.56.

5.2.4. Women aged 40 to 49 years

In total, 399 women in the whole cohort of 14 808 women died during the study period (**Article IV)**. All-cause mortality tended to be higher in the annual invitation group (RR=1.20; 95% CI 0.99–1.46) than in the triennial group. Out of those women with an incident BC diagnosed (207 women), 36 died from BC during follow-up. No significant difference in incidence-based BC mortality was observed in women invited annually as compared with those invited triennially (RR=1.14; 95% CI 0.59–1.27).

Slight excess in mortality from cancers, other than BC, was observed among those invited annually, but no explanation for this excess (*e.g.*, radiation-induced cancers) could be identified. In the triennial group, there were more violent deaths than in the annual group. In all-cause mortality, the follow-up time was slightly longer in both groups because prevalent BC cases were included.

In the long-term cohort study (**Article V**), a reduction in BC mortality was observed in the premenopausal (40-49) age group in Turku. In the youngest (premenopausal) group RR for mortality decline (in 10-year incidence-based mortality rates) during the years

1998-2009 was 51 percent at diagnosis (RR=0.49; 95% CI 0.27-0.91) and 59 percent at death (RR=0.41; 95% CI; 0.18-0.91). But compared with Helsinki and RoF simultaneously, this decline was not significant (P= 0.062).

Conclusion
In Turku, BC mortality appeared to be reversed during the study period. In contrast, in the reference residential areas, the BC mortality remained unchanged.

5.3. Prognostic variables and survival

In all, women aged 40 to 74 years, who attended screening, had a significantly higher BC-specific survival rate in this TurkuMSP study (**Article I**). These cancers, diagnosed in screening group, were more often localized (N0 *vs.* N1–3), smaller and histologically better differentiated (grade I *vs.* II-III) than the clinical cancers.

BC specific survival was significantly more favorable in the younger and elderly age groups: in the age group 40 to 49 HR was 2.47 (95% CI: 1.21-5.05), p=0.01; in the age group 60 to 69 HR was 2.14 (95% CI: 1.05-4.35), p=0.03; and in the age group 70 to 74 HR was 3.94 (95% CI: 1.48-10.48), p=0.003. Among women aged 50 to 59 HR was 2.00 (0.93-4.29), p=0.07, which was of borderline significance.

There was no significant difference in histological grade, axillary lymph node status, or size between BCs found in the first and in subsequent screening rounds.

After adjustment for clinicopathological variables and for age, the positive axillary nodal status, poor histological differentiation, and increase in tumour size were independent risk factors. In local (N0) BCs, a high histological grade, and a large tumour size are significant risk factors, whereas histological type and screening did not reach significance. If the cancer had already spread into the axillary lymph nodes (N1–3) by the time of the diagnosis, the risk of death tended to be lower in women who attended the screening, although the difference was only marginally significant (p=0.075). High histological grade remained a risk factor, whereas the size of the primary tumour had no effect on the probability of death if metastases were present in axillary lymph nodes.

Conclusion
BCs detected at mammography screening had more favorable prognostic factors than those detected outside of screening. In multivariable analysis the clinicopathological characteristics of the BC explains the survival declines of the screened women.

5.4. Prognostic variables and recurrence

When recurrence in relation to screening was evaluated during the TurkuMSP study follow-up (**Article II**), 93 of the screened patients (22%) and 38 of the unscreened patients (35%) were found to have developed recurrent disease. Seventy-four of 527 patients (14%) died of breast carcinoma. The figures were 52 of 418 (12%) in the screening group and 22 of 109 (20%) in the non-screening group, respectively.

Survival analysis revealed a significantly higher recurrence-free survival rate after the diagnosis of the primary malignancy for women in the screening group compared with the non-screening group. The risk of first recurrence (localized or non-localized) in the screening group was lower than in the non-screening group. The difference in risk between the two groups was already significant after two years of follow-up.

After five years of follow-up, 16 percent of screened women and 28 percent of unscreened women had experienced disease recurrence (p=0.001), and after 10 years, the corresponding rates were 21 percent and 34 percent, respectively (p=0.001). In age group analysis, the rate of first recurrence (localized or non-localized) was significantly lower for screened women compared with unscreened women in the 40 to 49-year-old and 60 to 69-year-old age groups after five years of follow-up, and these differences remained significant after 10 years of follow-up and also for the follow-up period as a whole.

Factors that were predictive for first recurrence (localized or non-localized) were also investigated. Univariate analyses identified the following factors (a) detection of the primary malignancy via a method other than screening, (b) receipt of multimodality treatment, (c) positive axillary lymph node status, (d) ILC, (e) size greater than 20-mm, and (f) poor histologic differentiation of the primary tumour to be associated with a high risk of recurrence. Data of screened *vs*. non-screened group did not differ significantly in terms of age or sociodemographic characteristics. However, in a multivariate analysis, the clinicopathological characteristics of the screened *vs*. non-screened explained the differences.

Survival analysis revealed no significant survival difference between these two detection groups after the detection of recurrence (HR=1.17; 95% CI 0.70 –1.94 [p=0.551]). Approximately half of all patients died from breast carcinoma within five years since the detection of recurrent disease.

The difference between the two detection groups in patients who died of other causes than BC was not significant. All BC related deaths were preceded by a non-localized recurrence, which either represented the first recurrence or followed a localized recurrence.

