Summary (EN)

SUMMARY

Chapter 1 introduces the motivation and overall topic of this thesis: breast cancer, and breast cancer screening. The causes, risk-factors, incidence, survival, and breast cancer mortality are described. Potential benefits of early detection through screening are: life-years gained, improved quality of life, breast cancer deaths prevented, correct reassurance among women without breast cancer. Potential harms of screening include false reassurance, overdiagnosis, overtreatment, false-positive screening test results, and to some extent the temporary uncertainty after screening, and exposure to radiation that can induce breast cancer. The scientific body of evidence on breast cancer screening that has been gathered in the past decennia, has led to the widespread use of mammography worldwide. However, there is no consensus about which screening strategy is optimal. This is the area where simulation models are used to make projections about the effects of various different screening strategies. In this thesis, we investigate how model predictions can be better understood and to what extent risk-stratification can increase the benefits of breast cancer screening.

Part 1: Breast cancer micro-simulation: methods, comparative modeling, and model validation.

Chapter 2 provides an overview of microsimulation screening analysis – Fatial diameters (MISCAN-Fadia) model. The four main components of the model: demography, breast cancer natural history, screening , and treatment are described in detail. The MISCAN-Fadia model distinguishes itself from many other models by using a biological entry such as tumor growth and tumor size to modeling the natural history of breast cancer. The effectiveness of treatment and the sensitivity of screening are both linked to tumor size. The model adopts a 'fatal diameter' concept which implies that a cancer is not curable anymore and basically represents distant metastasis of breast cancer. The model is able to simulate many screening and treatment strategies in a short amount of time with varying adherence to screening and treatment. In each simulation, women differing in risk, birthyear, and life expectancy can be included. The model produces estimates of lifeyears gained, breast cancer eaths prevented, stage distributions, overdiagnoses, and interval cancer. Recent model developments include radiation induces breast cancers, breast density, and cancer by molecular subtype.

Chapter 3 shows how the CISNET breast cancer models simulate DCIS. Since the introduction of mammpgraphy screening in the 1980's in the United States, the incidence of DCIS, which is seen as a precursor of breast cancer, increased substantially. Uncertainty remains about the natural history of DCIS because tumor onset and tumor progression cannot be observed. In the 5 CISNET models, invasive breast cancer can develop from preclinical screen-detectable DCIS, or preclinical undetectable DCIS. A part of preclinical

DCIS may also regress. The models estimate that a large part of screen detected DCIS are overdiagnoses: 34%-72% in a biennial 50 to 74 screening strategy. Overdiagnosis is defined as a screen detected tumor that in the absence of screening would not have been found. The model predictions show no association between the amount of DCIS- and invasive overdiagnoses. The large differences in predictions of overdiagnosed DCIS cases, which is also found in other scientific literature, reflects the uncertainty around the natural history of DCIS. This underscores the importance of active surveillance trials such as the LORD, LORIS, and COMET trial that can provide more observed data on DCIS natural history.

Chapter 4 presents an external validation that compares model predictions to observed data from the 'U.K. Age trial'. The trial compared annual mammography screening in women aged 40 to 49 to a control group who were offered usual care, which is no screening in this age group. The 5 CISNET models used demography, screening attendance, and mammographic sensitivity from the trial in combination with extant assumptions about the onset en natural history of breast cancer to predict the incidence and mortality in the intervention and control arm. The results show that the effect of annual screening on breast cancer incidence is reproduced quite well. The average breast cancer mortality reduction after 10 years of follow-up was underestimated by the models 15% (range: 13% to 17%) compared to 25% (95% CI, 3% to 42%) in the trial. After 17 years of follow-up, the trial showed a 12% (95% CI, -4% to 26%) non-significant reduction and the models 13% (10% - 17%) on average. We conclude that the models reproduced the long term effects of the age trial reasonably well. This suggests that the existing model structures, model input parameters, and assumptions are suitable for estimating the effect of screening on breast cancer mortality in this age group.

In chapter 5, investigates how model structures and assumpations about the preclinical duration of breast cancer influence model predictions. The Maximum Clinical Incidence Reduction (MCLIR) method is used and extended to disentangle the effects of tumor growth rate, timing of tumor onset, screening sensitivity, and treatment effectiveness. The models do this in a simplified setting of a single screen at age 62 with varying assumptions about test sensitivity and treatment effectiveness. The MCLIR method compares changes in the number of breast cancer cases and deaths in 4 scenarios: 1. no screening, 2. a screen with perfect (100%) sensitivity and perfect treatment (100% cure), 3. a screen with sensitivity of digital mammography and perfect treatment, 4. a screen with sensitivity of digital mammography and realistic (observed) effectiveness of treatment. The models predict a 19% to 71% reduction in clinical incidence and 33% to 67% reduction in breast cancer mortality as a result of a perfect screening test and perfect treatment. In the scenario with sensitivity of digital mammography and realistic treatment effectiveness, the prediction converge: 11% to 24% clinical incidence reduction and 8% to 18% breast cancer mortality reduction. The timing of tumor onset and its

influence of the preclinical duration had the largest impact on model predictions. Models with relatively fast progressing tumors also had a shorter preclinical duration. The MCLIR method can shed light on the root of the differences between model predictions and can be applied in other disease settings where the effects of screening are modeled.

