

Phd degree in Systems Medicine
(curriculum in Foundations of life sciences, bioethics and cognitive sciences)
European School of Molecular Medicine (SEMM) and University of Milan
Settore disciplinare. FIL/02

**ETHICAL ISSUES IN MAMMOGRAPHY SCREENING PROGRAMS AND
WOMEN'S DECISION-MAKING**

Giulia Ferretti

IEO, Milan

Matricola n. R10721 – R20

Supervisor: Prof. Gabriella Pravettoni, IEO and Unimi

Internal Advisor: Prof. Pier Paolo di Fiore, IFOM and Unimi

External Advisor: Prof. Stacy Carter, University of Sydney

Anno accademico 2016-2017

«He had nothing – no right, no duty, nor alternatives»
Arto Paasilinna, *The Howling Miller*

ABSTRACT

This dissertation deals with the ethics of mammography screening programs and related individual women's decision-making regarding whether to participate the program. While, on the one hand, mammography screening is proven beneficial in reducing breast cancer mortality at the population level, on the other hand routine screening also entails potential harmful outcomes for individuals such as *false positive* results and *overdiagnosis*. Intrinsic difficulties in evaluating the *magnitude* of benefits and harms of mammography, as well as in the identification of the target population, gave rise to a tremendous scientific, political and social debate, which is still ongoing. The latest up-to-date Western countries' guidelines recognize the complexity of assessing the net benefit of routine mammography screening, especially for women aged 40 to 49 who, nevertheless are *eligible* to participate programs on the basis of their personal evaluation and preferences. This dissertation argues that shared decision-making SDM constitutes the most effective way of respecting women's autonomy and incorporating their values in the decision-making process. Among different ethical theories, the dissertation claims that the ethics of care represents the most suitable normative ethical approach to justify and provide a concrete guide to SDM, which can also be applied to the inquiry of older women's mammography screening as well as to other clinical contexts. Finally, in order to provide physicians with a practical tool for eliciting women's values and preferences, the major themes of women experiencing breast cancer identified through a critical interpretative literature review are systematically presented and proposed as a basis for an empirical qualitative research on the issue.

TABLE OF CONTENTS

ABSTRACT	3
TABLE OF CONTENTS	4
LIST OF ABBREVIATIONS	7
INDEX OF TABLES AND FIGURES	9
INTRODUCTION.....	10
CHAPTER 1 - Prevention is better than cure	17
1.1. Introduction	17
1.2. Prevention is better than cure	18
1.3. Screening programs.....	21
1.3.1. Criteria for screening.....	21
1.4. Benefits of screening: mortality and morbidity reduction.....	23
1.5. General harms of screening	25
1.6. Cancer screening.....	29
1.7. Summary – Is prevention always better than cure?.....	33
CHAPTER 2 – Breast Cancer Screening.....	35
2.1. Introduction	35
2.2. The disease: breast cancer	38
2.3. Available treatments for breast cancer.....	39
2.3.1. Local treatments.....	40
2.3.2. Systemic treatments	42
2.4. The screening tool: mammography.....	44
2.4.1. Clinical trials: the need for scientific evidence.....	46

2.5. Benefits and harms of mammography screening	50
2.6. Recommendations, guidelines and mammographic screening programs	55
2.7. Summary	60
CHAPTER 3- Bioethics: methods and application	62
3.1. Introduction.....	62
3.2. Bioethical approaches and methodologies	63
3.3. Principle-based methodologies	64
3.3.1. Consequentialism	65
3.3.2. Deontology.....	66
3.3.3. Principlism.....	69
3.4. Concrete case analysis through principle-based methodologies	71
3.5. Virtue ethics.....	75
3.5.1. Defining virtues	77
3.5.2. Applying virtue ethics to bioethics	79
3.6. Care ethics	81
3.6.1. Features of the ethics of care.....	83
3.6.2. Defining care	88
3.6.3. The ethics of care in bioethics	90
3.7. Summary	92
 CHAPTER 4 - The ethics of mammography screening	 95
4.1. Introduction.....	95
4.2. A public health perspective on mammography screening	96
4.2.1. Public health ethics and screening.....	97
4.2.2. The principle of <i>utility</i>	99
4.2.3. Applying, specifying and balancing principles.....	101

4.3. Bioethics in mammography screening.....	106
4.3.1. Deciding what to do: delivering benefits, avoiding harms.....	107
4.3.2. Respecting autonomy: towards informed decision-making	111
4.3.3. Understanding options: statistical information and communication	113
4.3.4. Choosing the best option: information and preferences	116
4.4. Summary.....	118
 CHAPTER 5 - A different approach.....	 122
5.1. Introduction	122
5.2. Respecting autonomy: towards shared decision-making.....	124
5.2.1. Information and preferences in SDM: patient decision aids (PtADs)	130
5.2.2. Mammography screening PtDAs for women aged 40 to 49	136
5.3. Incorporating values in shared decision-making.....	139
5.3.1. Methodology.....	143
5.3.2. Content analysis: themes and moral concepts	150
5.4. Summary.....	158
 CONCLUSIONS	 161
 BIBLIOGRAPHY.....	 169

LIST OF ABBREVIATIONS

ACS – American Cancer Society

Als – Aromatase Inhibitors

AIDS – Acquired Immune Deficiency Syndrome

ALND – Axillary Lymph Node Dissection

BC – Breast Cancer

BCDDP – Breast Cancer Detection Demonstration Project

BCS – Breast-Conserving Surgery

CBE – Clinical Breast Examination

CT – Computed Tomography

CTFPHC – Canadian Task Force on Preventive Health Care

DA – Decision Aid

DIN – Ductal Intraepithelial Neoplasia

DM – Decision-Making

DCIS – Ductal Carcinoma *in situ*

ER – Estrogen

FBG – Fasting Blood Glucose

GP – General Practitioner

HBsAg – Hepatitis B Surface Antigen

HIP – Health Insurance Plan

HIV – Human Immunodeficiency Virus

IARC – International Agency for Research on Cancer

IDM – Informed Decision-Making

IGRA – Interferon Gamma Release Assay

LCIS – Lobular Carcinoma *in situ*

LIN – Lobular Intraepithelial Neoplasia

NBSSC – National Breast Cancer Study of Canada

NCI – National Cancer Institute

PDE – Principle of Double Effect

PEO – Population, Exposure, Outcome

PICO - Population, Intervention, Comparison, Outcome

PSA – Prostate Specific Antigen

PR – Progesterone

PtDA – Patient Decision Aid

RCT – Randomized Clinical Trial

SBE – Self Breast Examination

SDM – Shared Decision-Making

SLNB – Sentinel Lymph Node Biopsy

TNM – Tumour Node Metastasis

UK – United Kingdom

US – United States

USPSTF – US Preventive Service Task Force

WHO – World Health Organization

INDEX OF TABLES AND FIGURES

Tables

Table 1 - Wilson and Jungner's classical criteria for screening.....	22
Table 2 - Available preventive and early-detection cancer screening tests	31
Table 3 - Mammography screening trials: protocols and results.....	49
Table 4 - Current ACS, USPSTF, IARC, Cancer Australia and CTFPHC mammography screening recommendations for age groups	56
Table 5 - Moral considerations and related general principles	98
Table 6 - Paternalistic, IDM and SDM models of patient-physician relationship	129
Table 7 - Summary of the studies included in the review	147

Figures

Figure 1 - The relationship between illness and disease, and the roles of primary, secondary and tertiary prevention.....	20
Figure 2 - Sensitivity and specificity of screening tools and possible test results	27
Figure 3 - Statistical information on false positive results in conditional probability and natural frequency formats.....	115
Figure 4 - Graphical explanation of possible mammography screening results.....	133
Figure 5 - Infographics and natural frequency format of mammography false positive results	134
Figure 6 - Infographics representing mammography overdiagnosis	135
Figure 7 - Flowchart of the literature review.....	145

INTRODUCTION

This dissertation is a bioethical investigation of breast cancer screening programs and women's decision-making regarding whether to undertake routine mammography screening. In particular, the thesis addresses the questions regarding 1) the moral legitimacy of breast cancer screening programs as public health interventions, and 2) why and how physicians should involve women in a decision-making process aiming at eliciting and incorporating women's values and preferences.

Cancer is one of the leading causes of death around the globe and breast cancer is the most common among women in developed countries. Thanks to the advancements in screening technology and treatments for patients diagnosed with breast cancer, many promising approaches have changed the impact of cancer diagnosis dramatically for the better. Yet, notwithstanding these major improvements in breast cancer prognosis at all stages of disease, prevention and proactive management of risky breast lesions appears to be one of the best strategies to reduce fatalities from invasive breast cancer.

Historically, cancer was thought to advance along a series of progressive, increasingly dangerous steps and to show up with clinical symptoms in its late stages. This presupposition led to logical deduction that *early detection*, by breaking the sequence of disease development steps, must be beneficial for an affected individual. Hence, the diagnostic process changed towards the development of preventive medicine and diagnostic technology looking for evidence of disease in asymptomatic individuals.

In the breast cancer context, mammography screenings are considered the gold standard of *early detection* methods looking for the detection of tumours in their early pre-clinical and asymptomatic phase. The recognition and early treatment of such high-risk and/or pre-invasive lesions are known to help preventing progression to invasive disease and thus to reduce the overall breast cancer mortality at the population level.

By reducing cancer mortality, mammographic screenings are proven beneficial at the population level and therefore, in the past few decades, breast cancer screening programs became widespread in Western countries. However, the benefits of early detection – as it to say *mortality reduction* and *better prognosis* - come hand in hand with the possibility of unwanted potentially harmful outcomes for some individuals, such as *false positive* results and *overdiagnosis*. The former can be considered a diagnostic mistake that can be rectified after additional tests, while the latter occurs when benign or slow growing cancers are detected and subsequently treated. *False positive* test results improperly indicate the presence of the condition, but usually are proven mistaken after additional diagnostic interventions such as biopsy, radiation or even surgery. *Overdiagnosis*, instead, refers to the detection of a tumour that fulfils the pathological criteria for cancer, but which does not constitute a substantial health hazard for the patient. Indeed, *overdiagnosis* is the detection of a condition that would have not presented clinical symptoms, or led to death during patient lifetime.

The debate over the benefits and harms of mammography begun almost immediately after the introduction of screening programs, and cyclically draws renewed attention when new scientific studies regarding the magnitude of benefits and harms were reported. The “mammography debate” is a tremendous scientific, political and social debate, which has been in place in the last four decades and does not seem for the moment to be close to an end. The tone and means of the debate

have often been very forthright and sharp, bringing the “mammography controversy” to be one of the most publicly discussed scientific debates.

The controversy concerns both the magnitude and relevance of benefits and harms of mammography screening programs reported in several scientific studies. The *magnitude* refers to the extent to which benefits and harms are results of mammography screening. This kind of issues covers the quantification of positive and negative effects of the screening test, and thus represent a *scientific matter*. Instead, the *relevance* refers to the importance accorded to harms in relation to benefits of screening, namely the harmful side-effects on individuals and the mortality reduction in the given population. In this respect, issues regarding the *relevance* are *ethical issues* in that they represent the *value* or *disvalue* of different factors occurring within screening programs. The controversy regards both scientific and ethical issues, and it always intertwines various interests - such as individual and public ones -, and several stakeholders - agencies, policy makers, researchers, advocate groups.

Since the 1980s, most Western countries have introduced and implemented mammography screening programs addressing healthy and asymptomatic women older than 40. However, updates in the scientific evaluation of benefits and harms of breast cancer screening, as well as systematic reviews and meta-analysis of mammography RCTs, resulted in changes in the identification of the population of women to target and in recommended screening intervals. As a matter of fact, the latest up-to-date scientific evidence demonstrates that the benefit of undergoing breast cancer screening for women under 50 years old may be very little, and the cost in terms of *false positive* test results, unnecessary biopsies, *overdiagnosis* and subsequent *overtreatment* is relatively high.

In the last few years, following the latest publications of new data and evidence, the major agencies of Western countries - European Union, United States, Australia and Canada - have updated their guidelines on routine mammography screening. On the basis of the acknowledgment that current scientific evidence is either insufficient or low to assess the balance between benefits and harms of mammography for women aged 40 to 49, all guidelines identify women aged 40 to 49 as *eligible* for screening, yet delegate the decision whether to uptake mammography to individual women and their physicians.

The decision to undergo mammography, hence, depends on the *value* individual women place on the desirable effects – mortality reduction, better prognosis and eventually greater range of treatment options, as well as reassurance - and conversely on the *value* they place on the undesirable effects - especially *false positive* results and *overdiagnosis*. Therefore, given the fundamental role of patients' values and preferences in decision-making, different choices might be appropriate for individual women. The guidelines require physicians, not only to recognize and accept the variability of individual preferences in assessing the balance, but also to help women to arrive at decisions consistent with their own values and preferences.

Ethical issues emerge at all stages of population-based screening programs, from establishing a new screening procedure, to participants' recruitment and actually testing and monitoring the program. Hence, arising ethical considerations and analyses are of interest to citizens, health care professionals, and policy makers. The ethical analysis of mammography screening entails two kinds of moral inquiry. First, from the public health viewpoint, the analysis regards the moral justification of screening programs and particularly of mammography as means of public health effective interventions. Second, from a bioethical viewpoint, the ethical analysis focuses on the individual perspective and specifically on patient-physician models of

relationship, especially with regard to the mammography screening decision-making process for women aged 40 to 49. In addressing the ethical issues related to breast cancer screening programs, the thesis is structured as follows.