Conclusion

Fewer women were diagnosed with BC recurrence among the screened women study group related to BC incidence. In a multivariate analysis the BC size as well as histological type and grade were indicators for the lower BC recurrence. Recurrence-free survival rate after BC treatment was significantly more favorable among the screened women compared with women with BC found clinically. If the recurrence occurred, no difference in survival after recurrence was observed regardless of the screening history.

6. DISCUSSION

6.1. Overview of TurkuMSP

In addition to the results of the randomized controlled studies, the analyses of the outcome of the service screening cohort studies can be considered helpful in providing information on the applicability of trial results in routine practice. Between 1987 and 2009, the city of Turku, Finland, offered service-screening mammography for women aged 40 to 49 years. Women in this age group were gradually dropped from the screening programme during the last years of this period. Women aged 60 to 74 years were not screened regularly, the rate being affected by the difficulties of balancing the city's health budget. Regular screenings were carried out in all Finland for women aged 50 to 59 years.

This study follows the conventional logic with introducing and combining different methods in a single study and is called mixed methods research (MMR). This method is, generally speaking, quite useful for health care research (HCR).[199] In this study, a broader basis was established to compare how well these "real life" BC screening results were consistent with randomized study results and other epidemiologic study results. The present study results are quantitative, and qualitative aspects were excluded since the study was aimed at quantitative results.

The most important objective of this TurkuMSP study was to evaluate the effects of the Finnish mammography screening invitation programme within the framework of a long-term follow-up of several age groups in various residential areas (Turku, Helsinki, Tampere and rest of Finland).

The study team and I wanted to determine if the BC mortality could be decreased with the wider scaled screening programme, and if so, how those women who participated benefited from it.

When starting to interpret the results of this study and to discuss them, it is important to understand that it should be made with caution since there were no random control groups. In addition, the number of cases in some subgroups was fairly low for definite conclusions and all confounding factors were not known or possible to measure. Because of many statistical analyses performed in this study, some of the findings could be due to chance.

However, it should also be borne in mind that an attainable BC screening benefit (reduced mortality) is measured by longevity, while the nuisance caused by the screening programme mainly impairs the quality, not the quantity, of life or causes unnecessary additional costs. QALY (quality-adjusted life years) analysis would combine life quality and life quantity, but QALY-analyses was not the aim of this study.

6.2. BC Incidence

In these study results, there were differences in incidence levels in Helsinki and Turku compared with the rest of Finland (RoF). Helsinki and Turku represent urban areas whereas all rural populations were included in the RoF-database. A similar trend exists in another country; Canada resembles Finland because it has a low average population density. The Canadian Population Health Initiative, published in 2006 as a rural-urban comparative statistical analysis, showed very similar BC incidence trend differences.[200] They were very similar with the Finnish results described in this thesis. The incidences were significantly higher in urban areas compared with the rural ones. The variations in incidence levels in the different residential areas of Finland are as well in line with the changes, which exist in the Nordic countries.

The BC incidence level in Finland has steadily grown from 1950s (see Figure 6). During the 1980s the increase continued before the screening programme was started in our country (the incidence exceeded that of Norway around the year 1985, see Figure 2). Thus, the incidence increase cannot be due to any screening programme, because such programmes were not ongoing at that time. The reason for incidence trend intensification must reside elsewhere. One probability is urban growth.

There are various variables influencing the BC incidence such as reproductive (*e.g.,* small number of children), life-style (*e.g.*, alcohol consumption, obesity), urban environment and hormonal (especially hormone replacement therapy) factors (see chapter 2.2). The changes in these variables in Finland have been unfavourable, as in most developed countries, and these developments are sufficient to explain the continuous increase in the BC incidence level during the last decades. The increasing trend in the incidence could be observed in all residential areas pointing towards common background factors. The incidence in Helsinki was the highest at the beginning, and the difference in incidence was lowest over time. However, the incidence in RoF was low at the beginning of the study, but the incidence difference was greater over time. These findings most likely reflect the different stages of urbanization in these different residential areas and are not due to the implementation of mammography screening.

The incidence level change in the age group 60 to 74 was quite similar in all the residential areas in our study. However, only Turku performed mammography screening in this age group (**Article V**).

Due to the rigorous and prompt initiation of the screening programme from the year 1987 in Turku, compared with other residential areas, Turku BC cases have been diagnosed earlier in younger age groups. In the age group of 50 to 59 years, the incidence level in Turku increased the most rapidly during the first screening era period (1987-1997) after starting the mammography screening compared with the reference areas, but evened already during the last follow-up-period. This same effect seemed to happen among the women in the age group 40 to 49 but with a slower rate, until the second screening period.

These earlier diagnoses seem to cause small undulations in the Turku cumulative incidence curves for comparison (Figure 6), but the cumulative overall incidence results stayed unaffected. The order of magnitude remained constant for Helsinki, Turku, and the rest of country (in **Article V**) as well as Helsinki, Tampere, and Turku (in **Article III**).

6.3. Possible biases in mammography screening

Screening detects less aggressive BCs that grow slowly (*e.g.,* length bias) such that these tumours may not be a threat to the woman. The subsequent screening rounds should detect smaller, less aggressive tumours. According to our results, there were no significant differences in histological type or grade, axillary lymph node status, or size of breast tumours among the cancers found in the first and in later screening rounds. Therefore, the claim that mammography screening more often detects slowly growing and less aggressive tumours, and that without screening, these would never become clinically overt during women's lifetimes to threaten their lives, does not seem plausible. One explanation for the difference in survival may be the so-called "selection bias". The women, whose BC is found through screening or during the interval phase, are presumably those who accept and attend for screening. They may be generally more aware of their health and better placed economically than women who do not attend screening.

