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1. WHAT IS BREAST CANCER

Cancer is the uncontrolled growth of cells into a malignant tumor. Breast cancer usually begins in the lobules, ducts, or connective tissue of the breast. The lobules are the glands that produce milk in nursing women. The ducts are thin tubes that drain milk from the lobules to the nipple. The connective tissue, consisting of fibrous and fatty tissue holds everything together. Most breast cancers begin in the ducts called ductal carcinoma in situ (DCIS) or, less common, in the lobules (lobular carcinoma in situ). Non-invasive cancers are confined to the milk ducts or lobules in the breast and do not evade into normal tissues. The non-invasive cancers may be pre-cancer and are sometimes called stage-0 breast cancer. Breast cancers become invasive when they grow into healthy tissue and can eventually spread outside the breast (metastasize) to other parts in the body through blood vessels and lymph vessels. Breast cancer diagnosed at an early stage when it has not spread, is more likely to be treated successfully. Vice versa, women's chances of surviving breast cancer are much lower when the cancer has spread throughout the body and effective treatment becomes increasingly difficult.(1)

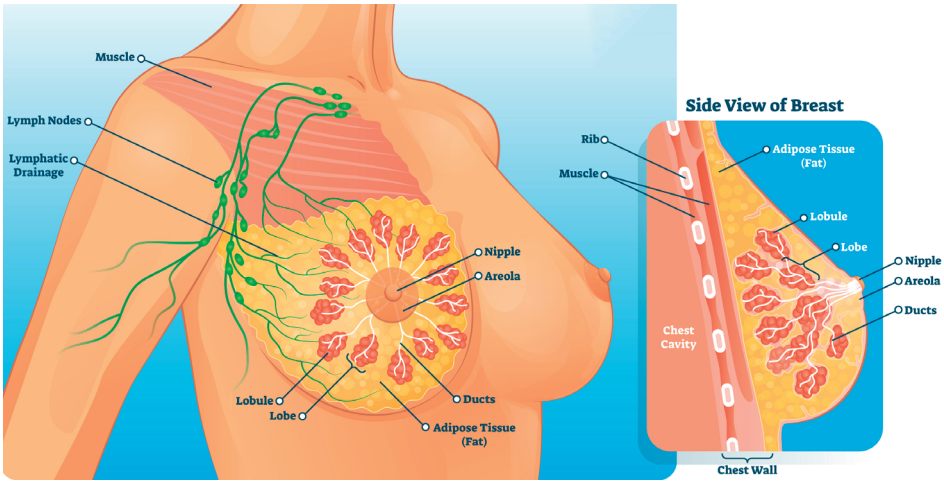

Figure 1 Anatomy of the female breast

Breast cancer staging

Breast cancer staging is used by doctors, hospitals, and others to characterize breast cancer upon diagnosis. Staging describes where the cancer is present in the body in relation to the primary tumor and in particular whether, and to what extent the cancer has spread. Staging is useful for guiding the treatment strategy and assessing the prognosis of the cancer. A widely used staging system for cancer is the tumor, node, metastasis (TNM) system.(2) The T refers to the size of the primary tumor from which the cancer

originates. The number of nearby lymph nodes involved is indicated with N. The M refers to metastasis of cancer and indicates whether the cancer has spread from the primary tumor to other parts in the body.

A similar staging system used by the Surveillance, Epidemiology, and End Results (SEER) program is the local-regional-distant system. In situ; abnormal cells, which may be a precursor of cancer, are present but have not spread to nearby tissue. Localized; cancer is present, but only in the organ where it started. Regional; the cancer has spread to nearby lymph nodes or organs. Distant; the cancer has spread from the place of the primary tumor to distant parts of the body.