Chapter 1 presents the general features underlying population-based screening programs, and introduces the fundamental concepts of public health prevention. Specifically, the Chapter provides a conceptual distinction between *prevention* and *early detection*, highlights the fundamental difference between *testing* and *screening*, and introduces the concepts of *morbidity* and *mortality* reduction as the fundamental objective and justification for the implementation of population-based programs. Because scientific evidence on the effectiveness of screening programs comes from randomized clinical trials (RCTs), possible biases in evaluating RCTs data are investigated with particular attention to *overdiagnosis bias*. The issue of general harms of screening procedures and tests is then introduced by analysing the concepts of *sensitivity* and *specificity*, as well as the occurrence of *false positive* and *false negative* results. The need for the assessment of an acceptable trade-off results as the major challenge for the evaluation of population-based screening programs is discussed. Finally, a closer look is devoted to cancer screening programs using the elements introduced and analysed throughout the Chapter.

Chapter 2 explores in details the issues related to mammography screening programs, from their introduction in the 1980s to the most updated Western countries' implementations. First, a brief overview on breast cancer burden in terms of *incidence* and *mortality* is provided, as well as insight on the major pathological characteristics and currently available treatments for breast cancer. Mammography tool is then introduced as the one of the most effective means for reducing breast cancer mortality, and a brief history of the clinical trials and the following debate are presented. Particular attention is devoted to the definition, quantification and burden

of *false positive* results and *overdiagnosis*, which currently constitute the major concern in breast cancer screening context especially for women aged 40 to 49 years. The Chapter closes by presenting the latest up-to-date recommendations for mammography screening currently adopted in Western countries breast cancer screening programs, and provides an analysis of content focusing especially on the identification of women aged 40 to 49 as *eligible* for routine mammography.

Chapter 3, on the basis of the interdisciplinary character of mammography screening, which entails a continuous relationship among different fields of activity, presents the main theoretical frameworks and methodologies commonly applied in bioethics in order to provide a comprehensive overview of the different ethical approaches that can be applied in addressing the specific moral issues of mammography screening. Specifically, the Chapter outlines the major principle-based (consequentialism, deontology and principlism) and non principle-based bioethical methodologies (virtue ethics and the ethics of care), by providing theoretical elements as well as methods of their application to concrete case analysis in order to introduce and explore possible bioethical approaches to mammography screening evaluation.

Chapter 4, by taking advantage of and systematically applying the theoretical elements presented in the previous Chapter, provides an ethical analysis of mammography screening from both the public health viewpoint and the individual perspective. Regarding the public health ethics analysis, the arguments focus on the moral justification of screening programs and particularly mammography, highlighting the intrinsic tension between the public and the individual perspective on health. While from the individual perspective, the ethical analysis focuses on patient-physician models of relationship (paternalism and informed decision-making), which are critically analysed with regard to mammography screening

decision-making process. Particular relevance is put on the challenges of understanding and communicating statistical evidence and on the uncertain balance between benefits and harms of screening. Following the age-group division endorsed by most of Western countries' guidelines, the ethical analysis addresses especially those women aged 40 to 49, who face the bigger uncertainty. The main argument of the Chapter aims at showing the unsuitability of both paternalism and informed decision-making model in providing an ethical guidance in the context of mammography screening due either to the lack of normative power or the failure in truly respecting women's autonomy.

Chapter 5 proposes shared decision-making (SDM) model of patient-physician relationship as a means to enable patients in making truly informed and value-based choices. The intrinsic fundamental role of the *partnership* between patients and physicians is described in details, and related to the ethics of care normative framework. A concrete methodology for the application of SDM in the context of mammography screening is provided, as well as an analysis of mammography patient decision aids (PtDAs) as effective tools to help patients understanding information and incorporating their values in the decision-making process. Furthermore, the Chapter argues in favour of the ethics of care as the most suitable normative ethical approach to justify and provide a concrete guide to SDM. Finally, in order to provide physicians with a insights on women's values informing decision-making, a review and a critical analysis of the literature on women's experience of breast cancer are presented and four major themes are identified.

CHAPTER 1

Prevention is better than cure

1.1. Introduction

The Chapter ahead presents the general concepts underlying population-based screening programs. The aim of the Chapter is to introduce the major concepts of prevention and to clarify the terminology related to the issue. Firstly, the chapter presents a brief analysis of modern medicine and outlines the implementation of preventive strategies. Following the World Health Organization categorization of *primary*, *secondary*, and *tertiary* prevention, preventive strategies are hence introduced and features of the three types of prevention are outlined. The distinction between *prevention* and *early detection* is highlighted and definitions of the two are provided, as well as the fundamental difference between *testing* and *screening*. The next paragraph deals with the main features of screening programs as widespread strategies of *secondary prevention*. Specifically, the aim, scope and rationale of screening programs are defined and the classic criteria for screening are analysed.

The next paragraph addresses the benefits of screening by outlining *morbidity* and *mortality* reduction at the population level as the fundamental objective and justification for the implementation of population-based programs. Because scientific evidence of *morbidity* and *mortality* reduction comes from randomized clinical trials that might be subject to biases, such biases are investigated with particular attention to *overdiagnosis bias*. The issue of general harms of screening procedures and tests is then introduced by analysing the concepts of *sensitivity* and *specificity*, as well as their

consequences (*false positive* and *false negative* results). The need for the assessment of an acceptable trade-off results as the major challenge for the evaluation of population-based screening programs and is hence discussed. Finally, a closer look is devoted to cancer screening programs using the elements introduced and analysed throughout the Chapter in order to provide the conceptual framework needed to understand the complexity and challenges of cancer screening programs.

1.2. Prevention is better than cure

The popular adage “prevention is better than cure” stems from the assumption that it is possible to distinguish between *illness* and *disease*. As pointed out by John Brodersen and colleagues (Brodersen, Schwartz, and Woloshin 2014), «*illness* refers to the subjective experience of disease – symptoms» (*ibid.* p.1), while «*disease* refers to the objective structural or functional abnormalities that can make people feel sick and may shorten life» (*ibid.*). Through improvements in technology it became possible to visualize pathological abnormalities that account for symptoms. In the twentieth century, medicine has gone through tremendous changes due to technological improvements and cultural shifts, of which the one of focusing on *disease* rather than on *illness* had a significant impact on modern medicine.

Traditionally, diagnosis and clinical management were based on clinical signs and symptoms together with patient’s medical history. The improvements in diagnostic technologies and the development of preventive medicine expanded the possibilities of medical intervention to the management of symptoms in chronic patients and the individuation of risks for developing a condition in asymptomatic individuals (Chiolero et al. 2015). The goal of medicine moved away from a pure cure-based approach and progressively shifted toward detecting and, whenever possible, preventing diseases. Modern pathology accounts mostly for the rise of preventive medicine, the branch of medical science that deals with methods of preventing the

occurrence of disease. Preventive medicine strategies can be divided in three realms on the basis of their core aim: primary, secondary, and tertiary prevention.

Primary prevention aims at preventing the initial occurrence of a disease and reducing its *incidence*. The widely accepted formal definition of *primary prevention* is any «action taken to avoid or remove the cause of a health problem in an individual or in a population before it arises» (WHO 2011, p.8). Examples of primary prevention actions are vaccination and access to clean water and sewage systems.

By contrast, *secondary prevention* aims at identifying the disease at an early stage, in order to reduce its associated *morbidity*¹ and *mortality*². A widely accepted formal definition of *secondary prevention* is that of «actions to detect a health problem at an early stage in an individual or a population, facilitating cure, or reducing or preventing spread, or reducing or preventing its long-term effects» (*ibid.*). The aim of secondary prevention is therefore the identification and early treatment of asymptomatic individuals who are either risk factors carriers or have developed pre-clinical disease, but in whom the disease is not yet clinically apparent.

Finally, *tertiary prevention* aims at reducing the progression of the disease, and at improving physical functioning and quality of life. The widely accepted formal definition is that of «actions to reduce the impact of an already established disease by restoring function and reducing disease related complications» (*ibid.*). Well-known examples of tertiary prevention are aspirin for patients who have had heart attacks, and anticoagulants for patients who have had ischemic strokes. **Figure 1** illustrates

¹ Morbidity designates the unhealthy state of individuals, meaning the state of being diseased. Prevalence is the measure used to determine the level of morbidity in a population (e.g.: the number of people having the disease).

² Mortality designates the state of being dead of an individual. Mortality rate is the measure used to determine the number of deaths due to a disease divided by the total population.

the relationship between illness and disease, and the role of primary, secondary and tertiary prevention (adapted from *Brodersen, Schwartz, and Woloshin, AMPIS, 2014*).

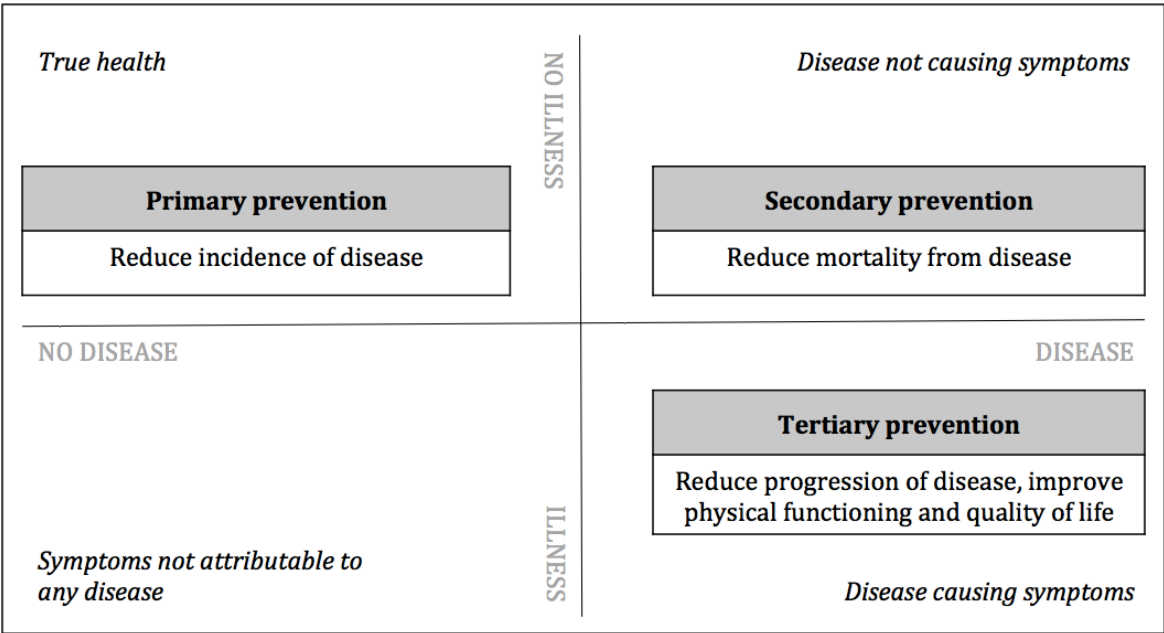


Figure 1 - The relationship between illness and disease, and the roles of primary, secondary and tertiary prevention

Before moving on, it is important to stress the distinction between *testing* and *screening*. Testing refers to those procedures performed on individuals who have already been identified at high-risk for the condition. Therefore, testing is a form of a diagnostic tool aimed at confirming the suspected disease. Screening, instead, refers to those procedures directed at an asymptomatic population, no member of which is considered to be at greater risk for the screened-for condition. Hence, a positive screening result only indicates a predisposition for the disease, and requires further investigation in order to confirm the diagnosis. For this reason it has been proposed not to name participants to these programs “patients”, for the term “patient” refers to the individual with clinical signs or symptoms of a disease (Breatthauer and Kalager 2013).

1.3. Screening programs

According to the World Health Organization (WHO)³, primary and secondary preventions are among the activities that include the institution of population-based *screening programs*. In medicine, “screening” may be broadly defined as the concept of detecting disease in individuals who have no clinical signs or symptoms of the screened-for condition. Juth and Munthe (2012) provide a definition of screening as «the use of medical investigation or testing methods at the initiative of health care or society for the purpose of investigating the health status of individuals with the aim of selecting some of these for possible further treatment from a large population of people that is not united by previously recognised risk or symptoms of disease» (Juth and Munthe 2012, p. 10-11). Population-based screenings refer to those tests offered to all individuals in a target population, as part of an organised program. Members of the target population often share some characteristics - such as gender and age - that may not be *per se* related to the screened-for condition, but which usually entail a potentially heightened risk for the disease. In population-based screening programs, hence, tests are systematically offered to all the individuals in a defined target group, none of which is previously considered at high-risk for the screened-for condition. Finally, the basic structure of any population-based screening program is made of four components: 1) the disease/condition, 2) the screening test, 3) the available treatment, and 4) the screened population (Newson 2011).

1.3.1. Criteria for screening

The general structure of screening programs and testing procedures were already structured in 1968 when the WHO proposed a framework of principles for the ethical evaluation of population-based programs (Wilson and Jungner 1968). The classical

³ Available at: <http://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html> (last accessed on 10.13.2017).

criteria for screening are listed in **Table 1**.

Wilson and Jungner's classical criteria for screening
1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognized disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognizable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case finding should be a continuing process and not a "once and for all" project

Table 1 - Wilson and Jungner's classical criteria for screening

The authors of the 1968's general criteria for screening programs did not establish any hierarchy between these principles, although they emphasised that the second – the principle regarding the availability of an accepted treatment – is of particular relevance (Wilson and Jungner 1968). Interestingly, the lack of hierarchy between ethical principles recalls the *principlism ethical theory* that Beauchamp and Childress proposed almost a decade later, in 1979 (Beauchamp and Childress 2013). Overall, the classical criteria framework emphasized that screening should be justified according to the seriousness of the disease screened, the availability of effective intervention in an early stage, the latent or early disease stage should be recognisable and examination methods should be acceptable to the public, the natural history of the disease, including its development from latent to active stage should be adequately understood.