The most important biases in screening studies are lead-time bias, selection bias, overdiagnosis, and length bias.

Lead-time bias
Mammography screening detects breast carcinomas during the preclinical stage as shown in **Article I**, thereby providing a "lead time" and, consequently, a survival advantage to women with screen-detected disease.[201] To properly estimate the effects of screening on incidence, one should also consider lead-time bias.[202]

When the first article of this TurkuMSP study was published (2003), De Koning [201] emphasized how important adjusting for possible biases is when interpreting survival curves.

In this study, the early diagnosis-based "lead-time" effect was recognized in Turku in all study age groups **(Article V**) but with clear recoil, which opened a window to scrutinize the long span survival results in **Articles I, II**, **and V** from a neutral perspective neither overestimating nor underestimating the lead-time bias probability.

However, in this study, the core results are therefore not based on survival comparisons between screened and non-screened women study arms but mortality figures.

Selection bias
As stated in this study **(Article I)**, one explanation for the difference in survival compared between participants *versus* non-participants of the screening may be the so-called "selection bias". Women with better awareness of their health are more likely to participate in screening programmes. But again, this has most importance when

concluding survival results. The focus of this study was comparisons of residential areas (**Articles III and V**) where the participation rates were very high and very kindred.

Selection bias may not have distorted the main results of this study.

Length bias and overdiagnosis

Length bias is the chance that women with more slowly progressing disease will be detected, with potentially longer survival in general, whereas overdiagnosis bias contains screen-detected lesions being labelled as cancer that would not have progressed to a clinical diagnosis over lifetime.

Length bias was avoided in this study by recording mortality results during very long follow-up **(**especially in **Article V)** and using similar statistical analyses in all residential reference areas.

Screening mammography programmes are able to find cancers and cases of *carcinomas in situ,* CIS (a non-invasive tumour in which abnormal cells that may later become cancerous and start to invade through the basal membrane of the breast ducts) that need to be treated. However, they can also find cancers and cases of CIS that will never cause symptoms or threaten a woman's life, leading to overdiagnosis of BC. Treatment of these latter cancers and cases of CIS is not needed and leads to overtreatment. Overtreatment exposes women unnecessarily to the adverse effects associated with cancer therapy.[167] There are two types of CIS, ductal (DCIS) and lobular (LCIS). DCIS comprises the majority of CIS[203]. Many studies have focused on DCIS. It is well known that mammography screening for BC finds CIS lesions, which may not develop into metastatic BC, if left untreated.[204] Levi et al. showed in their report [203] that 20 years after a diagnosis of CIS the cumulative risk of invasive BC was 26 percent, similar for lobular and for ductal CIS. The very recent report from Allen et al. (2014) showed that altered myoepithelial cells in DICS may predict disease progression and recurrence risk. This could, in the future, allow for stratifying patients with DCIS and the occurrence of overdiagnosis could lead to new decision-making processes.[205]

However, this MSP study was focused on invasive BC cases. In this study series, the major part of CIS cases were found through mammography examinations and none of the women with CIS died from BC. The amounts of CIS cases (during mammography screening period) were in accordance with other corresponding research results (see **Article V**). Therefore, screening for all cases of CIS, from the TurkuMSP study analyses, were excluded.

Overdiagnosis is possible also in invasive cancers.[206] [207] [208] In the Florence service-screening programme, the estimated overdiagnosis of invasive cancers was non-significant with 2 percent over a 10-year follow-up.[202] The very recent results from U.K. show that for triennial screening in women aged 47-73 BC mortality reduction was 18.1% percent (95% CI 17.3-19.0) and overdiagnosis 5.6 percent (95% CI5.1-6.1), respectively of all BC deaths and diagnoses, from age 40 to 85 years. For annual

screening in the same age range, BC mortality reduction increased to 35.0 percent (95% CI 34.3-35.7) and overdiagnosis to 7.6 percent (95% CI 7.1-8.1), respectively.[209]

The conclusions of this study was that the estimates of mortality reduction and overdiagnosis are highly dependent on screening frequency, age range, and uptake, which may explain differences between some previous estimates obtained from randomized trials and from service screening. In this TurkuMSP study (**Article I**), 5.1 percent of all screen-detected cases were of tubular type whereas only 1.6 percent among the non-screened were of this type. It may be a sign of overdiagnosis of invasive cancers (because this type of cancer has a more favorable prognosis), but of the accuracy of screening method as well. However, if BC screening should found a large-scale excess of small and indolent cancers (*i.e.,* overdiagnosis), there should be more cancers occurring in the city of Turku than in the reference residential areas. Since no such difference was seen between the cumulative incidences of invasive cancers in the residential areas studied, this study results do not support the view of a high rate of overdiagnosis of BC attributable to mammography screening programmes, as discussed by Zahl et al.[179]

In contrast to Zahl's methods, this TurkuMSP study provides precise screening data and long-term follow-up data, which may explain the difference between the studies.

In addition to mammography, some other factors may improve survival. A proportion of the decreased mortality may be attributable to increased breast health awareness among women and better availability of treatment options, as suggested by Feig.[210]

During the study period, BC treatment has evolved relatively uniformly throughout the country, following the commonly implemented BC treatment guidelines, thus reducing the effect of treatment as a confounding factor. From year 1987, all previously mentioned prerequisites allowed us to analyse changes in BC incidence and mortality in the three cities, Turku, Tampere, and Helsinki, with different screening histories before and after initiation of service BC screening. Although our total study population was large, some subgroups were small and the confidence limits were therefore wide. This indicates limitations in the precision of our point estimates.