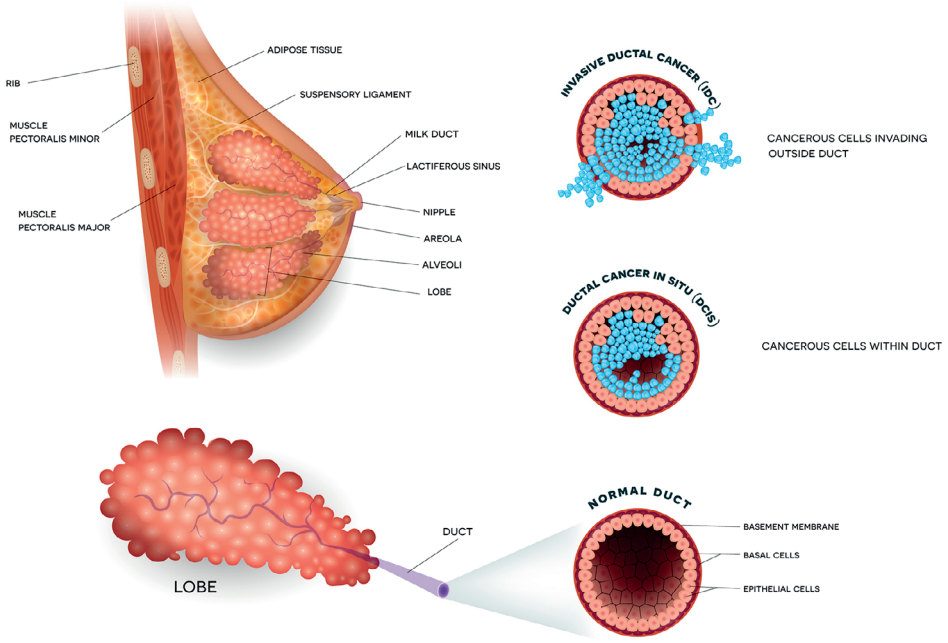

Figure 2 Ductal Carcinoma in Situ (DCIS) – non-invaiseve or pre-invasive breast cancer.

2. ETIOLOGY AND RISK-FACTORS OF BREAST CANCER

Research has identified hormonal, lifestyle, environmental and genetic factors that may increase the risk of developing breast cancer. (3) Breast cancer is likely caused by a complex interaction of genetic makeup and environment. While there are known risk factors, many women who develop breast cancer have no evident risk factors other than being women and in the age range of 50-74 when breast cancer incidence is the highest. As women get older, there are more opportunities for genetic damage in the breast and

Table 1 Overview of major and minor risk-factors of breast cancer.(3)

Breast cancer risk factors	Relative risk	Reference population
Personal information		
Age	20-30	Breast cancer at age 20 vs. at age 70
Body Mass Index	2	Obesity (BMI>30) vs. no obesity
Alcohol consumption	1.28	4 glasses containing alcohol vs. none
Breast density	4-6	Extremely dense vs. fatty breast
Hormonal / reproductive risk factors		
Age of first menarche	1.5	Before age 10 vs. after age 16
Age of menopause	2	After age 55 vs. before age 40
Age of first live birth	3	After age 35 vs. before age 19
Breast feeding	0.8	More than 4 years vs. No breast feeding
Use of hormonal replacement therapy	2	10 years usage vs. never
Family history of breast cancer		
First degree family history of breast cancer	3.6	2 first degree with breast cancer vs. none
Second degree family history of breast cancer	1.5	Second degree with breast cancer vs. none
Age of breast cancer onset	3	Onset before age 50 in sister vs. none
Ovarian cancer	1.5	Ovarian cancer in family vs. none
Personal history with breast cancer		
Atypical ductal hyperplasia	4	Ductal hyperplasia vs. no hyperplasia
Previous breast biopsy	2	No previous breast biopsy
Lobular carcinoma in situ (LCIS)	4	LCIS vs. no LCIS
Genetic breast cancer risk		
Single Nucleotide Polymorphisms	10	Top 1% vs. bottom 1% based on 77 SNPs
Mutations in BRCA 1/2	15	Mutation in BRCA genes vs. no mutation

the entire body. At the same time, the human body becomes less capable of repairing genetic damage that may cause cancer.

A previous breast biopsy, dense breasts, and a positive family history of breast cancer are strong risk factors for breast cancer. Inherited cases of breast cancer are often associated with mutations in genes BRCA1, BRCA2, ATM, CHEK2, and PALB2 which are known to increase breast cancer risk by a large factor.(4) Minor risk factors include reproductive factors such as low parity, and young age at first menarche which expose women to female hormones estrogen and progesterone that are linked to breast cancer onset and growth.(3) Breast cancer single nucleotide polymorphisms (SNPs) are common variations in the DNA sequence associated with small increases or decreases in breast cancer risk.(5) Polygenic risk combines information from multiple SNPs and could potentially achieve a degree of risk discrimination useful for population screening and be suitable to stratify risk in women of all ages.(6) Several other risk factors are related to personal behaviors, such as lack of exercise, alcohol consumption, smoking, and an unhealthy diet. While