These classic criteria have been developed into analytic frameworks that are still applied nowadays (Croswell, Ransohoff, and Barnett 2010), and have been

extensively quoted, criticized and revisited (Goel 2001). For example, some have argued that, unfortunately, it seems that they are not always applied for improving screening programs for cancer (Bretthauer and Kalager 2013). The importance of Wilson and Jungner's classic criteria is widely acknowledged, although they have been adapted to meet new medical challenges and priorities, such as developments in genetic medicine consequent to the sequencing of the human genome⁴. Thanks to rapidly advancing molecular diagnostic techniques, it is now possible to detect a growing number of diseases in their pre-pathological stage. Therefore, several approaches to genetic screening policy-making have been developed, based on different sets of criteria (Anderman et al. 2008).

1.4. Benefits of screening: mortality and morbidity reduction

The most important justification for the introduction of a population-based screening program is its efficacy in reducing morbidity and/or mortality associated with the screened-for condition (Juth and Munthe 2012). The need for strong evidence of incidence and mortality reduction is met by the performance of clinical trials aiming at proving the effectiveness of screening. Among different types of trials, randomized clinical trials (RCTs) are considered the "gold standard" for the scientific evaluation of clinical interventions, treatments, and diagnostic or screening tools (Breatthauer and Kalager 2013).

Nevertheless, even in well-designed RCTs, the evaluation of the efficacy of screening programs might be influenced by some powerful biases (Croswell, Ransohoff, and Barnett 2010). For example, individuals who voluntarily participate in preventive intervention programs tend on average to be wealthier and to live longer than those not taking part in such invitations. This bias is known as the *healthy*

⁴ For example, in 2003 the UK's National Screening Committee published its own criteria for assessing the viability, appropriateness, and effectiveness of screening programs, which hold in high regard the specific challenges of genetic screening.

volunteer bias, which can mislead researchers and policy-makers into believing that better outcomes might be due solely to early detection of the condition.

Moreover, as already mentioned, one of the primary aims of screening is to detect the disease in its pre-clinical phase in order to provide more effective treatments in terms of prognosis, survival and reduced mortality. However, advancing the date of diagnosis does not necessarily prolong the lifespan of an individual, who can be only aware of the existence of the condition for a longer period of time (Bretthauer and Kalager 2013). This bias in erroneously prolonging the survival time of patients with screen-detected diseases is labelled as the *lead-time bias*. In addition, screenings tend to detect indolent and slow-growing pathologies, while the more aggressive ones often show up between screening intervals (Croswell, Ransohoff, and Barnett 2010). The *length bias* hence leads to boost the effect of early detection on survival rates, when instead screening had only detected those conditions with innately more favourable prognoses.

Finally, as an extreme case of *length bias*, some screened-detected conditions would not even have clinically presented itself in an individual's lifespan, either because they have no growing potential, or because they develop so slowly that the individual would probably die of another cause before the disease could develop (Welch, Schwartz, and Woloshin 2011) (Zahl, Jørgensen and Gøtzsche 2013). In general, *overdiagnosis* occurs as a direct result of screening tests, use of increasingly sensitive tests, incidental findings on routine check-ups, and the widening of diagnostic criteria to define which conditions require interventions (Jørgensen and Gøtzsche 2009). However, *overdiagnosis* might also occur as the indirect result of clinicians' fear of missing a diagnosis and the related patients' need for reassurance (Chiolero et al. 2015). Finally, *overdiagnosis bias* involves a great potential harm to screening participants, who might be unnecessarily labelled with the screened-for

disease's diagnosis and consequently undergo unnecessary treatments and interventions (*overtreatment*), which generate harms and costs without providing any objective benefit (Plutynski 2012) (Carter et al. 2016) (Marmot et al. 2013).

Given the possible occurrence of such biases and the difficulties and costs of performing RCTs, reaching a consensus on the quantification of screening efficacy might be challenging, especially for diseases like cancer, whose outcome of interests (death or diagnosis) can occur over a 10-year long period of time. Indeed, several of the studies published on this issue reported contradictory results regarding the very same screening (Breatthauer and Kalager 2013).

1.5. General harms of screening

All population-based screening programs are designed to offer the benefits of either prevention or early detection, but inevitably entail some risks of harm for the participants. In general, the kinds of harms shared by all the programs may be grouped into three basic categories: 1) the inconveniences of participating in the program; 2) the unpleasantness of the test; and 3) the anxiousness of waiting for the test results (Dawson 2011). Certainly, the importance of these categories of harms may vary according to the nature of the screened-for disease, the test procedure and the participants' personal circumstances. For example, inconveniences of participating the program may depend on the distance between the domicile and the clinic performing the screening, as well as on the burdens of taking off work. And again, waiting for the results of an HIV test or a mammography creates more worries than waiting for the results of diabetes test because of the life-threatening nature of AIDS and cancer (Newson 2011).

As already mentioned, secondary prevention targets asymptomatic populations and usually the overwhelming majority of people participating the

program turns out not having the screened-for condition. The reassurance of not having the condition is usually considered a benefit outweighing the harms of inconvenience, unpleasantness and worries. Yet, it has been argued that such a reassurance is not often perceived as a massive benefit in itself, for the members of the screened population usually do not even consider having the condition prior to invitation to undergo the test (Dawson 2011).

Nevertheless, the above-outlined general harms are considered somewhat mild, especially in comparison to the possible damages that might emerge from inaccurate results of screening tests. Indeed, some tests are highly accurate, in that they are based on the presence or absence of antibodies or markers⁵ (Troop 2000). Given the binary nature of the test outcome, such screenings are highly accurate in discriminating between individuals who do and do not need further investigations. However, this is not always the case, for some conditions appear over a spectrum, presenting a continuous distribution of values and variables to be measured. Therefore tests for such conditions require a human judgment to interpret results and eventually detect abnormalities or changes accounting for a heightened risk⁶. In these cases, a threshold has to be defined in order to trigger further diagnostic investigations or treatments⁷. The threshold position in the distribution of variables should depend on morbidity and mortality associated with the condition in question, as well as on the resources available in specific health settings (Shickle and Chadwick 1994) (Dawson 2011).

Unfortunately, no screening test is perfect, in that its *sensitivity* (the proportion

⁵ For example the hepatitis B surface antigen (HBsAg) test for hepatitis B, and the interferon gamma release assay (IGRA) test for tuberculosis.

⁶ For example, the prostate specific antigen (PSA) test for prostate cancer, and the fasting blood glucose (FBG) test for pre-diabetes or diabetes, mammography for breast cancer and Pap smear test for cervical cancer.

⁷ A threshold is a cut-off point above which the result is considered positive and below which it is considered negative.

of positive results correctly identified as such) and *specificity* (the proportion of negative results correctly identified as such) cannot be 100% accurate at the same time. A test with high sensitivity will likely maximise the detection of the condition in the screened population, reducing the rates of false negative results, but inevitably increasing the rates of false positive results. On the other hand, a high specificity will maximise the detection of individuals without the condition, reducing the rates of false positive results while increasing the rates of false negative ones. In general, by lowering the threshold sensitivity increases, while by rising the threshold specificity increases (Dawson, 2011). Therefore, an increase in specificity is usually at the expense of sensitivity and *vice versa*, as shown in **Figure 2** (adapted from *Shickle and Chadwick, Journal of Medical Ethics, 1994*).

	Disease present	Disease absent
Test positive	True positive (A)	False positive (B)
Test negative	False negative (C)	True negative (D)
Sensitivity	Specificity	
The proportion of people with the disease in whom the finding is positive	The proportion of people without the disease in whom the finding is negative	
$A / (A + C)$	$D / (B + D)$	

Figure 2 - Sensitivity and specificity of screening tools and possible test results

There are benefits and costs associated with each of the four possible permutations of false positive and false negative results and there is always a trade-off between the two, so that policy-makers must agree to a reasonable level of false results (Troop 2000). Whenever a screening program is evaluated, true and false results are balanced in terms of benefits and costs both for the screened population as a whole and for individuals participating in the program. Usually, true positives tend to be considered more than the false ones, and the reassurance associated with negative

results also plays an important role in the assessment of a given program. However, the associated costs of false results on the individuals tend to be unaccounted for in the program evaluation (Dawson 2011).

Despite this seeming lack of attention paid to the burden of false results, the harm to individuals might be of great significance, both from the physical and the psychological viewpoint. In fact, false negative results – the failures in identifying the disease – entail the false reassurance and are liable to the development of the disease, which could possibly show up clinically within the screening intervals (Breatthauer and Kalager 2013). They might also result in a loss of confidence in the program and consequently in a drop in the number of individuals participating (Newson 2011). Finally and paradoxically, because of the litigations in response to false negative results, these can also prompt an increase in further diagnostic investigation for individuals with slightly abnormal results (Newson 2011).

On the other hand, false positive results – the erroneous detections of the disease - although usually ruled out after further investigation, raise three main reasons for concern. First, false positive results generate negative psychological consequences such as anxiety, depression and feelings of morbidity (e.g.: changes in the overall perception of an individual's health status) (Croswell, Ransohoff, and Barnett 2010). Second, they trigger a cascade of further diagnostic investigations, which can be more invasive than the screening test itself (e.g.: diagnostic biopsies for cancer) (Breatthauer and Kalager 2013) (Croswell, Ransohoff, and Barnett 2010). Finally, on the long-term, frequent false positive results can cause an economic burden both for the individual and for the health system (Dawson 2011).

The threshold of a screening test is therefore an important feature for the ethical evaluation of the program in question. In discussions regarding screening, the

trade-off between sensitivity and specificity is often referred to as a possible ethical dilemma, for it establishes a prioritization of some benefits over risks of harm (Plutynski 2012). While ethical grounds for prioritizations have been proposed⁸, other dubious factors may still influence the decision, including the public and the media perception of a condition and consequent political requirements to adopt public health intervention about the disease in question (Shickle and Chadwick 1994) as well as vested interests (Newson 2011) mainly pushed by the pharmaceutical industry (Goldacre 2012).

1.6. Cancer screening

Cancer is the second leading cause of death worldwide, accounting for approximately 12 millions new cases and 8 millions deaths per year (WHO 2012). Hence, it represents a massive burden, which is expected to increase due to growth and aging of the population. The World Health Organization (WHO) estimates that a substantial proportion of cancer burden can be prevented through the wide dissemination and application of existing scientific cancer control knowledge, especially primary and secondary prevention that are known to significantly reduce fatalities from cancer (American Cancer Society 2015). Among the strategies of prevention, screening tests for some types of cancers have been proven effective in reducing *morbidity* and/or *mortality* at the population level, and therefore several developed countries have introduced population-based programs. Cancer screening is indeed one of the most important examples of population-based screening programs, especially for the “five big killers”: cervical, colorectal, breast, lung and prostate cancer that account for most of the worldwide cancer-related burden of disease (WHO 2012).

⁸ Shickle and Chadwick claim that sensitivity should be prioritized when the missed diagnosis can cause severe consequences to the individual or the society, while the consequences of a false positive result are not substantial. On the other hand, specificity should be preferred when the diagnosis of the screened-for disease creates anxiety or stigma, further diagnostic investigation is particularly burdensome and there are other available means of early detection (Shickle and Chadwick 1994).

In general, cancer screenings – just like all screenings - aim at detecting individuals who are at heightened risk for developing the condition, or already have the condition in its early pre-clinical asymptomatic phase (Breatthauer and Kalager 2013). This double strategy of screening reflects the above-mentioned categorization of tests' procedure in either *prevention* or *early detection* of the disease. The purpose of preventive strategies is to detect and remove precursor lesions and thereby reduce the incidence (morbidity) within the screened population. Conversely, early detection strategies aim at detecting early stage of the disease in order to provide more effective treatments resulting in reduction in mortality rates within the screened population.

Some cancer screening tests are able to identify individuals who need treatment for the condition in question (e.g.: cervical smear test for cervical cancer, colonoscopy for colorectal cancer), while others identify individuals at high risk for developing the condition. These individuals will then require further investigation in order to confirm the suspected condition and establish whether they need treatment (e.g.: mammogram for breast cancer, chest X-ray and computed tomography (CT) scan for lung cancer, PSA test for prostate cancer). **Table 2** summarizes the features as well as the preventive or early detection approach of the most common screening tests currently available for cervical, colorectal, breast, lung and prostate cancer.

Any screening test for a given condition can be more or less intrusive for participants, and as any medical procedure, entails some possible harms or side effects. Therefore, a traditional concern regards whether the harms of the screening procedure are outweighed by the benefits to participants (Jørgensen 2013). This concern comes to be especially important in the context of cancer screening, because of the specific features of the test itself and the enormous burden of cancers worldwide. As mentioned above, the assessment of the balance between benefits and

harms provides the rationale for the introduction and implementation of screening programs. Nevertheless, evaluating such balance might be a hard task, in that several issues and different perspectives shall be taken into account (Plutynski 2012).

	PREVENTION Detecting and removing precursor lesions Reduce incidence	EARLY DETECTION Detecting early stage of the disease Reduce mortality
Cervical cancer Cervical Smear test	YES	YES
Colorectal cancer Faecal Occult Blood Tests (FOBT) Colonoscopy Flexible Sigmoidoscopy	NO YES YES (distal colon)	YES YES YES (distal colon)
Breast cancer Mammography Ultrasonography Magnetic Resonance Imaging (MRI)	NO NO NO	YES YES YES
Lung cancer Chest X-ray Computed Tomography (CT)	NO NO	YES YES
Prostate cancer Prostate Specific-Antigen (PSA)	NO	YES

Table 2 - Available preventive and early-detection cancer screening tests

Beside the possibility of false positive and false negative results, another common pitfall of cancer screening programs is the occurrence of *overdiagnosis* (Hofman 2014). There is no consensus on the definition of *overdiagnosis* and several interpretations have been proposed, often leading to misunderstandings among experts (Welch and Black 2010) (Marmot et al. 2013) (Chiolero et al. 2015) and great confusion in the debate regarding cancer screening (Moynihan, Doust, and Henry 2012) (Brodersen, Schwartz, and Woloshin 2014) (Parker, Rychetnik, and Carter 2015) (Carter et al. 2016). In general, *overdiagnosis* is the diagnosis of a condition that would have not presented its clinical symptoms, or led to death during patient's lifetime (Welch, Schwartz, and Woloshin 2011). Specifically, in the context of cancer, *overdiagnosis* refers to the detection of a tumour that fulfils the pathological criteria for cancer, but which does not constitute a substantial health hazard for the patient (IARC 2016).