6.4. BC Mortality

This TurkuMSP study showed that mortality results are in line with the global results (Figure 1) and results in the Nordic Countries (Figure 5). This is consistent with two facts: Firstly, as a consequence of randomized studies, population-based breast carcinoma screening programmes were launched in more than 20 countries since the late 1980s and early 1990s.[152] Since then, study reports of decreased BC mortality, concluded to be attributable to service mammography screening, exist.[128 129 130 131 132 153 211] In these reports, a 16 to 48 percent reduction of BC mortality among women aged 40 to 69 occurred after the initiation of a screening programme compared to no screening. The same is true in the U.S., where a study, from 1979 to 2000 and based on modelling techniques, showed that the proportion of the total reduction in the rate of

death from BC attributed to screening varied in the seven models from 28 percent to 65 percent (median 46%), with adjuvant treatment contributing the rest.[212]

Secondly, rapid development of a more efficient BC therapy modalities occurred during the 1990s. Especially, the role of adjuvant therapy has proved to be important because local treatment alone appeared to be insufficient care for approximately 30 to 40 percent of patients (Rutqvist 1998)[213]. As Hortobagyi et al. (2001) notes in their review,[214] adjuvant chemotherapy significantly reduces BC recurrence and mortality, and the effect lasts up to 15 years since diagnosis. Nowadays, it is well recognized that BC can often be a systemic (micro-metastatic) disease that benefits from these modern treatments, but the dosing and schedule of administration of systemic therapies are equally important factors to be fulfilled as stated by Saurel et al. (2010) in their review.[215] Mandelblatt et al. (2013) have used two simulation models to estimate the potential reductions in the year 2025 in BC deaths through optimizing treatment use, increasing screening use, and obesity prevention in the U.S. These assumptions show that a potential of approximately 36 percent could be achieved due to high-quality system treatment and screening (two thirds of this by treatment and one third by screening). Eliminating obesity could improve these results further seven to 10 percent.[216]

Elderly age

During the 1960s and 1980s, case–control studies and meta-analyses were published,[217] [218] including findings among women aged 55 to 74. The results of the Diagnostisch Onderzoek Mammacarcinoom (DOM) project (Utrecht) showed a 46 percent reduction in BC mortality[219] and a study from Nijmegen residential area showed about a 45 percent drop among women aged more than 65.[220] Further, Olsen et al.[221] reported 18 to 42 percent decreases in breast carcinoma mortality in comparable groups by age at death in Copenhagen, which was attributable to screening and other developments. Humphrey et al. (2002) conducted a meta-analysis, which showed that an absolute risk reduction existed in older women who were screened.[218]

In Finland, mortality reduction, attributable to service screening, was reported earlier to be 24 percent among women screened at ages 50 to 64[16] and at 19 percent among women screened at ages 50 to 59 in Helsinki.[19] Encouraging results on the benefits of screening in the elderly population have continued.[222] [223] [224] Also, randomized breast carcinoma screening trial results suggested that the impact on mortality is more pronounced among women starting BC screening at the age of 60 to 69 than among those starting at a younger age.[147]

Incidence- and invitation-based mortality decline in Turku in the oldest groups compared with the reference areas was 25 to 28 percent **(Article V)**, and is in line with results from many countries.[132] [225] [226] [227] [228] These results were obtained by case control methods or by using a reference group. In this study, two reference cohorts from homogenous multi-residential areas were included. They had solid and known differences in background risk factors, but at the same time had similar treatment modalities and screening participation rates.

Based on results of this study **(Article III)**, the reduction in mortality due to mammography screening is consistent throughout this age group.

The mammography-screening programme in Turku is an effective and long-standing tool to decrease mortality levels in the elderly age groups. Based on all available data, no other consistent explanation exists for the decrease in mortality level among the elderly women in Turku except for the screening programme.

Assessment of the effectiveness of mammography screening in elderly birth cohorts is of importance, as the incidence of BC and BC-refined mortality in elderly birth cohorts is high, and incidence is increasing in older age groups.[229 230] In the elderly population, treatment modalities are often limited because of other diseases and conditions, and elderly patients may therefore not receive all the benefits from new and effective BC treatments, which underline the importance of early diagnosis in this group. In Finland, the average life expectancy of women is approximately 83 years,[231] which also justifies the assessment of the benefit of service mammography screening in the elderly population.

These facts lead to the question of when the screening programme should be discontinued? Walter and Schonberg have studied this topic recently (2014)[232] and concluded that for women with a life expectancy of more than 10 years, deciding on whether the potential benefits of screening outweigh the disadvantages becomes a value judgment for patients who require a realistic understanding of screening outcomes.

Young age (premenopausal women)

There has been a lot of debate and concern about the value of screening of women aged 40 to 49. Our results suggest that women aged 40 to 49 may also have an advantage from BC screening by mammography, as shown by other authors[233 234 235 236 237] but the lower BC incidence and for example, the more limited sensitivity of mammography with the dense breasts must also be taken in account.[238]

No evidence of a difference in incidence-based (refined) mortality from BC between the annual and triennial screening invitations under the age of 50 was observed **(Article IV)**.

However, a very clear decline was seen in Turku during the years 1998-2009 in this age group, but only marginally significant (at diagnosis) when compared with reference residential areas (P=0.062). **(Article V).**

These results show an improvement over Italian,[239] Icelandic,[240] and Swedish[241] results. However, due to the rather small population and low BC mortality rate in this youngest age group in Turku, the mortality level reductions were non-significant. As BC incidence in this younger age group is low and adjuvant treatments are very efficient, the implementation of mammography screening in this age group is less clear and cannot be recommended in our country based on the current evidence.