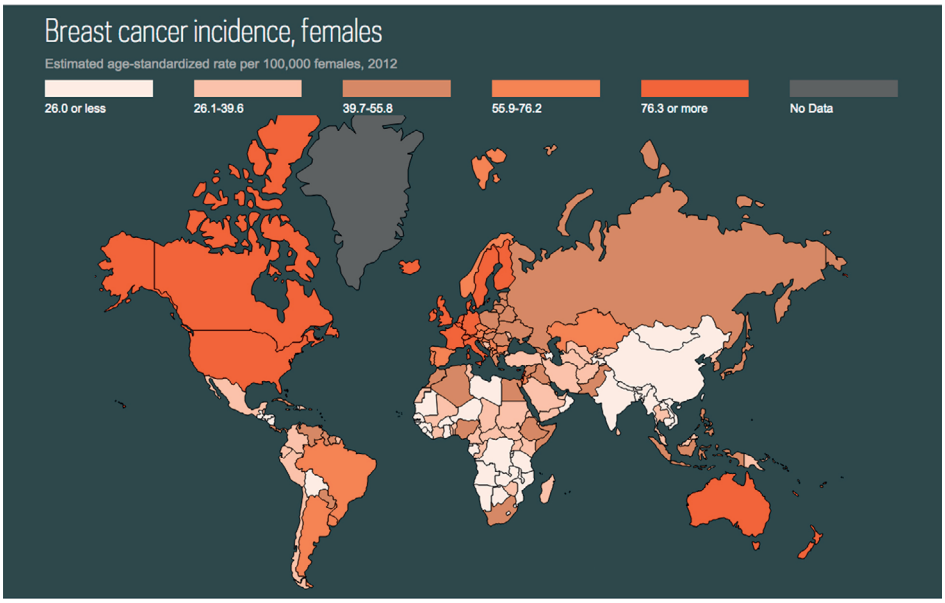

Figure 3 Worldwilde female breast cancer incidence in 2012. All incidence rates are age-standardized to the 1960 world population. Source: Ferlay J. Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No 11.

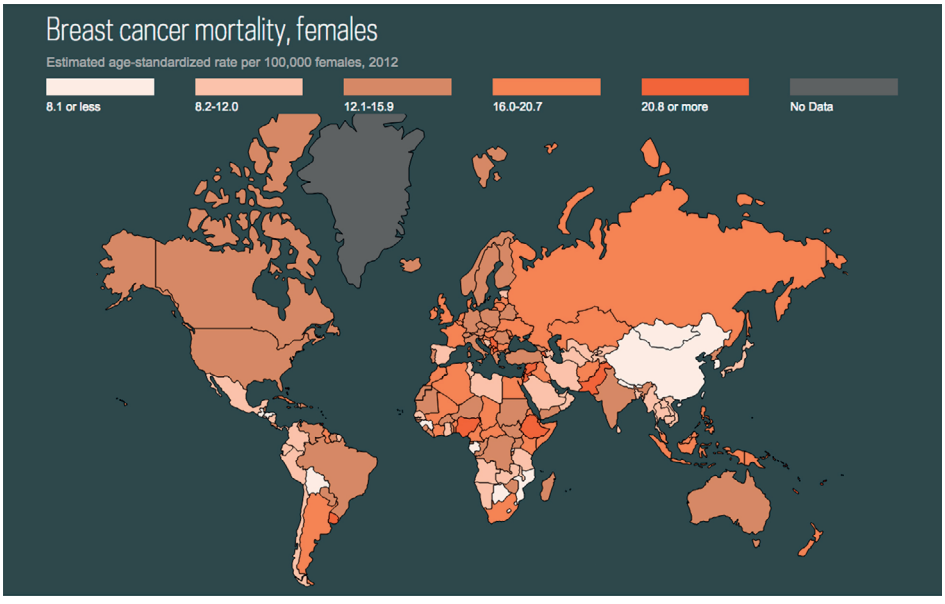

Figure 4 Worldwilde female breast cancer mortality in 2012. All mortality rates are age-standardized to the 1960 world population. Source: Ferlay J. Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No 11.

many known factors increase the risk of developing breast cancer, a large part of breast cancers are due to random, unpredictable, mistakes in DNA copying which is essential for cell division and life itself.