Notably, in the context of cancer the inability to identify reliable predictors for the progression from detected high-risk lesions to invasive carcinoma prevents the individualization of risk-management and often treatment is recommended to all patients in order to reduce the risks of recurrence and mortality (Brodersen, Schwartz, and Woloshin 2014). Therefore, in addition to the burden of false-positive test results mentioned above, *overdiagnosis* exposes patients to lengthy and unnecessary additional diagnostic tests and possible worthless treatments and interventions (*overtreatment*) and disease surveillance that are known to cause physical and psychosocial harms, especially in cancer context (Marmot et al. 2013). As it is well known, every treatment has side effects that, on the side of patients, are typically outweighed by the gained benefits. The side effects of cancer treatments such as surgery, chemotherapy, and radiation therapy are very burdensome and often significantly challenge patients' quality of life and overall well-being, resulting in great psychological distress.

Among cancer screenings, the quantification of benefits and harms is a complex task because of the differences between studies' designs, statistical interpretation of RCTs data – including possible biases - and lack of consensus on the definition of harms, often leading to great scientific as well as public debates. These difficulties are especially evident for early detection screening programs such as PSA test for prostate cancer, CT and chest X-ray for lung cancer, and mammography for breast cancer. However, lately a growing body of literature has been focusing on harms entailed in cancer screening contexts – and especially on *overdiagnosis* -, eventually resulting in a change in guidelines and recommendations regarding specific screening tests. For example, results from two distinct meta-analyses of RCTs have supported the discharging of the routine use of PSA tests for prostate cancer, which has been carried out for decades (Chapman, Barratt and Stockler 2010)

(Djulbegovic et al. 2010) (Ilic et al. 2013). As new evidence from meta-analyses and systematic reviews becomes available, cancer screening programs should be re-evaluated in light of eventual shifts in the quantification and assessment of benefits and risks (Plutynski 2012).

1.7. Summary – Is prevention always better than cure?

The shift from *illness* to *disease* and the implementation of preventive medicine represent an historical change in modern medicine. While on the one hand preventive population-based programs are beneficial at reducing morbidity and/or mortality at the population level, on the other hand screening programs entail the possibility of great harms for the individuals. Given the threshold between *sensitivity* and *specificity*, some individuals in the screened population will necessarily receive a *false positive* or a *false negative* result from the test. The first will be ruled-out after additional diagnostic tests mainly causing mild psychological distress, while the latter could possibly result in the development of the condition between screening intervals and therefore in a poorer prognosis despite the initial reassurance. Another possible harm of screening program is *overdiagnosis*, which has the potential of resulting in *overtreatment* and hence in a great unjustifiable harm to the individual.

Therefore, while prevention and early detection are promising and effective approaches to reduce fatalities – especially from cancer – at the population level, still the burden to individuals participating screening programs can be significantly high. From the public health perspective, the ethical evaluation of screening programs relies on the balance between benefits and harms at the population level, setting an acceptable trade-off between the collective good of reducing morbidity and/or mortality, and the individual harm of screening pitfalls. However, individuals undergoing screening should be informed about the possible harms and should have the possibility of deciding whether to take the risk of possible harms for the sake of

possible benefits. In other words, individuals should be enabled to assess the balance of benefits and risks of screening, beside collective considerations. Finally, as new evidence from systematic reviews and meta-analyses on benefits and risks – especially *overdiagnosis* - becomes available, population-based screening programs should be re-evaluated and guidelines should eventually change according to the latest up-to-date scientific evidence.

CHAPTER 2

Breast Cancer Screening

2.1. Introduction

Mammography for breast cancer is the most hotly debated screening program, and it has always been since its introduction in many Western countries in the late 1970s and 1980s. Organized population-based screening programs most commonly offer standard mammography and are «characterized by invitations to join a target population at given intervals, systematic recalls for the assessment of detected abnormalities, and delivery of test results, treatment, and follow-up care, with regular monitoring and evaluation of the program and a national or regional team responsible for service delivery and quality» (Lauby-Secretan et al. 2015, p. 2355). Generally mammography screening programs target women between the age of 40 to 75, by offering X-ray examination every two or three years. Nevertheless, differences in the age-group settings and in the regularity for check-ups arise among countries and have varied widely over the past few decades (Reynolds 2012). These differences are due to the acceptance and/or revision of new evidence about the effectiveness and safety of the screening test (Feig 2014).

Shifts in guidelines and consequently in nation-wide breast cancer screening programs closely followed the famous “mammography controversy” or “mammography debate”, a tremendous scientific, political and social debate which has been in place in the last four decades and does not seem for the moment to be close to an end. The tone and means of the debate have often been very forthright

and sharp, bringing the “mammography controversy” to be one of the most publicly discussed scientific debates. Indeed, the controversy regards both scientific and ethical issues, and it always intertwines various interests - such as individual and public ones - and several stakeholders - agencies, policy makers, researchers, advocate groups (Begg 2002).

The controversy concerns both the magnitude and relevance of benefits and harms of mammography screening programs described in several studies. The *magnitude* refers to the extent to which benefits and harms are results of mammography screening. This kind of issues covers the quantification of positive and negative effects of the screening test, and thus represent a *scientific matter*. Instead, the *relevance* refers to the importance accorded to harm in relation to benefits of screening, namely the harmful side effects for individuals and the mortality reduction in the given population. In this respect, issues regarding the *relevance* are *ethical issues*: they clearly represent the *value* or *disvalue* of different factors occurring within screening programs.

Even though the “mammography debate” seems to revolve either on disagreement regarding the scientific matter of the quantification of benefits and harms or on disagreement regarding the ethical evaluation of screening programs, at a closer look there is no such sharp theoretical distinction. On the contrary, *scientific/epistemological* and *ethical* aspects are highly interrelated in the debate, often resulting in greater confusion and misunderstandings (Juth and Munthe 2012). For example, a recent study shows that values appear to inform experts’ position in breast cancer screening debate both at the *epistemic* level - concerning how evidence should be created and used - and at the *ethical* level - regarding what has to be considered good, right and important (Parker, Rychetnik and Carter 2015).

As seen in Chapter 1, the basic structure of any screening program entails four components – the disease, the screening tool, the available treatment, and the target population – each of which needs to comply with the classic criteria in order for the screening program to be justifiable (see Chapter 1.1.2 *Criteria for screening*). The Chapter ahead aims at investigating each of the four components of breast cancer screening programs. First, a brief overview on breast cancer burden in terms of *incidence* and *mortality* is provided, as well as insight into the major pathological characteristics and definitions of tumour *stage* and *grade*. Second, currently available treatments for breast cancer are presented, divided in *local* – surgery and radiation therapy - and *systemic* ones – chemotherapy, hormonal therapy and targeted therapy. Together with a brief explanation of each of the clinical options, the major side effects are analysed especially in terms of the overall wellbeing of patients. Third, mammography as a screening tool is introduced and a brief history is outlined in order to highlight the major concepts and themes characterising the debate, from the *early detection gospel* to the first controversy. Specifically, the focus is placed on clinical trials as a means for scientific evaluation of the effectiveness and safety of mammography. Following the argument of Chapter 1, *Paragraph 2.5*. analyses the fundamental benefits in terms of mortality reduction and better prognosis, as well as the possible harms. Particular attention is devoted to the definition, quantification and burden of *false positive* results and *overdiagnosis*, which currently constitute the major concern in breast cancer screening context especially for women aged 40 to 49 years.

The last paragraph presents the latest up-to-date recommendations for mammography screening currently adopted in Western countries, and provides an analysis of their content focusing especially on the 40 to 49 years age group. Finally, a brief overview of national breast cancer screening programs shows how

Western countries have received and applied recommendations by eventually providing mammography to women aged 40 to 49 who voluntarily require the screening.

2.2. The disease: breast cancer

Cancer is one of the leading causes of death around the globe and breast cancer is the most common type of cancer among women with an approximate estimation of half a million deaths per year (WHO 2012). Breast cancer alone accounts for 15% of all cancer deaths among women. In developed countries, the incidence of breast cancer is higher than in developing countries, accounting for half of the worldwide breast cancer yearly new cases (Ginsburg et al. 2017). However, breast cancer mortality in developed countries accounts only for 38% of the total number of deaths due to cancer worldwide (Torre et al. 2015).

Incidence and mortality rates' international variations are due to the differences in availability of early detection strategies and in breast cancer related risk factors, which are both associated with cultural and social features. Indeed, not having children, use of contraceptives and hormonal therapy, as well as overweight or obesity, physical inactivity and alcohol consumption are well-known risk factors for developing breast cancer; whereas, having children and breastfeeding are commonly associated with the reduction of risk for breast cancer (*ibid.*). It has been argued that the 30% incidence rate's rise that occurred in the 1980s and 1990s in developed countries was likely due to such changes in reproductive and hormonal factors, as well as to the introduction of screening programs (Svendsen et al. 2006) (Jørgensen 2013). At the same time, the decrease in mortality rates in developed countries has been attributed to early detection and improvements in treatment (Glaziou and Houssami 2011). However, there is

no wide consensus regarding the respective contribution in reducing deaths from breast cancer (Autier et al. 2010) (Jatoi 2011) (Youlten et al. 2012).

Breast cancer is defined as the condition whose first site of tumour growth is within the breast tissue (American Cancer Society, 2015). The breast is composed of mammary glands for milk production – lobules – and ducts connecting gland to the nipple. Breast cancer is referred to as *in situ* when the tumour is confined to the ducts or lobules – e.g.: ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). When the tumour has spread from ducts and lobules to the surrounding breast tissue and/or elsewhere in the body (*metastatic* breast cancer), the cancer is labelled as *invasive*.

At the time of diagnosis, the tumour size, its invasiveness, and the eventual involvement of lymph nodes determine the *stage* of cancer⁹, ranging from *in situ* (stage 0) to metastatic cancer (stage 3)¹⁰. The growing and the spreading potential of the tumour determine the *grade*, ranging from slow growing and less likely to spread (grade 1) to fast growing, aggressive and likely to spread (grade 4) (American Cancer Society 2015).

2.3. Available treatments for breast cancer

Depending on the stage and grade of breast cancer, different treatment options are available. Typically treatment begins with surgery, followed by radiation therapy, chemotherapy, hormonal therapy, and targeted therapy, which can be grouped

⁹ The TNM (Tumor, Node, Metastasis) is another staging system used for breast cancer, especially in clinical trials setting. The TNM system considers three features of cancer: the primary tumour size, the number of regional lymph nodes involved, and the presence of distant metastases (ACS). Available at: <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html> (last accessed on 10.13.2017).

¹⁰ Generally cancers are graded from 1 to 4, but grading systems may vary among different types of cancer. For example, breast and prostate cancers have their own grading systems, respectively the Nottingham grading system and the Gleason scoring system (NCI). Available at: <https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis/tumor-grade-fact-sheet#q4> (last accessed on 10.13.2017).

into local treatments and systemic treatments. Local treatments include surgery and radiation therapy, while systemic treatments include chemotherapy, hormonal therapy and targeted therapy. The latter four can be used both as curative treatments and as neo-adjuvant treatments, either before or after surgery (American Cancer Society 2015).

2.3.1. Local treatments

Surgical intervention aims at removing as much of the tumour as possible and at assessing the cancer state and grade. The choice of a surgical approach mainly depends on the tumour size and localization. Breast-conserving surgery (BCS) - *lumpectomy*, *partial* or *segmental mastectomy*, and *quadrantectomy* - involves the removal of the portion of the breast containing the tumour as well as some of the surrounding healthy breast tissue. Simple mastectomy, which is the most common type, consists in the removal of the entire breast, whereas radical mastectomy involves also the removal of all the axillary lymph nodes and of the pectoral muscles (American Cancer Society 2015). Psychological studies investigating the overall wellbeing in breast cancer survivors who underwent either BCS or simple/radical mastectomy show little if no difference in the long-term outcome due to the type of surgery (Parker et al. 2007). However, women who underwent mastectomies usually report a worse body image compared to women who underwent BCS (Janz et al. 2007), while on the contrary report less fear of recurrence of cancer (Hartl et al. 2003).

During any type of surgery, the removal of lymph nodes from the armpit is a common procedure to determine the *stage* of cancer. It can be performed either as sentinel lymph node biopsy (SLNB), which involves the removal of a few of the first lymph nodes, or as axillary lymph node dissection (ALND), in which many of the lymph nodes under the arm are removed. While this procedure is necessary to

40

assess whether the tumour has spread into other areas of the body through the lymphatic system, it may also result in developing lymphedema (American Cancer Society 2015). Lymphedema is an incurable condition caused by the impairment of the lymphatic system, which implies fluid retention and thereby swelling in the arm and hand. It has been shown that lymphedema related arm morbidity problems might significantly affect physical functioning and psychological wellbeing of breast cancer patients (Kornblith and Ligibel 2003).

By shooting high-energy rays, *radiation therapy*, aims at destroying tumour cells while at the same time controlling and preventing their division. It is almost always recommended after breast-conservative surgery and at times after simple or radical mastectomy. There are two types of radiation therapy: 1) external beam radiation, which aims at destroying tumour cells from outside the body and is usually administrated over an approximately six-week period of time; and 2) internal radiation, which consists of a short-term introduction of a radioactive source into the tumour site (American Cancer Society 2015).

The most common side effects of radiation therapy that usually dissipate within a few days after the treatment include skin reaction surrounding the treated area, pain, swelling of the breast and fatigue (Buchholz 2009). The possible long-term side effects of radiation therapy include the reduction of reconstructive options, breastfeeding problems and lymphedema development when radiation targets the armpit. The development of another cancer due to radiation exposure and heart diseases are very rare. Because of their commonly transitory nature, radiation therapy side effects do not affect patients' wellbeing in the long term (Buchholz 2009).