6.5. Prognostic variables

The effectiveness of population-based BC mammography screening in terms of improving BC survival was examined with a focus on clinicopathological variables such as the size, histological type, and grade of invasive BC and also the axillary nodal status of the patients affected. From the beginning of this screening programme in 1987, a cohort of 36 000 women in a well-defined geographical urban area was followed-up for a median of six and a maximum of 13 years (**Article I**). The female population had become familiar with the screening policy, and the attendance rate was high. Up until 1998, the screening was free of charge. In some age cohorts, a screening fee resulted in a low attendance rate from 1998 onward, and the years 1987 to 1997 were therefore chosen for the study.[101]

The most common histological types are ductal and lobular, and these together account for most of all BCs. Slow-growing, tubular cancers outnumbered other types in the screened group, but no significant differences existed in other specific types of BC. In this particular study, a pathologist who was specialized in classifying breast tumours, reclassified all the BCs, and hence excluded any classification bias (See **Article I**). In a series of patients with tubular T1N0 breast carcinoma, followed-up for a median of 18 years, there were no recurrences. [242] Although the tubular type of BC was overrepresented among women who attended screening, there was no significant difference in survival between the screened and the clinical groups with respect to ductal and lobular *versus* special types of cancer. Furthermore, histological type was not a risk factor for death in the Cox multivariate analysis in women with either N0- or N1–3-BC. However, the number with specific types was quite low compared with the number with ductal and lobular histology. Mammography screening detects BCs in their preclinical phase, thus giving a "lead time" with a consequent survival advantage for women with screen-detected BCs. This is unequivocal.

The TurkuMSP study results (**Article I**) showed that participating in screening programme found different BCs from the point of prognostic variables. There were many significant differences compared with the non-screened women. The most important explanation for the beneficial effect of screen-detected cancers is the absence of axillary lymph node metastasis, good histological differentiation grades of BC, and small tumour size. Thus, our results are in line with earlier observations defining the prognostic value of these variables.[127 243 244] Moreover, screening may have a beneficial effect even in women whose cancer had spread into the axillary lymph nodes but the analyses did not reach the significance (p= 0.075) (**Article I**).

The value of breast carcinoma screening in the prevention of recurrent disease was unknown.[245 246] This MSP study (**Article II**) showed that breast carcinoma recurrence rates were significantly lower among screened patients compared with unscreened patients after five years and 10 years of follow-up, with this trend holding true for the follow-up period as a whole. Olivotto with co-workers[245] (British Columbia, Canada) as well as Magee and co-workers[246] (the United Kingdom) have reported significant differences in the five-year recurrence rates in favor of screened compared with unscreened women. Factors such as tumour size, lymph node involvement, and

histologic grade are significant predictors of both recurrence-free and overall survival.[207] In addition to these findings, the TurkuMSP study demonstrates that detection of BC outside screening is an independent predictor of recurrence (**Article II**).

Significantly fewer women got recurrence among the screened study group but if recurrence occurred, no difference was observed compared to the earlier screening history. This fact is in accordance with the results that also survival was significantly better among women who were participating: the benefit in survival and the benefit regarding mortality are achieved through the avoidance of recurrence. This theory is in line with the many study results that screening participation save lives by reducing BC related mortality.[9 207 208 247 248]

6.6. Invitation intensity

The purpose of TurkuMSP study was also to compare the effect of the screening policy with annual and triennial invitation intervals on incidence-based (refined) BC mortality. There was no evidence of a differential effect.

Because of the lack of a control group with no screening, we cannot determine whether this result was due to no effect of mammography screening in this age group or whether the effectiveness of triennial screening is similar to that of annual screening.

A more intensive screening policy for younger women is recommended by Tabár et al, (1987)[157] and Venta et Goodhartz (1996)[249] because BCs in younger women are considered to be more aggressive. A short screening interval was also proposed because the sensitivity of mammography screening is lower in women aged 40 to 49 years (Bailey et al, 2010).[166] In previous randomized studies, various screening invitation intervals, ranging from 12 to 24 months, have been used.[161 165] The results with Markov-chain models of breast tumour progression to determine the optimal screening interval with the data from the Swedish trials suggest that the screening interval is critical for women aged 40 to 49 but less so for older women (Duffy et al, 1997).[250] Based on available results of randomized controlled trials, Tabár et al (1989)[251] proposed that the screening interval should be no more than 18 months for women aged 40 to 49 years. Consequently, for women aged 40 to 49, a three-year mammography screening interval was modelled to result in only a small, four percent reduction in mortality (Duffy et al, 1997).[250]

The invitation design that we implemented resulted in a substantial variation in the median number of invitations. Previous studies[157 161 165 250 251] indicate that the possibility of equal effectiveness of a screening algorithm with 2.8 invitations and with 9.2 invitations between ages 40 and 49 years is not credible. The possibility remains that the programme provided only a marginal effect overall at most.

However, IBM calculations (**Article V**) showed a notable but non-significant difference in favour of screening in the age group 40 to 49 years.

6.7. Treatment

In Finland, the tradition of using Evidence Based Medicine (EBM) is followed in the medical field. This has a historical background. Already in 1881, Finnish doctors established a scientific doctors' society called *Duodecim*. This society started to publish a scientific journal of the same name since 1885. Currently, this society is one of the leading providers of a global EBM database in co-operation with the publishing house John Wiley & Sons Ltd., which promotes, sells, and distributes the English language version of EBM Guidelines on behalf of *Duodecim* worldwide (except in Finland).[252] Practicing Finnish doctors use this Finnish database frequently.[253] These guidelines allow for a universal BC treatment, nationwide, in all hospitals and doctors consultation appointments.