3. BREAST CANCER EPIDEMIOLOGY

Breast cancer incidence worldwide

Breast cancer is a major health problem with an estimated 2.1 million new cases and 0.63 million breast cancer deaths worldwide in 2018. (Figure 1, 2) In many developed countries around 1 in 8 (13%) women are diagnosed with breast cancer in their lifetime. (7)

Age-specific breast cancer incidence

Breast cancer correlates strongly with age regardless of race or ethnicity. At age 50 around which most women start screening, 200 cases per 100,000 women are observed in the United States. The peak in incidence lies between ages 70 and 80. This age-specific pattern is seen in most western countries.

Breast cancer incidence over time

Invasive breast cancer incidence has seen a sharp increase in the United States up to the year 2000. (Figure 5) After 2000, there was a drop in incidence up to 2003 which was followed by a period of relatively stable incidence levels. These changes over time have been attributed to the increase in use- and performance of mammography, changes in hormone use after 2000, risk factor prevalence, and differential birth cohort effects. The use of Hormone Replacement Therapy (HRT) was reduced in 2000-2003 as it became apparent at the time that it was associated with increased risk of breast cancer.(8, 9) This led to a decrease in breast cancer incidence up to 2003.

Breast cancer mortality

Breast cancer mortality was relatively stable up to the mid-nineties of the 20th century and gradually declined thereafter. The decrease in breast cancer mortality has been attributed to the increase in screening, better access to healthcare, and advances in breast cancer.(10, 11)

Breast cancer survival

Survival rates are an estimate of the percentage of patients who survive for a given period of time after a cancer diagnosis. Relative breast cancer survival compares survival among women with breast cancer to women of the same age without breast cancer.

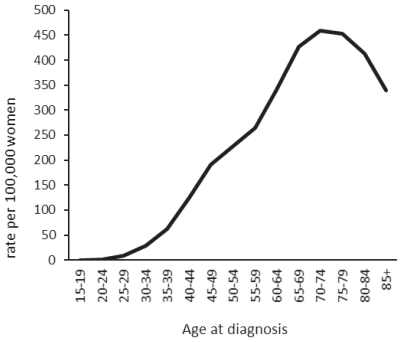

Figure 5 U.S. BC incidence by age, 2011-2015.

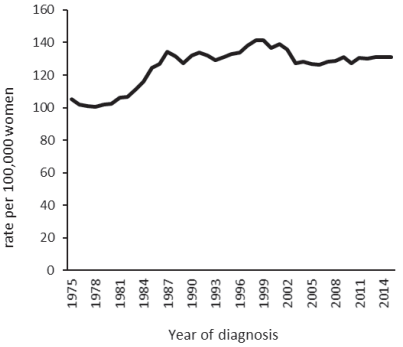

Figure 6 U.S. BC incidence - age-adjusted

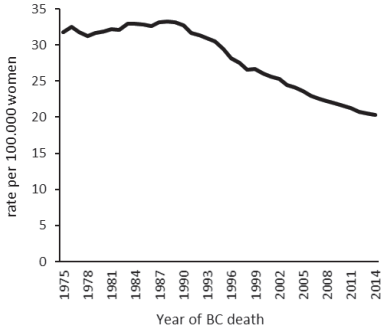

Figure 7 U.S. BC mortality, age-standardized '75-'13

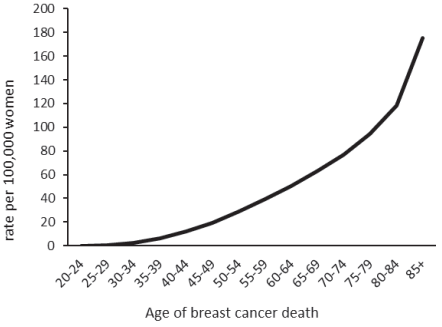

Figure 8 U.S. age-specific BC mortality '11-'15

Based on data over a 14-year period from 2000 to 2014, the 10-year survival rate for U.S. women diagnosed with breast cancer was 83.3% and varied strongly by stage at diagnosis. (Figure 8)

4. PRIMARY PREVENTION OF BREAST CANCER

Primary prevention aims to prevent disease before it begins. This is typically done by changing unhealthy behavior or prevent exposure to hazardous chemicals or situations. In breast cancer, the modifiable risk factors include postmenopausal obesity, alcohol consumption, physical inactivity, and exposure to radiation. A healthy bodyweight, balanced diet and regular physical activity reduce breast cancer risk and improve general health as well. A balanced diet is one that consists of sufficient fruit, fibers, vegetables, healthy fats, proteins and preferably no or little red or processed meat and added salt. In a proper diet the total caloric intake should maintain a healthy body mass index to prevent obesity. Physical activity should ideally be at least 30 minutes of walking, biking