2.3.2. Systemic treatments

Chemotherapy, by travelling through the bloodstream affects the body as a whole and therefore is considered a systemic treatment. It uses a combination of drugs to target and destroy rapidly multiplying cells, but can also damage and destroy healthy cells. Chemotherapy can be recommended before or after surgery, and for advanced breast cancer. Neo-adjuvant chemotherapy is given before surgery to shrink the tumour size and thereby allowing less extensive surgical intervention, as well as evaluating tumour response to drugs. Adjuvant chemotherapy is administered after surgery to reduce the risk of cancer recurrence by targeting those tumour cells that might not have been removed or have already spread out of the tumour site, but could not be detected by imaging tests. Finally, it is used to treat invasive and metastatic breast cancers (American Cancer Society 2015).

Among the several types of breast cancer treatments, chemotherapy has the most important side effects in the short-term as well as in the long-term, and therefore accounts for the greatest burden of cancer therapy. In the short-term period after every dose, patients usually experience fatigue and asthenia, generalised weakness and malaise, hair loss (Ganz et al. 2004). Although these side effects usually dissipate within few weeks, they can nevertheless continue for months after the end of the treatment. On the other hand, long-term side effects of chemotherapy include the possibility of menstrual changes, low fecundity and even infertility, early menopause, physical and psychological symptoms such as pain and fatigue that have a great impact on patients' wellbeing and quality of life (Ganz et al. 2004) (Bower et al. 2006). In younger women, infertility and premature menopause are further associated with psychological distress due to lack of chance of realizing significant life-plans such as starting a family (Duric and Stockler 2001) (Schnipper 2001) (Avis, Crawford and Manuel 2004).

Hormonal therapy is administered to women whose cancers respond to oestrogen (ER-positive breast cancer) or progesterone (PR-positive breast cancer) hormones, which stimulate their growth and spread. Hormonal therapy may work either by lowering hormonal levels¹¹ or by blocking hormonal effects¹² on cancerous cells. In order to ensure lower oestrogen levels, pre-menopausal women might be also advised to undergo surgical removal of the ovaries or their temporary shut down (American Cancer Society 2015). The use of hormonal therapies is usually recommended for a 5-year long period of time. Due to the lowered levels of hormones, side effects may involve menopausal symptoms such as menstrual changes and hot flashes and sweat, depression, and fatigue. However, they tend to dissipate after treatment, and are usually withstood and tolerated by patients (Ganz et al. 2004). However, long-term side effects including premature and permanent menopause can also occur – as in the case of ovarian ablation.

Targeted therapy represents the promising application of new biomedical frontiers in molecular breast cancer research. For example, among different breast cancers types, approximately one fifth presents tumour cells with a heightened level of the HER2 growth-promoting protein. New drugs with specific antibodies have been developed to stop the growth of cancerous cells by directly targeting HER2 protein¹³. In general, because of the specific action of antibodies on particular proteins, targeted therapy produces fewer side effects than chemotherapy (American Cancer Society 2015). Moreover, the kinds of side effects are usually mild and less disabling, and therefore mostly well tolerated by patients (*ibid.*).

¹¹ *Aromatase Inhibitors (AIs)* prevent the aromatase enzyme from producing estrogen. They are usually prescribed to menopausal women, yet they can be used also in premenopausal women.

¹² *Tamoxifen* is one of the most commonly used drugs for hormonal therapy. It works by preventing estrogen from binding to tumour cells and promoting their growth.

¹³ *Trastuzumab* is one of the most commonly administrated targeted therapies for breast cancer.

2.4. The screening tool: mammography

The history of mammography can be traced back to 1913 when Albert Salomon first reported his work on visualizing breast cancer through radiography of mastectomy specimens. Salomon's studies created fresh opportunities of combining radiological, clinical and microscopic anatomy of breast pathology in order to distinguish between benign and malignant diseases (Gold 1992). Yet, even though X-ray was becoming a familiar diagnostic tool, it took a few decades before mammography turned out to be an accepted technology.

In 1930 Stafford Warren reported on the use of clinical mammography in live patients in order to confirm the suspect of breast cancer (Stafford 1930). This is the first report of the use of X-ray as an adjunct to clinical breast examination (CBE) for the diagnosis of breast cancer. However, it was not before the beginning of the 1960s that mammography caught on again thanks to the work of two American radiologists, one regarding the improvement of the mammographic technology, the other related to the use of mammography as a screening tool.

In 1960 Robert Egan described a new technique to solve the technical problems of mammography in order to produce high-quality mammograms. Egan's technique was applied to diagnostic mammograms showing encouraging results in detecting cancers that were not previously detected by surgeon's CBE (Egan 1960). The next year Jacob Gershon-Cohen reported the findings of his research on healthy women, demonstrating that mammography screening could detect breast cancers that could not be identified by CBE (Gershon-Cohen et al. 1961), helping thus in spreading the gospel of mammography as an innovative tool in breast cancer early detection (Ingleby and Gershon-Cohen 1960).

In the early 1960s, these important technical innovations and improvements found a fertile ground for mammography to be publicly accepted due to the political, social and health movements' convergence in the US (Reynolds 2012). The public discourse on breast cancer was primarily centred on the theme of *early detection*. The leading idea was that cancer could be best cured through an aggressive treatment in its early stages (Patterson 1987). This medical view stemmed from the adoption of a *linear-progression model* of carcinogenesis interpretation and explanation. Indeed, historically cancer was thought to advance along a series of progressive, increasingly dangerous steps. This presupposition led to logical deduction that early detection, by breaking the chain of disease development, must be of benefit for an affected individual (Croswell, Ransohoff and Kramer 2010).

Therefore, massive public education campaigns were launched targeting women and focusing mainly on breast and reproductive cancers. Magazines, newspaper, radio broadcasts, lectures and educational brochures were widespread delivering a threefold message: 1) it was highly possible to cure cancer in its early stages; 2) early detection and treatment allowed for a better cancer treatment; and therefore 3) regular medical check-ups of healthy women were essential to effectively tackle the cancer threat (Reynolds 2012).

The *early detection* promotion remained a constant focus and brought about the second factor facilitating the mammography spread and acceptance. Indeed, women's behaviour begun being labelled as "good/wise" or "bad/foolish" by following or not the ACS early detection principles (Gardner 2006). In this climate, the mammography approach held growing appeal and enthusiasm. The public had welcomed the gospel of *early detection* and the technological improvements of mammography provided a tool (Reynolds 2012). Nevertheless, a concrete proof of

the value of mammography in reducing mortality was still missing. Again, scientific developments were about to help for mammography validation and further dissemination.

2.4.1. Clinical trials: the need for scientific evidence

As mentioned in Chapter 1, scientific evidence about screening effectiveness in reducing *morbidity* and *mortality* provides both the rationale *and* the justification for the implementation of population-based programs. By the 1960s, improvements in bio-statistical methodologies had led researchers to better evaluate therapeutic and diagnostic interventions (Feig 2014). Among the strategies, randomized controlled trial (RCT) was especially important to the mammography endeavour. A RCT is a scientific experiment aiming at reducing biases while testing a new treatment. Participants are randomly assigned either to the intervention group and receive the treatment, or to the control one and receive standard treatment of care. In the context of breast cancer screening by mammography alone or in combination with physical examination (both CBE and self breast examination - SBE), seven population-based randomised clinical trials¹⁴ have been conducted:

- The HIP trial (Shapiro, Strax and Venet 1971) (Shapiro 1977) (Shapiro 1997);
- The Swedish Two-County trial (Tabàr et al. 1989) (Tabàr et al. 1995) (Tabàr et al. 2015);
- The Malmö Mammographic Screening Trial (Nystrom et al. 2002);
- The Stockholm Trial (Frisell et al. 1997) (Nystrom et al. 2002);

¹⁴ In population-based RCTs, intervention and control groups' participants are randomly selected from a target population (Feig 2014).

- The Gothenburg Breast Screening Trial (Bjurstam et al. 1997) (Bjurstam et al. 2003);
- The Edinburgh Trial (Roberts et al. 1990) (Alexander et al. 1999);
- The UK Age Trial (Moss et al. 2005) (Moss et al. 2006) (Johns and Moss 2010).

There has also been one non-population-based randomised clinical trial¹⁵, the National Breast Cancer Study of Canada (NBSSC) (Miller et al. 1992) (Miller et al. 2014). Finally, the Breast Cancer Detection Demonstration Project (BCDDP) has been carried out in the US (Feig 2014). Interestingly, the BCDDP represents a case study on the effects of the enthusiasm for screening, which eventually leads to decisions and policies that are not evidence-based.

Historically, the Health Insurance Plan of Greater New York (HIP) trial is the first scientific validation of the effectiveness of mammography as a screening tool, applying Egan's technique. In 1963 the HIP mammography trial formally began and the first results substantially supported researchers' suppositions (Shapiro et al. 1971): the death rate of women in the screening group was significantly lower than among those in the control group; and mammography could detect early-stage cancers that CBE alone could not identify (Shapiro 1977). However, for women in their 40s, no statistically significant difference in mortality reduction was shown between those in the screening and control groups. Nevertheless, in 1973 the Breast Cancer Detection Demonstration Project (BCDDP) was launched in the US. Usually, a demonstration project is undertaken once the validity of the intervention at stake has already been proven (Reynolds 2012). However, despite the HIP trial lack of evidence about benefits of mammography for women younger

¹⁵ In a non-population-based trial, intervention and control groups' participants are randomly selected from people who voluntarily participate the study (Feig 2014).

than 50 years old, the BCDDP enrolled women 35 to 74 years old for an annual screening¹⁶ (Baker 1982).

In the fall of 1974 the gospel of *early detection* was further promoted by President Gerald Ford's public announcement of First Lady Betty Ford breast cancer diagnosis and consequent radical mastectomy. Mrs. Ford's breast cancer had been found during a medical check-up. Mrs. Ford was the first high-profile public figure going public about her cancer and praising *early detection* for her excellent prognosis, hence actually corroborating the message of the value of *early detection*. As a consequence of the public share of Betty Ford's experience, women eagerly joined screening clinics throughout the US.

Thanks in part to the so-called "Betty Ford effect" (Welch, Schwartz and Woloshin 2011), the BCDDP completed the round of screening in its first year of application. Simultaneously with this tremendous spike in screening rates, a significant increase of breast cancer incidence was observed, reinforcing in turn the public request for mammography (Reynolds 2012). Raffle and Grey described this phenomenon as the "popularity paradox" (Raffle and Grey 2007), for which, the more cancer testing is performed, the more cancers are detected and diagnosed, leading to an increased sense of risk and of benefits of testing, which in turn stimulate the request for more testing.

The BCDDP results were far more positive in terms of screen-detected cancers than those of the HIP trial (Baker 1982). Nevertheless, as already said, the

¹⁶ The BCDDP annual screening modality consisted in CBE, mammography, breast thermography, and instruction for BSE. Breast thermography is a technology sensing temperature differences in order to detect cancer. Metabolic activity and vascular circulation in pre-cancerous lesions and developing cancers are usually higher than in normal breast tissue and result in temperature variations in the breast, which can be detected by thermography. However, in the second year of the project, thermography was discontinued owing to lack of effectiveness in detecting early stage of breast cancers (Holleb 1992).

BCDDP was not designed as a scientific study, hence there was no control group and therefore there was no chance of answering the question whether or not screening could result in breast cancer mortality reduction (Feig 2014).

From the mid-1970s, inspired by the HIP trial, 6 RCTs were performed in Europe and one national study in Canada (NBSSC-1 and NBSSC-2). The major aim of such trials and studies was to provide scientific evidence regarding mammographic screening effectiveness in reducing mortality among the screened-population. While the HIP trial had found a statistically significant reduction in breast cancer deaths, it could not demonstrate the value of mammography alone as a screening test, because of its combination with annual CBE. Therefore 6 out of the 8 clinical trials offered mammography screening alone, in comparison with standard care, while 1 offered annual mammography and CBE. Protocols and results for women of all ages at entry into the 9 clinical trials are shown in **Table 3** (adapted from *Feig, Radiologic Clinic of North America, 2014*).

Trial	Years	Age at Entry (y)	Frequency of Mammography (mo)	CBE	Follow-up (y)	Mortality Reduction %
HIP Trial	1963-1969	40-64	12	Annual	18	22
Malmo	1976-1986	46-69	18-24	None	20	22
Two-County	1979-1988	40-74	23-33	None	30	32
Edinburgh	1979-1988	45-64	24	Annual	14	22
NBSSC-1	1980-1987	40-49	12	None	13	0.3
NBSSC-2	1980-1987	50-59	12	Yes	13	-2
Stockholm	1982-1988	40-64	28	None	16	10
Gothenburg	1982-1988	40-59	18	None	14	21
UK Age Trial	1991-2005	39-41	12	None	10	17

Table 3 - Mammography screening trials: protocols and results

Of the 9 screening clinical trials, 7 showed evidence of benefit from screening. Breast cancer mortality reduction was statistically significant in each of the 4 trials (HIP, Swedish Two-County, and Edinburgh) and in combined results from the Stockholm, Malmö, Östergötland, and Gothenburg trials, and marginally significant in the Gothenburg trial. Only the NBSSC found no evidence of benefit. Possible explanations for the variance between NBSSC results and those of the other RCTs include poor technical quality of mammography, improper study design, and control group contamination with advanced cancers (Feig 2014).