The Finnish Breast Cancer Group (FBCG) is a society for clinicians who are involved in BC activities (oncologists, surgeons, radiologists, pathologists, specialist nurses, *etc.*). This society has regular bi-annual scientific and clinical practice meetings and its own newsletter, which strengthens further uniform national treatment practice activities that are based on international treatment guidelines.[254] Multidisciplinary medical staffs exist for BC diagnostic and treatment purposes. These Finnish institutions spread and apply the most current BC treatment, nationwide.

The women in the present TurkuMSP study lived in the city of Turku and were treated according to the same treatment guidelines. Consequently, the treatment modality does not explain the survival differences between women who attended and who did not attend for screening. In the present study, the key question was: did BCs found among women who were invited for screening behave differently from the cancers found among women who did not get an invitation?

Using homogenous age groups with solid and known differences in prognostic background variables, but at the same time with similar participation rates and similar treatment modalities, can provide valuable information. Special attention must also be focused on consistent evidence-based treatment conventions over a long time span[253] and on BC treatment.[255] During this study, this special attention was noted.

In another report, the beneficial effects of screening compared to breast carcinoma treatment costs were discussed. Over a five-year follow-up period, the mean treatment costs per patient diagnosed with breast carcinoma between 1987 and 1993 was 1.3 times greater for unscreened women compared with screened women. The estimated savings resulting from early treatment were 26 to 30 percent when measured as a proportion of the screening costs for 1987 to 1993.[256]

6.8. Screening and treatment combination

Achieving a BC mortality rate of zero is practically impossible because there are some BCs that are very aggressive and despite the overall favorable prognosis for women who have undergone BC screenings, unpredictable BC recurrences and deaths are observed even among those who had T1N0M0 disease. In this subset of T1N0M0 patients a high Ki-67 immunopositivity was the strongest predictor of recurrence.[257]

The BC research field is rapidly advancing. Increased awareness of this disease promoted by celebrities and national awareness programmes fuel the development of new therapies for women who have BC. Without a doubt, there will be new therapeutic discoveries made in the next decade. However, studying therapy effectiveness was not the focus of this study.

Mammography screening programmes, as such, are still very important for identifying women with early BC and thus improving survival results. Also screening methods may constantly improve as shown by using tomosynthesis in combination with digital mammography: the recall rate has been decreasing and the cancer detection rate has been increasing. A combined approach of early detection plus best treatment practice would be the most effective method to reduce nationwide BC mortality in the future.[258]

Screening-treatment combination targets are primarily designed: (a) to find all BCs at a local stage before they have spread, and (b) to prevent recurrence. When the BC is metastatic initially or at recurrence, similar treatment efficacy results and survival outcomes are observed in these two groups.[259] This is in accordance with this study results (**Article II**).

As shown in this study, there still are differences between the residential areas of Finland regarding BC screening activities of different age groups and cohorts. Also the Finnish Ministry of Health (The Institute of Screening Task Force) has paid in 2013 attention to that apparently the best way to implement screening in Finland has not yet been achieved. In the future, the best practice should be a nationwide responsibility for screening organizing, rather than that at the level of the municipality or region.[260]

To achieve this, health policy structure should be re-evaluated and this thesis recommends that policies shift away from the traditional structure in which municipalities dictate *e.g.,* screening policies but rather policy should be orchestrated at a national level.

A multidimensional change in BC Finnish health policies occurred during the last four decades (1970-2010). The challenge is to understand the impact of these changes due to the background risk factors, treatment, screening, and how these all affect BC. Developing a "Finnish" way of using national sources of background risk statistics combined with health record data banks could open, in the future new ways to utilize information retrieval and data-mining for advanced risk analyses. If this could be implemented, BC mortality rates could be reduced even further.

Basically BC screening is legitimate as long as the BC treatment modalities can cure also aggressive and spread BC. If this progress of treatment excellence will be achieved, discovery benefits of early detection are reduced and may be judged to be *de minimis*.

6.9. Benefits and harms of mammography screening

In general, there are two separate research concepts related to the benefits of mammography screening: reduced BC mortality and the disadvantages of screening

(e.g., false positives, unnecessary follow-up examinations involving re-calls, additional radiology, biopsies, etc., including overdiagnosis (Lancet, 2012).[261] This editorial introduces the results of the Independent UK Panel on Breast Cancer screening, [262] which states that routine breast screening leads to a 20 percent relative risk reduction compared with no screening. This means for every 235 women invited for screening, one BC death will be prevented, and this represents 43 BC deaths prevented per 10 000 women aged 50 years invited to screening for the next 20 years. Additionally, the Panel found that some overdiagnosis occurs. Nineteen percent of BCs diagnosed in women invited for screening would not have caused any problem if left undiagnosed and untreated (a rate of 129 per 10 000 women). This recommendation did not receive the Panel's full support.