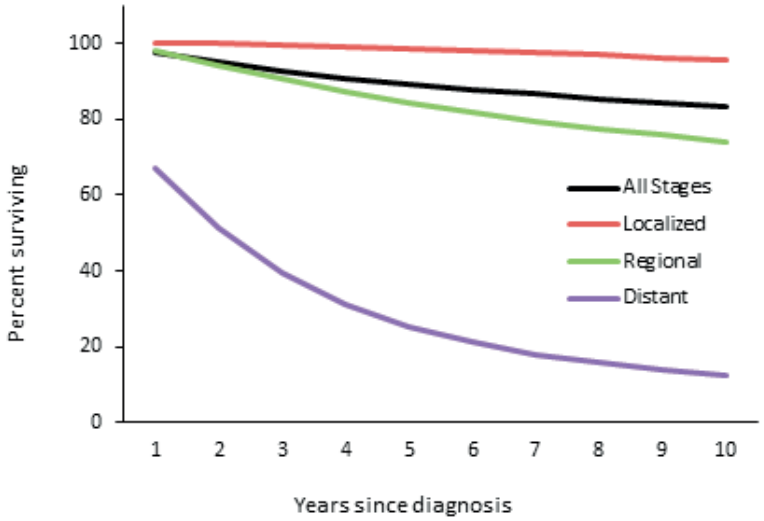

Figure 9 U.S. Survival Rates by Time Since Breast Cancer Diagnosis, 2000-2014.

or other sports according to the world cancer research fund. Further, primary prevention among high risk women may entail the use of medications that modulate estrogen receptors such as tamoxifen and raloxifene.

5. SECONDARY PREVENTION OF BREAST CANCER

Screening aims at finding breast cancer in early stages of the disease when tumors are less likely to have spread in the body. Screening can find in healthy, asymptomatic women in multiple different ways. For example, breast self-examination is a screening technique which allows women to examine their breast tissue at home for any physical or visual changes. More modern screening techniques include the use of digital mammography, ultrasound, magnetic resonance imaging (MRI), or Tomosynthesis. Mammography is an X-ray image taken of the breasts called a mammogram which has relatively high sensitivity and specificity. (12) Mammograms and other medical imaging techniques, allow radiologists to look for changes in breast tissue that could be pre-cursor, or early stage breast cancer.

Benefits of screening

True positives screening outcomes correctly identify abnormalities in the breast as cancer. True negatives correctly provide reassurance when no cancer is present in the breast. Chances of successful treatment and survival are higher for breast cancer diagnosed at

an early (localized) stage. Screening increases the number of early stage breast cancer and thereby improves breast cancer survival of the majority of screen-detected cancers. Next to life years gained, averting breast cancer deaths is an important goal of screening. In the absence of screening, more cancers are diagnosed at a more advanced stage of breast cancer. Consequently, more advanced treatment is necessary and if the cancer is lethal, life years are lost or quality of life is significantly reduced. Overall, regular screening at the population level provides large benefits for a small number of women, and harms among the majority of women who undergo screening but never develop breast cancer.