In addition to statistical evidence proving a significant mortality reduction, two main social and cultural factors helped the spread of mammography screening programs: undergoing screening was seen as 1) a means to enable women taking personal responsibility for their health; and 2) as a way to improve women's odds against breast cancer fatalities (Lerner 2001). The *early detection* gospel changed dramatically from the "do not delay" early-century message to the "go in search" admonition, and the public demonstrated a wide acceptance of the concept that perfectly healthy people should undergo regular screening programs (Klawiter 2008, p. 95). Second, the definition of breast cancer itself has broadened from the only invasive tumours, to *in situ* pre-malignant lesions such as ductal carcinoma (DCIS) and lobular carcinoma (LCIS) (Welch, Schwartz and Woloshin 2011) (Reynolds 2012).

2.5. Benefits and harms of mammography screening

By reducing cancer mortality, mammographic screenings were proven beneficial at the population level and therefore, in the past few decades breast cancer screening programs became widespread in developed countries (Feig 2014). Moreover, *early detection* of breast cancer leads to a greater range of treatment options, including less-extensive surgery - breast-conserving surgery such as *lumpectomy*, *partial* or

50

segmental mastectomy, and *quadrantectomy* - as well as less-intrusive therapies with fewer burdensome side effects - in some cases even the option to forgo chemotherapy (American Cancer Society 2015).

However, as seen in Chapter 1, some problems can occur at the individual level. Conceptually the problems occurring in breast cancer screening can be due either to the limitations of screening tests, or to the uncertainty of estimating further development of high-risk or pre-invasive lesions and/or slow growing cancers (Brodersen, Schwartz and Woloshin 2014). A major limitation of mammography is, indeed, its *sensitivity* (see Chapter 1.4. *General harms of screening*), which is still lacking the capacity to discriminate between early-stage breast cancers requiring treatment or not. Several studies have shown that tumour biology can be very heterogeneous and that not all high-risk and/or pre-invasive lesions progress in the same manner, while some might remain dormant in their latent stage for the entire lifetime, or even spontaneously regress (Hanahan and Weinberg 2000) (Hanahan and Weinberg 2011) (Croswell, Ransohoff and Kramer 2010) (Jørgensen 2013) (Zarvadas et al. 2015).

Currently, the benefits of *early detection* – namely mortality reduction, better prognosis, and a greater range of treatment options - come hand in hand with the possibility of unwanted potentially harmful outcomes for some individuals, such as *false positive* results and *overdiagnosis* (Jørgensen 2013). As seen in Chapter 1, the former can be considered a diagnostic mistake that can be rectified after additional tests, while the latter occurs when benign or slow growing cancers are detected and subsequently treated. *False positive* test results improperly indicate the presence of the condition, but usually are proven as mistakes after additional diagnostic interventions such as biopsy, radiation or even surgery. Nevertheless, even if eventually ruled out, *false positive* results bring

unnecessary stress, anxiety and health risks due to the subsequent diagnostic exposure to additional tests such as biopsy or surgery that inevitably expose patients to the potential complications entailed by any medical intervention (Welch, Schwartz and Woloshin 2011).

Overdiagnosis, instead, refers to the detection of a tumour that fulfils the pathological criteria for cancer, but which does not constitute a substantial health hazard for the patient. Indeed, *overdiagnosis* is the detection of a condition that would have not presented any clinical symptoms, or led to death during patient's lifetime (Welch et al. 2016). Since there is nothing to cure, *overdiagnosis* therefore entails that patients undergo a needless therapeutic plan consisting of additional diagnostic tests, unnecessary treatment (*overtreatment*) and disease surveillance that are known to cause physical and psychosocial harms (Ormiston-Smith, Scowcroft and Thomson 2013).

The debate over the potential benefits and harms of breast cancer screening began immediately after the national programs were established and agencies all over the world recommended further research and implementation of screening programs. Clinicians, researchers, lawmakers, and advocacy groups – that is to say, all the actors engaged in the field of breast cancer screening - participated in the debate raising questions and claims from their specific viewpoint. In the 2000s the debate intensified due to the publication of systematic and independent reviews showing lower benefits of mammography than originally calculated and significant *overdiagnosis* rates due to population screenings (Koning 2003) (Mandelblatt et al. 2009). The debate focused especially on the breast cancer mortality reduction due to screening programs; the quantification of possible harms (particularly of *overdiagnosis*); and the communication of this information to women invited for screening.

Moreover, it is particularly difficult to compare data from different clinical trials because of disagreements about either their validity or the parameters of outcomes quantification (Marmot et al. 2013) (Jørgensen 2013) (Carter, Coletti and Harris 2015). This is particularly tricky for *overdiagnosis* for which the only evidence comes from the statistical modelling or data from observational studies carried out in population-based screening programs (Lauby-Secretan et al. 2015) that show a rise in screenings and the incidence of the given disease in the setting of stable mortality rates (Puliti, Miccinesi and Paci 2011) (Welch, Schwartz and Woloshin 2011) (Carter, Coletti and Harris 2015). This means that it is possible to assess whether *overdiagnosis* occurs only at the population level, whereas it is extremely difficult, if not impossible at all, to assess whether it occurs at an individual level, and in fact patients will (most likely) never know if they were overdiagnosed and overtreated (Morrow, Schnitt and Norton 2015).

The estimates of the magnitude of *overdiagnosis* due to mammographic screening vary widely among different studies and they range from 5% to 50% (Welch and Passow 2014) (Elmore and Etzioni 2015). Yet, there is no consensus about the precise magnitude nor on the preferred method of estimation: for example such high rates of *overdiagnosis* might be due to lack of adjustment to cancer risk and *lead-time bias* and contemporaneous trends in incidence (Beckmann et al. 2015). Some authors claim that once these methodological limits of screening are resolved, the estimates will possibly decrease to 5-10% (Puliti et al. 2012) (Lauby-Secretan et al. 2015).

In the past few years, researchers have targeted this lack of consensus by conducting meta-analyses of multiple clinical trials and evaluation of modelling and observational studies from different settings in order to provide the best possible evidence on mammographic screening benefits and harms (Gunsoy,

Garcia-Closas and Moss 2012). Among these studies, the 2013 Cochrane review *Screening for breast cancer with mammography* (Gøtzsche and Jørgensen 2013), by conducting a meta-analysis on 7 of the randomized trials mentioned above, represents the first strongly reliable evidence on the issue. The review estimates a mortality reduction due to mammographic screening of 15% with a rate of *overdiagnosis* of 30%, meaning that for 2,000 women invited to screening programs for 10 years 1 will be saved, while 10 will be overdiagnosed and 200 will receive a *false-positive* result.

In the same year, the report commissioned by Cancer Research UK and the English Department of Health *The benefits and harms of breast cancer screening: an independent review* (Marmot et al. 2013) seemed to finally solve the case by presenting a systematic review and meta analysis of 11 trials, the Cochrane review results and several observational studies. Therefore, it currently represents the latest accurate and up-to-date quantitative estimates of benefits and harms of breast cancer screening. The report states, on the one hand, that breast cancer screening programmes are likely to deliver about a 20% mortality reduction at ages 55 to 79; and on the other hand, that the best estimate of *overdiagnosis* for a population invited to be screened is of the order of 19%.

The controversy regarding routine screening for women in their 40s persists because of a level of unease with the current understanding of benefits and possible harms (risks) of mammography, and because of its translation into screening guidelines and recommendations (Feig 2014). Breast cancer is one of the most common causes of death among women aged 40 to 49 (Armstrong et al. 2007), and therefore holds a critical position in this age group. Yet, the incidence of breast cancer is lower among this age group than among women older than 50. In light of this, the breast cancer burden appears to be low for a population-based

screening program. Data suggest that more than 98% of women do not develop breast cancer between age 40 and 49 (*ibid.*), but can undergo the risks of population-based programs, especially in terms of *false positive* results and *overdiagnosis*. In other words, current up-to-date evidence indicates that women aged 40 to 49 undergoing routine mammography screening will decrease their risk of dying from breast cancer, but at the same time will increase their risk of receiving a *false positive* result, and thereby of undergoing unnecessary further investigation; as well as increase their risk of mastectomy (*ibid.*) and *overdiagnosis*, which likely entails *overtreatment* (Morrow, Schnitt and Norton 2015).

2.6. Recommendations, guidelines and mammographic screening programs

Systematic reviews and meta-analyses of randomised clinical trials are widely accepted as the highest level of evidence for guiding policy decisions on medical interventions. Most developed countries adopt evidence-based recommendations on cancer screening for which agencies such the US Preventive Service Task Force (USPSTF), the American Cancer Society (ACS), the International Agency for Research on Cancer (IARC), Cancer Australia and the Canadian Task Force on Preventive Health Care (CTFPHC) are held responsible. In fact, based on their recommendations, policy makers and regulatory bodies decide which programs to implement, which population to target and invite at given intervals, how to organize recall strategies as well as results' and treatments' delivery and follow-up care, and which institutions are responsible for service delivery and quality (Lauby-Secretan et al. 2015). As research and analyses of randomised clinical trials evolve, evidence-based regulation should constantly update guidelines to the latest and most accurate estimate of benefits and harms of screening programmes (Juth and Munthe 2012).

In the last few years, the major agencies of Western countries - European Union, US, Australia and Canada - have updated their guidelines based on the analysis and evaluation of the newly available data (Jørgensen et al. 2017). Specifically, the CTFPHC released the latest breast cancer screening recommendations guidelines in 2011 (Canadian Task Force on Preventive Health Care 2011), the IARC in 2014 (Lauby-Secretan et al. 2015), Cancer Australia in 2015¹⁷, the ACS in 2015 (Oeffinger et al. 2015), and the USPSTF (Siu 2016). It is worth recalling that, being a means of *secondary prevention* (see Chapter 1.2 *Screening programs*), all mammography screening guidelines refer to those «asymptomatic women aged 40 years or older who do not have pre-existing breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation» (Siu 2016, p. 280). **Table 4** sets out the recommendations subdivided by age groups.

Table 4 - Current ACS, USPSTF, IARC, Cancer Australia and CTFPHC mammography screening recommendations for age groups

ACS ¹⁸	40-44 years of age	45-54 years of age	>55 years of age
-------------------	--------------------	--------------------	------------------

¹⁷ Position statement available at: <https://canceraustralia.gov.au/publications-and-resources/position-statements/early-detection-breast-cancer> (last accessed on 10.13.2017).

¹⁸ «A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening» (Oeffinger et al. 2015, p. 1603). From patients' viewpoint, a strong recommendation stands for the interpretation that «most individuals in this situation would want the course of action, and only a small proportion would not» and therefore «most individuals should receive the recommended course of action» (*ibid.*, p. 1600). Qualified recommendations indicate there is clear evidence of benefits of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening» (*ibid.*, p. 1603). For patients, «the majority of individuals in this situation would want the suggested course of action, but many would not. Patient preferences and informed decision making are desirable for making decisions» and therefore «clinicians should acknowledge that different choices will be appropriate for different patients and that clinicians must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision» (*ibid.*, p. 1600).

Strong recommendation for routine screening women >45 years of age	Eligibility to annual screening (Qualified recommendation)	Annual screening (Qualified recommendation)	Annual screening or eligibility to continue screening annually (Qualified recommendation)
USPSTF¹⁹	40-49 years of age	50-74 years of age	>75 years of age
	Eligibility to biennial screening (Grade C)	Biennial screening (Grade B)	No recommendation (Grade: I statement)
IARC	40-49 years of age	50-69 years of age	70-74 years of age
Sufficient evidence of overdiagnosis and psychological burden of false positive results for all the age groups	No recommendation (Limited evidence of mortality reduction)	Biennial screening (Recommendation) Sufficient evidence of net benefit	No recommendation (Sufficient evidence of mortality reduction)
Cancer Australia	40-49 years of age	50-74 years of age	>75 years of age
	Eligibility to biennial screening	Biennial screening	Eligibility to biennial screening
CTFPHC²⁰	40-49 years of age	50-69 years of age	70-74 years of age
	No routine screening (Weak recommendation)	Screening every 2 to 3 years (Weak recommendation)	Screening every 2 to 3 years (Weak recommendation)

¹⁹ Grade B means that «the USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial». Grade C means that «the USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small». I statement means that «the USPSTF concludes that current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined» (USPSTF) available at: <https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions> (last accessed on 10.13.2017).

²⁰ «Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that most women would want the recommended course of action, but many would not. For clinicians, this means they must recognize that different choices will be appropriate for individual women, and they must help each woman arrive at a management decision consistent with her own values and preferences. Policy-making will require substantial debate and involvement of various stakeholders. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, and there is more variability in the values and preferences of patients» (Canadian Task Force on Preventive Health Care 2011, p. 1993).

At first glance, the intricacy of and differences among recommendations are overwhelming, and indeed they mirror the complexity of evaluating the effectiveness and safety of mammography screening. As seen in the introduction of the present Chapter, differences in what evidence is considered and what constitutes a net benefit for recommending screening is a matter of both *scientific* and *ethical* values adopted by experts (Parker, Rychetnik and Carter 2015). In general, through RCTs, systematic reviews and meta-analyses a good level of evidence has been achieved for assessing the net benefit of breast screening for women older than 50 years, and thereby all the guidelines recommend routine screening for this age group. Yet no consensus regarding the net benefit for those aged 40 to 49 has been reached. As a matter of fact, systematic reviews and meta-analyses of multiple clinical trials show that the benefit of undergoing breast cancer screening for women under 50 years old may be little, and the cost in terms of *false positive* test results, unnecessary biopsies, *overdiagnosis* and subsequent *overtreatment* is relatively high (Armstrong et al. 2007) (Mandelblatt et al. 2009).

The rationale behind the *eligibility*, *grade C*, *weak* or *qualified recommendations* for mammography screening in women aged 40 to 49 lies on the acknowledgment that current scientific evidence is either insufficient or low to assess the balance between benefits and harms. The decision to undergo mammography depends on the *value* individual women place on the desirable effects (decreased absolute risk of mortality, better prognosis and eventually greater range of treatment options, as well as reassurance) and conversely on the *value* they place on the undesirable effects (especially *false positive* results and *overdiagnosis*). Therefore, given the fundamental role of patients' values and preferences in decision-making, different choices might be appropriate for

individual women. The guidelines require clinicians, not only to recognize and accept the variability of individual preferences in assessing the balance, but also to help women to arrive at decisions consistent with their own values and preferences.