After publishing this Panel report,[262] a very divergent opinion arose[263] and the authors of the Panel report were replying that correspondents variously suggested that their independent UK Panel on Breast Cancer Screening misinterpreted the benefits of breast screening and either underestimated or overestimated the risk of overdiagnosis. The authors also stated that it was just such divergent views that led to convening of the panel. A month after these position papers appeared, another leading journal published an article by Bleyer and Welch (2012). They concluded that nearly a third of all newly diagnosed BCs are overdiagnosis cases, and that screening is having, at best, only a small effect on the rate of death from BC.[264]

The recent update of benefits and harms of BC screening is at the moment from a full report[144] stemming from the Independent UK Panel on Breast Cancer Screening. The Panel considers that the major harm was that of overdiagnosis. They concluded that some cancers detected by screening were overdiagnosed.

However, there exist no data to answer this controversy over overdiagnosis. This led to the Panel to focus on two estimates. Firstly, in invasive and DCIS cases that were diagnosed throughout the rest of woman's lifetime, the Panel thought that the best evidence came from three RCTs that did not systematically screen the control group at the end of the screening period and followed these women for several more years. In the second, the Panel also considered the information from observational studies, but the variation in results of overdiagnosis varied across the range of zero to 36 percent of invasive BCs diagnosed during the screening period. For this reason, the Panel had no reason to favor, finally, one set of estimates over another.

The recent Euroscreen Working Group report (2012) states[193] that the plausible estimates of overdiagnosis range from one percent to 10 percent. Substantially higher estimates are due the lack of adjustment for BC risk and/or lead-time. Also, the recent incidence analyses from Norwegian women failed to detect any significantly increased cumulative incidence in screened versus non-screened women aged 52 to 79 years.[265] The results presented here are in line with this study. Their conclusion is worth considering: "a more careful diagnostic work-up for women during initial prevalence screening and careful considerations of necessary treatment are needed".

Of course, the overdiagnosis as such is not the only "burning question" of BC screening benefits and harms. Qualitative factors like false-positive cases with

unnecessary repetitive tests and invasive procedures such as biopsies and overtreatment (including the related mental stress) require serious and constant attention, but if unnecessary deaths are avoided, the core of ethical discussions is reached. Many authors [266] [267] [268] state that to maximize the benefit of mammography screening, decisions should be individualized based on patients' risk profiles and preferences. Decision aids would have the potential to help patients integrate information about risks and benefits with their own values and priorities. However, they are not yet widely available for use in clinical practice.[267]

Service screening in Europe achieves a mortality benefit at least as great as the randomized controlled trials and the chance of saving woman's life by population based mammography screening (of appropriate quality) is greater than that of overdiagnosis (Euroscreen Working Group, 2012).[269] This working group also started the discussion of using balance sheet assessing the trade-offs in BC screenings.[194]

This TurkuMSP study cannot alone resolve this discrepancy of two separate research encampments but the "real-world" results of this study, represented with one more urbanized (Helsinki) and one less urbanized (RoF) and one "rather similar" (Tampere) references, can also be considered more reliable than study results drawn from vulnerable linear trend assumptions from non-homogenous populations or materials other ways vulnerable for biases.[179] [180] [264] [270] As Moss et al. (2012) have pointed out, the BC mortality trend analyses cannot be used with confidence in the screening impact assessment but other methods and individual data are necessary to properly quantify the effect.[196] An overdiagnosis estimate around 36 percent is unfeasible in the light of TurkuMSP results, but zero to 10 percent is realistic and our results of the impact of screening on BC mortality are also in line with the most reliable proportional studies.[193] Autier and Boniol asked (2012) for explanations why some of the IBM studies on breast screening effectiveness did not match the results of a Swedish randomized study.[271] Here, these Turku MPS study results do match.

This study results showed a 25 to 28 percent decline in incidence-based BC mortality calculated for invitation groups. A recent nationwide Nordic study report showed a 43 percent reduction in BC mortality among women who attended the screening in the national mammography screening programme in Norway[211], and also another very recent Norwegian report (2014) strengthened the results of this study with their conclusion that an invitation to modern mammography screening may reduce deaths from BC about 28 percent.[272]

As stated in the summary article regarding the Euroscreen reporting, [191] [269] pooled estimates of BC mortality reduction among women invited to screening were 25 percent in incidence-based mortality studies and 38 percent among women actually screened. These TurkuMSP study results strengthen this evidence discussed above but not the deviating assumptions presented recently (2013).[195]

6.10. Age group dependent differences

In this study, the significance of the results was divided into different age groups showing significant results among the elderly women age groups but non-significant results among the youngest (pre-menopausal) group. However, it must be remembered that the random effect can extend over the significance of the border (P=0.05) in either direction, especially when the number of cases is limited.

7. CONCLUSIONS

Women, who had invasive BC detected at screening, had a significantly higher survival rate than women with clinically detected BC. The difference started to appear already during the first follow-up years and was evident in all age groups. Screening revealed BCs that were more often local, smaller, and well-differentiated, all well-known factors that indicate better survival. The prognostic importance of these factors became apparent also in this study when, in a multivariate analysis, these factors explained most accurately the higher survival rate of the screened women. The strongest prognostic factor for survival was the axillary lymph node status. Among women whose cancer had spread to ipsilateral axillary nodes, a screening possibly improved survival after adjustment for BC size and grade (**Article I)**.

The recurrence-free survival rate after BC treatment was significantly higher among screened women compared to women whose BC was found clinically, but there was no difference in survival after recurrence. In a multivariate analysis, BC size, histological grade, and type were independent predictors for breast cancer recurrence, whereas cancer detection determined by screening, age, or the type of treatment given were not (**Article II**).

Although mammography screening appears to detect BCs associated with higher survival and lower recurrence, the possible role of lead-time, length, and selection biases on these end-points cannot be ruled out.