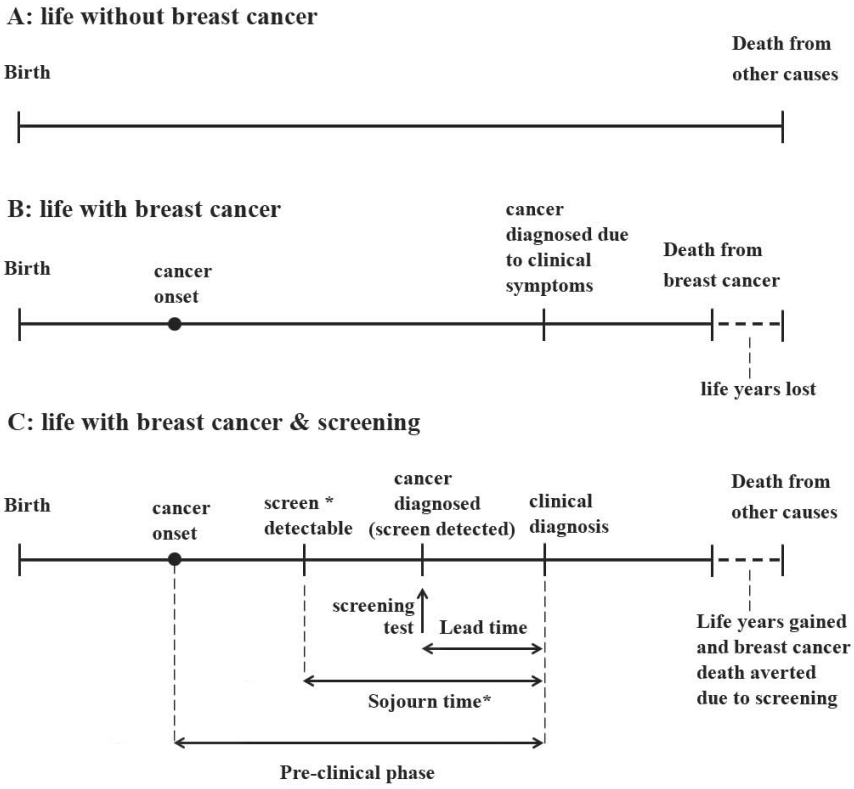

Figure 10 Three possible life-history scenarios. A: women without breast cancer, B:women with breast cancer who are not screened, C: women with breast cancer who are screened. In scenario C, the pre-clinical phase is the period of time between tumor inception and clinical diagnosis in the absence of screening. The *sojourn time* for a screening test, e.g., mammography, is the period of time within the pre-clinical phase that a cancer can be screen-detectable; this period can also be termed the *pre-clinical screen-detectable phase*. The point when the cancer is detected by screening depends on when the screening test is performed and the sensitivity of the screening test. The period before the sojourn time represents a period in which the tumor is present but undetectable by mammography. Should the sensitivity of mammography improve, or new types of screening tests evolve, the point of screen-detectability would be closer to tumor inception.

harms of screening

On mammograms, tissue may show up that looks like breast cancer, but may in fact be benign (non-cancerous) tissue. If the abnormalities are flagged as breast cancer and additional imaging shows that there is no cancer, this is called a false positive screening that may cause unnecessary anxiety and distress. One other important harm of breast cancer screening is over diagnosis. Overdiagnosis is the diagnosis of breast cancer by screening that would never have caused symptoms and be diagnosed in the absence of screening in a woman's lifetime. Besides false positives and overdiagnoses, false negative screening outcomes can also be harmful. False negatives may provide a sense of false reassurance while in fact cancer is growing in the breast. Lastly, regular screening increased the overall exposure to ionizing radiation and could lead to radiation-induced breast cancer in some cases.

Quality of life

Through screening, cancer diagnoses are advanced in time and in the majority of cases treatment can be less invasive and still be curative. In general, this results in a better quality of life for women who are diagnosed with breast cancer. For the majority of women who will never be diagnosed with breast cancer, mammography screening involves planning, travel, and waiting time. Before the actual mammogram, women may feel anxious or worry about the possible abnormal outcomes of the screening. Undergoing screening means that women have to undress from the waist up and may feel pain, pressure and discomfort in their breasts from the mammogram. After the examination, it takes some time before women are notified about the outcomes of the screening. This waiting period could be experienced as uncertain and stressful, but may be worth the reassurance, be it early diagnosis of breast cancer. Because women differ in their willingness to accept the harms of screening for potential benefits, a personal consideration is advised before attending screening.

6. BREAST CANCER TREATMENT

The majority of breast cancers will eventually metastasize without treatment. To prevent breast cancer death after diagnosis, the tumor is surgically removed and the patient usually receives adjuvant treatment to help decrease the risk of breast cancer recurring. Effective adjuvant treatments are commonly called systemic treatment and include: radiation, chemotherapy, and hormone therapy. There are additional supplemental treatments which might increase the effectiveness of these three treatments, but chemical, radiation, and hormonal treatments are the first ones considered to successfully treat breast cancer.(13)

If breast cancer is contained in the breast regions, localized treatment is considered. To help prevent local recurrence, a surgeon will try to remove the tumor, possibly with surrounding tissue, and treat the patient with radiation. The molecular nature of the tumor may also determine whether chemo- and/or hormonal therapy is used. Systemic treatment comes into play when breast cancer has spread or metastasized to the lymph nodes. In this stage of breast cancer, surgery alone is not curative anymore and systemic therapies are considered. Neoadjuvant breast cancer treatment is applied before surgical intervention aiming to stop the cancer growth and shrink the tumor size before surgical intervention.(14)

In the past, radical mastectomy of the breast was much more common. This involved surgery to remove the entire breast including the axillary lymph nodes and chest wall. Today, this medical procedure is less common and lumpectomy, i.e., breast conserving surgery, is more common. Lumpectomy aims to remove the cancer while preserving as much of the normal breast as possible.