Part 2 – Quantifying the harms and benefits of breast cancer screening among women in the United States

In chapter 6, the harms and benefits of eight screening strategies varying in starting age and interval are estimated by 6 cisnet models. The target population was average risk women and women at increased breast cancer risk due to their breast density or co-morbidity. Biennial screening from ages 50 to 74 prevented 7 breast cancer deaths on average compared to no screening. Annual screening in the same age ranges would prevent 3 additional breastr cancer deaths, but would increase false-positives by almost 2.000 per 1.000 women screened over a lifetime. Starting annual screening at age 40 showed similar harms and benefits among women with 2 to 4 times the average risk. Women with moderate to severe comorbidity could stop screening at age 66 or 68. All 6 models conclude that starting screening at age 40 leads to a small benefit in terms of life years gained and breast cancer deaths prevented, but the increase in false positives and overdiagnoses is substantial. This quantitative analyses shows that biennial screening among average risk women is most efficient. Policy makers cab use this information to inform their decision about breast cancer screening policy.

In chapter 7, six breast cancer simulation models are used to assess the relative contributions of screening and treatment to the trend in breast cancer mortality between 2000 and 2012. Given the improvements in treatment and new adjuvant therapies which were given to breast cancer patients in these periods, the analysis focuses on combination of breast cancer subtypes estrogen receptor (ER) positive and human epidermal growth factor receptor (HER) 2. In 2000, the models estimate a 37% (27%-42%) breast cancer mortality reduction vs. no screening. 56% of this reduction is explained by breast cancer treatment and 44% by screening. However, in 2012 the total breast cancer mortality reduction is estimated at 49% (39%-58%) of which 37% is explained by screening and 63% by improvemens in treatment. For 3 out of the 4 subtypes it holds that treatment has made a larger contribution to the decline in breast cancer mortality, except for the ER-/HER2- tumors where the contributions of screening and treatment are estimated as approximately equal. The models conclude that in 2000 to 2012 the continued decline in overall breast cancer mortality can be explained for a larger part by new and improved treatments than by screening in this period.

Chapter 8 investigates to what extent the exposure to the ionizing radiation of repeated mammography screening contributes to breast cancer and breast cancer death. Prior research was based on 4 views per screening and did not account for breast size

and breast thickness, nor false-positives, diagnostic work-up, and variations in radiation dose caused by breast augmentation or breast positioning during screening. This study accounted for these factors because of their impact on the overall radiation dose and consequent radiation induced breast cancers. We estimated the radiation induced breast cancer in 8 screening strategies varying starting age (40, 45, 50) and screening interval (annual, biennial, hybrid). The benefits of annual screening of 100.000 women between ages 50 and 74 are estimated at 968 breast cancers prevented, but would also induce 125 breast cancer and 16 breast cancer deaths through radiation. Among women with large breasts, 8% receives more radiation doses during screening and this was estimated to cause 266 breast cancers of which 35 would lead to breast cancer death per 100.000 women screened. The results in this study show that it is important to account for variations in radiation dose from and after screening when determining the number of radiation induced breast cancers and breast cancer deaths.

Part 3: Projecting the lifetime harms and benefits of risk-based breast cancer screening.

In chapter 9, the effects of screening among women with varying breast density and risk are quantified. Three CISNET models simulate the effect of annual, biennial, and hybrid screening between ages 50 and 74 or 65 and 74. We distinguished four density groups spanning between almost entirely fat to extremely dense breast tissue. Increased breast cancer risk caused by other factors was modeled by including 4 relative risk groups: 1.0 (average risk), 1.3, 2.0, 4.0. The results show that in all screening intervals, the breast cancer deaths prevented and life years gained increased with breast density as well as increases in relative risk from other factors. At the same time, false positives and unnecessary biopsies decreased while overdiagnoses increased. The results in this study show that breast density and increased risk due to other factors can be useful in the formation of risk-based screening guidelines.

In chapter 10 we investigated the effects of screening based on breast cancer family history and small DNA variations and how these relate to the results of age-based screening guidelines. Two CISNET models estimated the effects of screening strategies with starting ages (30, 35, 40, 45, 50) and stopping age 74, and screening intervals (annual, biennial, triennial, hybrid). Among women younger than age 50 with a first-degree family member diagnosed with breast cancer; about 9% of the population, starting screening before age 50 would gain 44% life years and avert 24% breast cancer deaths compared to starting screening at age 50. However, the increase in the number of mammograms among these women also led to 25% more overdiagnoses and false positives would double. Screening based on polygenic risk gained 19% additional life years, prevented 11% breast cancer deaths, and overdiagnoses and false positives increased by 10% and 26%. Screening based on breast cancer family history and polygenic risk resulted in the

largest increase in benefits compared to current USPSTF guideline screening. This study showed that risk stratified screening can lead to fewer breast cancer deaths and more life years gained among women who are at increased risk of breast cancer due to polygenic risk and family history.