On the basis of the CTFPHC and IARC recommendations, Canada and several European countries²¹ - as well as Australia, with the only difference of extending the middle group to women aged 74 years - carry out national breast cancer screening programs that provide a formal written letter of invitation to publicly-funded biennial screening for women aged 50 to 69, while women prior to age 50, who are nevertheless eligible to freely participate the program, do not receive any invitation. Given the different health care system established in the US, annual or biennial mammography screening for women aged 40 years and older – as recommended by the ACS and suggested by the USPSTF - is covered either by the Insurance plans governed by the Affordable Care Act, or by Medicaid, or by Public Employee health plans (NCI)²².

²¹ In the European Union, 25 out of the 28 member States are «planning, piloting or rolling out breast cancer population-based organized screening programs. A target age wider than the maximum recommended target age for population-based screening of 50 to 69 years has been adopted by Austria, Czech Republic, France, Greece, Hungary, Italy, Netherlands, Portugal and Sweden» (IARC 2017, p. 17). «All the countries in the EU except Bulgaria, Croatia and Slovak Republic have national breast cancer screening policy mandated by a law or an official recommendation. There is no population-based breast cancer screening programme in Bulgaria, Greece and Slovak Republic. The screening programme is not supported by public fund in Luxembourg and only partially supported in Portugal. In all other EU countries the breast cancer screening programme is public funded. All the countries having screening programmes send written invitations to the eligible women through the screening registries except Lithuania, Portugal and Romania. In these countries the invitation letters are sent through the primary health care or through the general practitioners. Written consent for screening is required in Belgium, Croatia, Cyprus, Czech Republic, Hungary, Ireland, Italy, Lithuania, Netherlands, Poland, Portugal, Romania and Slovenia» (IARC 2017, p. 19).

²² Available at: <https://www.cancer.gov/types/breast/mammograms-fact-sheet#q1> (last accessed on 10.13.2017).

2.7. Summary

Breast cancer is the most commonly occurring cancer among women and accounts for approximately half a million deaths per year (WHO 2012). However, improvements in treatments at all stages of the disease and *early detection* strategies have changed the impact of breast cancer significantly for the better. In particular, the wide implementation of population-based mammography screening programs constitutes an effective strategy for *early detection* of breast cancer, which in turn allows for better prognosis and greater range of treatment options for individual patients. Breast cancer screening has been extensively studied and debated, often leading to harsh discussions especially regarding the balance between benefits and harms of mammography. Indeed, recent studies have shown that the benefits might be lower than originally estimated, and that the magnitude of harms might be higher, especially in terms of *false positive* results and *overdiagnosis* for women aged 40 to 49. Consequently, evidence-based recommendations have acknowledged that the assessment of balance between benefits and harms of mammography screening cannot be objectively determined. On the contrary, the assessment depends on the values and preferences that each individual woman places in determining what constitutes a worthwhile benefit and what constitutes a great harm. Most of the Western countries that establish population-based screening programs have accepted this line of reasoning and therefore eventually provide free mammography to women younger than 50 years old. In order to empower women eligible for mammography screening in making informed choices, clinicians are required to provide information regarding benefits and harms, as well as to help individual women to reach a decision consistent with their values and preferences. Therefore the focus shifts on the individual process

of decision-making in which clinicians and women engage, the firsts providing information, the latter assessing their own balance based on personal evaluation. In this respect, some new relevant issues and questions arise, mainly related to the patient-physician relationship, and hence to the bioethical field. What are the physicians' duties? How should they communicate complex probabilistic information to women? Do they have any moral obligation in empowering women? Which values do women refer to when deciding whether to undergo mammography screening? How can physicians incorporate women's values in the decision-making process? Is there any duty to help women to explore their preferences and values in order to reach a consistent decision? The next Chapter analyses the major methodologies applied in bioethics to frame and face concrete moral problems within the clinical setting in order to provide an ethical framework suitable to answer such questions.

CHAPTER 3

Bioethics: methods and application

3.1. Introduction

Breast cancer screening programs represent a very promising and effective strategy in reducing mortality and allowing for a wide range of early treatment options, which are more effective and less burdensome for patients. However, they also involve several complexities in the assessment of net benefit for participants, and especially for women aged 40 to 49. Beyond the lack of quality scientific evidence on benefits and harms, moral concerns arise at the individual level regarding the ways in which eligible women decide whether to undergo mammography. In this respect, the major ethical issues are related to the empowerment of women for consistent decision-making, which requires the providing of information and the incorporation of individual preferences and values (Chapter 2). This line of ethical analysis pertains to the field of medical ethics that traditionally addresses issues regarding patient-physician relationship. At the same time, as a means of *secondary prevention* breast cancer screening programs are inherently directed at an asymptomatic population and seek to provide benefits in terms of the decrease in mortality rates at the target population level (Chapter 1). Therefore, given the interdisciplinary character of mammography screening that entail a continuous relationship among different fields of activity, bioethics constitutes a promising approach of inquiry and analysis. However, bioethical literature on screening is very much in its early days. Therefore, the Chapter ahead presents the main theoretical frameworks and methodologies

commonly applied in bioethics in order to provide a comprehensive overview of the different ethical approaches that can be implied in addressing the specific moral issues of mammography screening.

3.2. Bioethical approaches and methodologies

Bioethics is a branch of ethics dealing with moral questions and issues arising from technological improvements in biomedical science and clinical medicine together with concerns regarding the power historically exercised by physicians and researchers over patients. In this respect, bioethics can be interpreted as a modern-day kind of traditional medical ethics, which mainly focused on patient-physician relationship, on the virtues of the “good” physician, and on patients’ rights. Differently, bioethics engages in a more reflective and critical enterprise by not limiting the field of inquiry to patient-physician relationship, which traditionally entails the development and adherence to a moral code. First, bioethics aims at better understanding the issue at stake, even by posing deep philosophical questions regarding for instance the value and quality of human life, the concept of *person* and that of *personal identity*. From its inception, the main bioethical issues of inquiry have been research on human subjects, organ transplantation, genetics, death and end-of-life, and reproductive issues. Nevertheless, as science progresses and new technologies become available in biomedicine, new questions arise – as I argue it is the case for population-based mammography screening programs. Second, bioethics field of inquiry includes issues of public policy and citizens’ involvement, as well as control and direction of science and clinical research. Third, bioethics is by nature an interdisciplinary enterprise in that it crosses the boundaries of philosophy, ethics, medicine, biomedical sciences, economics, law and public policy in order to provide a comprehensive understanding and eventually practical solutions or proposals (Kuhse and Singer 2009).

One of the central theoretical issues in bioethics regards the methodology to be applied in reasoning and facing moral questions. Bioethics is commonly considered a form of applied ethics, in that it seeks to solve moral disagreement by applying existing ethical theories to the biomedical field (Rachels 2009). Among different theoretical approaches, bioethics usually employs those of normative ethics, which is defined as the branch of ethics dealing with identifying what is right – and what is wrong – and what individual human beings *ought* to do or seek to achieve and realize by voluntary actions (*ibid.*). Therefore, the methodology used to determine how to guide human actions is one of the central issues in bioethics. The evaluation of different methodologies has to consider how bioethical theories, perspectives and frameworks can guide actions in practical circumstances.

The methodologies most commonly applied in bioethics can be grouped in principle-based methods and non-principle-based methods (Steinbock 2007). Among the first, *consequentialism*, *deontology* and *principlism* are the more widespread and accepted methodologies. *Virtue ethics* and the *ethics of care*, instead, are two of the more representative approaches among non-principle-based methodologies. In this Chapter, each of the methods is outlined, some general critiques are presented and some examples of their application are alleged. Because virtue ethics and care ethics are less applied in bioethics than principle-based approaches, the Chapter devotes a longer introduction to their moral theory, and then moves on to present their application to the medical context. A brief historical background is therefore presented in order to properly root virtue and care ethics methodologies within health care ethics.

3.3. Principle-based methodologies

In contemporary bioethics, principle-based methods are generally considered the dominant ones. The common feature among principle-based methods is the claim

that general moral concepts, such as principles or rules, should guide moral reasoning (Childress 2009). However, these methodologies encompass a wide range of different and more specific methods, each emphasizing principles and/or rules, but not necessarily sharing other features (Steinbock 2007). For example, the appeal to general principles might occur only in case of conflict or uncertainty about the most appropriate way of action in specific circumstances. Conversely, some of these methodologies call for an explicit principle-based approach in moral reasoning. Finally, the principles and rules entailed in moral deliberation represent respectively the most general and the more specific guides of action. Hence the difference between principles and rules lies in different degrees of generality and/or specificity. For example, *beneficence* and *autonomy* represent general guides to actions and therefore are considered principles; while *respect for privacy* and *confidentiality* represent moral rules that specify the more general principles (Childress 2009).

3.3.1. Consequentialism

In general, consequentialism is a moral approach that assesses the morality of actions solely on the basis of their consequences. Therefore there are no *per se* right or wrong actions. Contemporary consequentialism emphasizes the role of intended ends and anticipated effects of the action in question. Nevertheless, in moral reasoning the intended ends should be subordinated to the probable and expected overall actual consequences. At present, *utilitarianism* is the leading and most influential consequentialist theory (Copp 2007).

For utilitarian consequentialists, the *principle of utility* provides the fundamental reference for assessing the rightness or wrongness of actions (Hare 2009). The principle of utility is defined as the requirement of producing the greatest good for the greatest number (Singer 2011). Utilitarian theory, therefore, is further defined by the main characteristics of *welfarism* and *aggregation*. The first refers to

the identification of utility as the maximization of welfare; while the second specifies that such welfare has to be calculated by summing the positive consequences for all those involved in the effects of the action. Yet, a *value theory* – a definition of what counts as welfare and therefore as positive consequences - needs to be provided. Currently, the most prominent definitions of values refer to pleasure, happiness, individual interests and preferences (Copp 2007).

Finally, utilitarianism's approaches may differ on the basis of the *obligation theory* adopted – the identification of the best way to pursue the maximization of good consequences. Advocates of *act-utilitarianism* claim that the obligation to act depends only on the maximization of welfare. Hence, while assessing different courses of action, the one expected to produce the best consequences should and ought to be pursued (Singer 2011). The absolute prioritization of the principle of utility over other principles and moral rules prevents act-utilitarians from facing moral dilemmas arising from conflicting principles. Contrary to that, *rule-utilitarians* adopt an *obligation theory* focused on the application of rules that, if implemented, would produce a maximization of positive consequences (Hooker 2002). The moral agent, therefore, seeks rules that can be impartially justified due to their appeal to the principle of utility.

3.3.2. Deontology

As opposite to consequentialism, deontological theories focus on actions rather than on their consequences. The etymology itself of the word deontology (*deon*, duty) suggests that the emphasis of moral consideration is on duties. Moral duties derive directly from absolute moral principles. Hence, actions are right or wrong depending on their conformity with or negation of absolute principles. Some features other than - or in addition to - their effects make actions right or wrong, and therefore obligatory or not permitted. Moreover, in moral reasoning and decision-making, and

especially in case of a conflict between different moral claims, deontological considerations and rules are always prioritized.

As outlined above, the utilitarian appeal to the principle of utility aims at solving moral conflicts in the way that maximizes the good of the majority of the *community* of specific individuals involved. Deontology, instead, seeks to provide a *universal* principle, which can be recognized and applied by *any* individual in *any* circumstance. The universalistic claim of the absolute principle requires it to be founded on some features shared by all individuals despite the cultural, religious and/or personal differences. In contemporary bioethical debate the two most important and applied deontological principles are *respect for autonomy* and *sanctity of life*. Both of them rely on the concept of a common shared human nature, which comes to have a distinctive significance in ethical theory. Nevertheless, the first derives from a secular liberal approach, while the latter is an expression of religious tradition and the two are often considered competitors.

The secular principle of *respect for autonomy* emphasizes humans' intellectual nature as the foundation of the possibility of self-reflection, self-determination and even morality itself. From this viewpoint, rationality and self-determination are the fundamental features of human life and ought to be respected. Conversely, the principle of *sanctity of life* stems from the religious viewpoint of human life as having an inalienable and fundamental value in itself. The two approaches may overlap in pointing directions within bioethical debate, yet they may also come into conflict regarding specific issues such as euthanasia and abortion. Advocates of the principle of respect for autonomy usually - yet not always - recognize and promote the moral right of individuals to autonomously choose whether to undergo any medical procedure, despite the potentially negative outcomes. In traditional moral philosophy, autonomy refers to the individual's capability and right to self-

governance and self-determination (Engelhardt 1996) (O'Neill 2004). Therefore, at the same time, autonomy means the possession of mental capabilities such as understanding, intending and voluntary decision-making, and the freedom from external constraints in exercising such capabilities. The autonomous individual acts according to his/her personally chosen plan of life, of which health care and management represent only a part. Therefore, the principle of *respect for autonomy* requires the acknowledgment of individuals' capacities and life-perspectives, including personal views and beliefs. Of course, respect for autonomy requires individuals to be properly informed, with informed consent to clinical treatments being a well-known and implemented prerequisite of any medical intervention.

The abstract universal conception of the *principle of autonomy* is generally intended as entailing *negative duties* of non-interference with the decisions and choices of others, and therefore it imposes no *substantive duty* on anyone (Engelhardt 1996). In this sense, medicine came to be conceptualized as contractual relationship between health providers and patients, with the goal of deciding on a course of treatment. Both of them are considered equal, rational and independent moral agents. The *principle of autonomy* aims at preventing possible interferences by providing mainly rules guiding the exchange of information to guarantee an autonomous decision-making process. Clinicians' primary duty is therefore to disclose all the information that particular patients need to take an informed autonomous decision (*ibid.*). This implicit model of physician-patient relationship seems to be structured around the need of choosing between different options, with clinicians possessing specific medical knowledge, and patients picking the option better suiting their goals, values and preferences. In this narrow sense, the medicine endeavour risks to end up being a service to be provided with the only constrain of refraining from unauthorized actions involving others.