7. EVIDENCE ON BREAST CANCER SCREENING

Large randomized trials have been introduced in 1960's and '70's and conducted throughout to the early 2000's. These include the New York Health Insurance Plan (HIP) (15), Malmö I and II (16), Swedish two county trial(17), Canada I and II (18), Göteborg (19), Stockholm(20), and the UK age trial(21). These trials compared breast cancer incidence and mortality among women invited to screening to women not invited to screening. While most studies found a reduction in breast cancer mortality from screening, controversy about the harms of breast cancer screening remains. In 2013, an independent panel extensively reviewed published work about the evidence on breast cancer screening to reach conclusions about the benefits and harms.(22) They found that 43 breast cancer deaths are prevented and 129 cases are overdiagnosed per 10,000 women screened triennially for 20 years from age 50 onwards in the UK.

In 2014, the International Agency for Research on Cancer (IARC) convened 29 independent experts from 16 countries to review the scientific evidence of various methods of screening for breast cancer.(23) The IARC concludes that women in the age range of 50 to 69 invited to mammography screening have a 23% breast cancer mortality reduction. Older women, in age ranges 70-74 also observed a substantial reduction in risk of breast cancer death. The reduction in risk of breast cancer death in studies among women aged 40 to 49 was less pronounced. Estimates of the cumulative risk of false positive results differ between organized programs and opportunistic screening. The cumulative risk of having at least one false-positive is about 20% for a woman who had 10 screens between the ages of 50 and 70 years. Overdiagnosis was estimated to be in

the range of %1 to 10% of all breast cancer diagnoses, with point estimate of 6.5% based on data from European studies that adjusted for both lead time and trends in incidence between screened and unscreened women.

8. CURRENT BREAST CANCER SCREENING GUIDELINES

Breast cancer screening guidelines recommending who should undergo screening, how often and at what ages vary within and among developed countries. The United States Preventive Services Task Force (USPSTF) 2016 guidelines recommend that women aged 50 to 74 years of age be screened with digital mammography every two years. According to the USPSTF, screening before age 50 is an individual decision women should make including their values about the (possible) harms and benefits of screening and attitude towards breast cancer risk.(24)

The American Cancer Society (ACS) recommends that women between ages 40 and 45 should have the choice to be screened based on their own considerations. Women between ages 45 and 54 are recommended to undergo annual mammography, followed by biennial screening between ages 55 and 74.(25) The International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), recommends women aged 50 to 69 to be screened and is next to the USPSTF one of the least intensive screening guidelines.(23) Overall, these guidelines agree that women aged 50 to 69 should be screened and vary to some extent in screening initiation and stopping age and screening interval.

9. MOVING TOWARDS RISK-BASED BREAST CANCER SCREENING

Historically, breast cancer screening guidelines have been age-based even though we know that at any given age there is variability in breast cancer risk due to earlier mentioned risk factors. By better understanding which women are at increased or decreased breast cancer risk, risk stratification can target screening to those who are most likely to benefit from different screening strategies than currently recommended. This could individualize breast cancer care and potentially reduce the population-level harms of screening and increase the benefits. Projections for groups of women differing in risk due to family history, breast density, polygenic risk, and other risk factors have been made under various screening and treatment interventions by breast cancer simulation models in the chapters of this thesis.

10. THE USE OF MODELS NEXT TO RANDOMIZED CONTROLLED TRIALS

Randomized clinical trials (RCT) are considered the gold standard to assess the effectiveness of breast cancer screening and treatment interventions. However, there are several reasons why modeling is essential to complement and extend the evidence from randomized trials. First, RCTs to assess screening and treatment interventions with cause of death as primary outcome are time consuming and relatively expensive to set up. Second, lifetime follow-up is difficult logistically as participants may move abroad, are lost to follow-up, or decide to stop their participation. Consequently, the long-term benefits and harms of medical interventions such as screening are difficult to assess. Third, trials are usually set up to evaluate a limited number of interventions. In screening this would be different starting ages, intervals, and treatment regimens. Fourth, in RCTs ethical concerns have to be taken into account. If routine screening of healthy women is part of usual practice, it could be unethical to include a non-screening (control) group in the trial that is at increased risk of late stage cancer. Finally, trials usually provide outcomes in a specific setting, for a specific group of people in a certain region with screening and treatment methods available at that time. We know screening and treatments methods have improved since the large mammography trials and are likely to have a different impact on breast cancer detection and breast cancer mortality. Simulation models can synthesize data on breast cancer epidemiology, population demographics, screening accuracy, and treatment effectiveness from different sources and produce outcomes for multiple screening and treatment strategies among varying risk groups.