No evidence for a significant difference in incidence-based (refined) mortality from BC was found between the annual and triennial screening invitation groups in a female population that was aged less than 50 (**Article IV**).

When comparing the older women (aged 65 – 69 years) in Turku with the women in two other Finnish cities (Helsinki and Tampere), a significant change in BC mortality during years 1987 to 1997 was observed only in Turku and was largely driven by a decrease in BC mortality (**Article III**).

In **Article V,** BC incidence and mortality in Turku were compared with Helsinki and the rest of Finland, over a longer time period (1987-2009). There were no significant differences in BC incidence among the areas, but BC mortality in women aged 75 to 84 was more than 20 percent lower in Turku as compared with Helsinki or with the rest of Finland. The lower BC mortality in Turku among women aged 75 to 84 was, however, only suggestive, because the differences with other areas were not consistently significant.

The TurkuMSP study demonstrated how challenging it is to understand the impacts of various medical interventions when many factors influence the outcomes simultaneously. Thus, the study of these specific factors must occur over a long time span, as performed in this study. The results of this study allude to future research that should further monitor the impact of these two prominent factors; *i.e.*, early diagnostics with mammography and/or other more advanced diagnostic methods versus improving treatment modalities.

Although unresolved questions about the value of population-based mammography screening persist, it can be concluded that the BC screening programme, among women aged 40 to 74 in the city of Turku, was suggestive for a decrease of BC mortality in elderly age groups due to mammography screening. This finding needs, however, confirmation from further studies before a recommendation to expand mammography screening for women up to the age of 74 years can be made.

APPENDIX

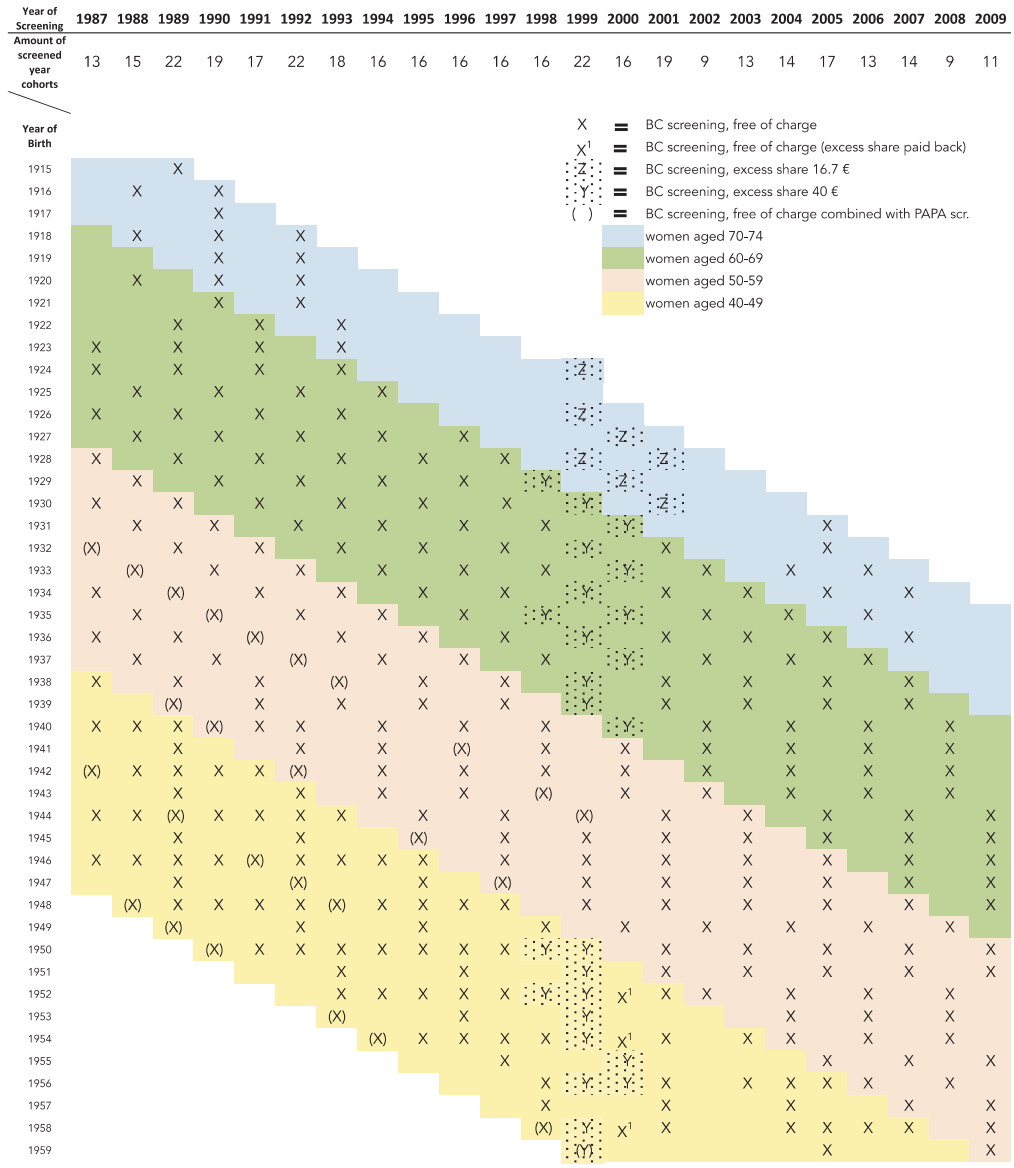

Figure 14. Summary of TurkuMSP with detailed information of invitation scheme, transitory charges of screening, and age groups

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