Microsimulation model MISCAN-Fadia

In this thesis, MISCAN-Fadia which is an acronym for Microsimulation Screening Analysis – Fatal Diameter is used to make predictions about breast cancer incidence and mortality following from varying screening and treatment strategies, Chapter 2 of this thesis (26). The model simulates individual life histories from birth to death, with and without breast cancer, in the presence and in the absence of screening and treatment. Life histories are simulated according to discrete events such as birth, tumor inception, metastasis, and death from breast cancer or death from other causes. The model consists of four main components: demography, natural history of breast cancer, screening, and treatment. The impact of screening on the natural history of breast cancer is assessed by simulating continuous tumor growth and the "fatal diameter" concept. This concept implies that tumors diagnosed at a size that is between the screen detection threshold and the fatal diameter are cured, while tumors diagnosed at a diameter larger than the fatal tumor diameter metastasize and lead to breast cancer death.

Collaborative modeling

Erasmus Medical Center part of a collaborative modeling initiative called the cancer intervention and surveillance modeling network (CISNET). We use statistical modeling to improve understanding of cancer control interventions in prevention, screening, and treatment and their effects on population trends in incidence and mortality. Models are used to guide public health research and priorities, and they can aid in the development of optimal cancer control strategies. Collaborative modeling can enhance the rigor of modeling research using multiple independent models to answer the same research question. Conclusions supported by multiple independently developed models provide greater credibility than conclusions obtained from a single model.

11. RESEARCH QUESTIONS AND THESIS OUTLINE

This thesis consists of three main parts: 1. Breast cancer micro-simulation modeling, 2.Quantification of current breast cancer screening practice among average-risk women in the United States. 3. Outcome projections of risk-based screening strategies. This thesis concludes with a discussion of the work in this thesis in relation to the field of breast cancer screening.

PART 1: BREAST CANCER MICROSIMULATION: MODEL, METHODS, COMPARISON, AND VALIDATION

***Research question 1*: How can model description, comparison, and validation contribute to a better understanding of model predictions?**

Chapter 2 provides an overview of the past, current and future applications of breast cancer simulation model MISCAN-FADIA. In chapter 3, different approaches to modeling the natural history ductal carcinoma in situ are compared. Chapter 4 presents an external validation and comparison of CISNET models´ breast cancer incidence and mortality predictions to the observed clinical trial outcomes. Chapter 5 investigates the impact of model structure and model assumptions about tumor onset and progression on predictions of breast cancer incidence and mortality.

PART 2: QUANTIFYING THE HARMS AND BENEFITS OF AGE-BASED BREAST CANCER SCREENING IN THE UNITED STATES.

***Research question 2*: What are the benefits and harms of current age-based breast cancer screening in the United States?**

In chapter 6, the contributions associated with screening and treatment to breast cancer mortality reductions by molecular subtype-specific breast cancer are evaluated. In chapter 7, six simulation models use U.S. national data on incidence, digital mammography performance, treatment effects, and other-cause mortality to evaluate screening outcomes among average risk women. In chapter 8, we estimated the distributions of radiation-induced breast cancer incidence and mortality from digital mammography screening while considering exposure from screening and diagnostic mammography and dose variation among women.

PART 3: PROJECTING THE HARMS AND BENEFITS OF RISK-BASED BREAST CANCER SCREENING IN THE UNITED STATES

***Research question 3*: To what extent can risk-based breast cancer screening improve the harm-benefit ratio of current age-based screening guidelines?**

In chapter 9, we estimated the outcomes for various screening strategies in the U.S. tailored to women aged 50 years or older with various combinations of breast density and relative risk. Chapter 10 assessed screening approaches using first-degree family history (FH) and polygenic risk scores (PRS) to identify women for risk-based screening.

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PART ONE: Breast cancer microsimulation: model, methods, comparison, and validation