3.3.3.Principlism

Principlism, as the name itself suggests, is another principle-based methodology often applied in bioethics. The term generally refers to the framework proposed by Tom Beauchamp and James Childress in *Principles of Biomedical Ethics* (Beauchamp and Childress 1979), which is considered a milestone in bioethical literature. It is important to highlight that principlism was not designed to be a comprehensive ethical theory alternative to deontology or consequentialism. On the contrary, it suggests a theoretical framework for solving moral conflicts in biomedical context. Hence, principlism is specifically an ethical framework employing general and unranked moral principles recovered from different traditional ethical theories. By incorporating deontological along with consequentialist principles, it proposes a *pluralistic* approach to bioethical conflicts.

The pluralistic nature of principlism entails that principles and rules are *prima facie* binding. The *prima facie* conception of principles holds that more than one moral principle can be applied in certain circumstances. Therefore, the right action has to be assessed by looking at all the morally relevant aspects of the particular case and has to be identified through a practical judgment. Moral principles and rules are not ranked: there is no prioritization among them, and clearly there is no *absolute* principle from which all the others are derived from or refer to. Nevertheless, when facing a concrete and specific moral conflict in a particular context, some considerations and therefore related principles and derivate rules can outweigh others and come to play the central role in justifying a course of action. Principlism, lacking a ranking of principles, does not assign in advance weight to different principles, yet the importance of each of them has to be evaluated within specific context and circumstances – that is to say, while engaging in concrete case analysis. Finally, the principles provide guidance in the process of resolution of moral conflicts

by providing ethical justification to different possible courses of action and thereby helping in deciding whatever should or ought to be done.

There are four primary principles identified as foundational for biomedical ethics: respect for autonomy, beneficence, non-maleficence, and justice (Beauchamp and Childress 2013).

The principle of *respect for autonomy* is rooted in the democratic liberal political and moral tradition of individual's freedom of choice and self-determination. In traditional moral theories, as seen above, autonomy refers to the capabilities of self-governance and therefore respect for autonomy requires the acknowledgement and enhancement of self-determination. Hence, respect for autonomy in its broad formulation involves both negative obligations/duties as well as positive obligations/duties. In clinical context, physicians' negative duties entail to neither obligate nor force patients to undergo medical procedures, for which patients' consent is (almost) always mandatory. As positive duties, physicians ought to provide patients with all the information needed to make a truly informed and voluntary choice, as well as the adoption of actions that fosters patients' individual decision-making.

The principle of *non-maleficence* relies on the often quoted maxim «*primum non nocere*» - «above all, do no harm». In common morality, most of the rules can be traced back to the principle of non-maleficence in that they require avoiding causing harm, such as do not kill, do not disable, do not cause pain, do not deprive from pleasure. Bioethical literature reports similar but more specific rules and prohibitions grounded in the principle of non-maleficence. The most prominent examples of non-maleficence-based rules entail the moral obligation not to neither intentionally nor negligently cause harm to patients.

The principle of *beneficence*, roughly speaking, entails the moral duty to act for the benefit of others. In medical context it is usually referred to as the most important demand to take care of patients. However, it might come into conflict with the principle of non-maleficence, for any medical intervention or procedure inherently includes the possibility of harm. For example, in the case of mammography test, the physical pain of undergoing the test itself can be considered a harm, which the principle of non-maleficence would require to be avoided. Nevertheless, the benefit of early detection outweighs the harm of the test and therefore mammography screening appears to be morally justifiable.

The principle of *justice* has many different specifications, yet the most commonly applied states that «like cases should be treated alike» (*ibid.*). In this general formulation, the principle does not assert the role of justice in different contexts, but it only states that in situations in which individuals are alike, they ought to be treated alike. Therefore, it lacks a substantive guide in decision-making, while it calls for taking into account equity and equality when deciding about possible courses of action. Different approaches and theories of justice have been developed in philosophy, and as principlism does not aim at presenting a theory, it takes advantage of and incorporates each of such theoretical concepts of justice depending on the concrete and specific circumstances at stake. In other words, principlism adopts a mixed usage of principles of justice derived from the main available theories. The choice of adopting one concept of justice over another strictly depends on the case in question.

3.4. Concrete case analysis through principle-based methodologies

As outlined above, principle-based methods aim at engaging in bioethical reasoning and addressing moral concerns and possible conflicts through the application of ethical theories. Among the possible range of ethical theories, some are

comprehensive – such as utilitarianism and deontology - while other approaches provide a list of *unranked principles* to guide moral analysis and deliberation. Nevertheless, in order to effectively address specific moral concerns regarding concrete cases, general principles and rules need to be applied. Broadly speaking, the evaluation and judgment of and the solution sought in possibly arising moral conflicts within the medical context depend on the ethical theory we decide to endorse. Specifically, given the general and indeterminate nature of principles proposed by the principle-based methods of consequentialism and deontology, as well as principlism, a connection between principles and concrete case has to be operated.

Connecting general and abstract principles to concrete cases might not always be a simple task. Indeed, three major difficulties may occur: 1) it might be unclear whether a concrete case falls under one principle or another; 2) in a specific situation the very same principle might point in different directions concerning the best course of action to be undertaken; and 3) while engaging in moral reasoning, a real or apparent conflict – or even dilemma - between principles might rise doubts about prioritization and thus possibly results in a decisional impasse. Therefore, a model of connection between principles and cases shall be used. In this respect, Richardson proposed three models of connection to resolve concrete ethical problems (Richardson 1990), which are defined as schemes «of what it would be to bring norms to bear on a case so as to indicate clearly what ought to be done» (*ibid.*, p. 281).

The first model of connection consists in the direct *application* of principles to concrete cases. In this respect, it represents a purely deductive approach to ethical problems entailing a deductive inference that subsumes the cases under general rules. The process of subsuming cases under principles is based on the individual faculty of moral judgment. However, the *application* framework does not always function effectively, for some requirements must be fulfilled. Indeed, the principle's

weight can be *a priori* established, and thereby, the principle does not come into conflict with other equally weighting principles (Steinbock 2007). In accordance with the presented bioethical methodologies, it clearly appears that the deductive model of *application* can effectively work only within an *absolute principle* framework – such as deontology in its secular or religious form. Nevertheless, even adopting a deontological approach often does not prevent from encountering conflicts between moral rules and claims. Indeed, the analysis of a specific case may uncover the possibility of different possible courses of action based on the adoption of two different moral rules, which can both be deducted from the same absolute principle. For example, as Christine Korsgaard points out (Korsgaard 1986), the deontological duty *not to lie* might come into conflict with the duty to *prevent harm* leading to a moral dilemma. Imagine that someone is willing to kill your friend you're hiding upstairs; the murderer knocks at the door asking whether your friend is inside. By telling the truth, you would be somehow an accomplice and therefore, while respecting the duty *not to lie*, you would violate the duty to *prevent harm*. On the other hand, by lying to the murderer you would *prevent the harm* to your friend by violating the duty *not to lie*. The dilemma resolution hence requires a further level of case analysis and specification and/or balancing of rules and principles (Richardson 1990).

Conversely, the adoption of *prima facie* sets of principles such as principlism requires a slightly different approach to conflict resolution. Indeed, a possible way of solving concrete ethical problems without engaging in further specification and balancing of ethical principles is to arrange them in an *a priori* order that explicitly holds a rank among the principles and rules. A bioethical framework might for instance establish that the principle of autonomy always outweighs the principle of beneficence in those concrete cases in which the subject is a competent adult whose

clinical choices are under analysis (Engelhardt 1996). Further, a possible ranking system can hold that non-consequentialist principles always outweigh the consequentialist ones (Veatch 1995). However, appealing only to the deductive model of principles *application*, even in light of a ranking system, might not resolve all conflicts. Therefore, another mean of reducing or eliminating eventual conflict consists in *specifying* the general principles (Richardson 1990).

As mentioned above, many moral rules are specification of more general principles, and function as guides in concrete situations. Therefore, the identification of specific rules of behaviour results by *specifying* principles – for example rules of informed consent specify the *principle of autonomy*, and the duty not to kill specifies the *principle of non-maleficence*. The process of specification consists in restricting the scope and range of a general principle to concrete situations and thereby possibly increasing its weight against other conflicting principles within concrete case analysis. In this respect, *specification* works as a guide in determining the concrete meaning, range and scope of general moral principles and therefore might be an effective means for guiding actions (Beauchamp and Childress 2013).

Nevertheless, even if the meaning, range and scope of a principle have been determined by *specification*, the question regarding its weight might still persist. *Balancing* principles hence represents a way of trying to resolve the conflict by determining which principle weighs more in specific circumstances. This process consists in the intuitive *balancing* of moral considerations in order to assess the weight they come to have in concrete cases (*ibid.*). The question of balancing regards the explanation and/or justification to provide in prioritizing a principle or rule over competing ones with no direct call to the more general principles. In the case of principle-based methods entailing *prima facie* duties – such as principlism – the rightness or obligation of acts depend on their adherence to general moral principles.

However, some acts in concrete circumstances may present features adherent to some principles but that at the same time may contravene other principles. In the previously mentioned example of lying, telling the murderer the truth would cause a great harm, while lying to the murderer would prevent it. The moral problem regards the judgment of which duty among *veracity* and *harm prevention* outweighs the other. In this case, the consequences of veracity are far much worse than the violation of veracity itself. Of course such a specific judgment cannot be formulate on the basis of *a priori* formulation, for within a *prima facie* conception of principles both duties are morally binding, other considerations being equal (Richardson 1990).

The most common and strong critique of the principle-based approaches – and especially of principlism - is that they fail to provide a comprehensive theory, and therefore no concrete guide for action is available to the agents (Clouser and Gert 1990). Specifically, the process of *balancing* the various principles and rules in the case of conflicts appears to excessively rely on intuition. In other words, the criticism relates to the methodology of applying general principles to concrete cases, which is labelled to be insufficiently deductive. Therefore, by leaving room for individual subjective intuition in the conflict resolution processes, principle-based methods involve an arbitrary element (*ibid.*).

3.5. Virtue ethics

The principle-based approaches focus on acts, which might be justified by their adherence to general moral principles (deontology), by their maximization of positive consequences and effects (consequentialism), or by a mix of the two (principlism). By contrast, virtue ethics draws attention to the agent and his/her character, moral judgment, motivations, and emotions. This viewpoint stems from the call for a return of moral philosophy to focus on virtue and character in order to establish normative ethical theory, instead of emphasising the role of duties and actions in morality

eventually resulting in rigid moral codes (Anscombe 1958). Among the different forms of virtue ethics that were developed in the twentieth century, almost all share three major concepts derived from ancient Greek philosophy, in particular Aristotle's well-known *Nicomachean Ethics*. The three concepts employed by virtue ethics are *arête* (virtue or excellence), *phronesis* (practical wisdom), and *eudaimonia* (loosely translated as happiness or flourishing).

Arête - Virtues are the excellent traits of character and dispositions to act held and exercised by the agent. Being dispositions rather than habits, virtues entail a way of feeling, noticing, valuing, expecting, desiring, choosing among different ways of action, and reacting to concrete circumstances in a characteristic way. James Rachels provides a definition of virtue as «a trait of character, manifested in habitual action, that it is good for a person to have» (Rachels 2007, p. 178). Virtue ethics focuses on the importance of the kind of person we should be and become in order to live a good life, rather than on the actions we should perform. To be virtuous means to be a certain kind of person with a complex mind-set who adopts a distinctive set of considerations as reasons for embarking on an action as well as not undertaking it.

Phronesis – Practical wisdom can be defined as the knowledge and understanding that enable the agent to do the right thing in specific concrete circumstances. Exercising and improving practical wisdom is a part of the (potentially never ending) process of moral self-education. Life experience is a fundamental aspect influencing practical wisdom, in that it enables to understand and prioritize the morally relevant features of a situation by taking into account what is truly important in human life.

Eudaimonia – The purpose of human life is to achieve a state of *eudaimonia*. The most common translations of the term are *happiness* or *flourishing* considered as

the kind of happiness that is lasting, deep and worth having. By performing and exercising the one's distinctive functions at their best level it is possible for the individual to achieve a state of *eudaimonia*. Because virtue ethics advocates and proponents conceive human beings as inherently rational and social, the exercise of both rationality and morality is what constitutes and leads to *eudaimonia*. Therefore, possessing virtues and exercising them with practical wisdom in order to make good choices and act well are the two pre-requisites to achieve a state of *eudaimonia*.

3.5.1. Defining virtues

In general, moral virtues are the virtues of human beings as such, those that make a life worth living and promote the exercise of specifically human characteristics, those characteristic that should be fostered in people. Providing a conclusive and comprehensive list of virtues is a hard task, nevertheless Rachels (Rachels 2007) provided what he defined a partial yet reasonable start:

Benevolence	Fairness	Reasonableness
Civility	Friendliness	Self-confidence
Compassion	Generosity	Self-control
Conscientiousness	Honesty	Self-discipline
Cooperativeness	Industriousness	Self-reliance
Courage	Justice	Tactfulness
Courteousness	Loyalty	Thoughtfulness
Dependability	Moderation	Tolerance

However, one thing is to provide a list of virtues, another thing is to explain what being virtuous means. In trying to understand what exactly virtues consist of, it might be useful to proceed with an example. Beside and beyond the fact that each virtue has its own features and characteristics, the example might serve as a guide for further reasoning by analogy and examination of other virtues. Let's take the virtue of *loyalty* - and specifically *loyalty to friends and family* as outlined by Rachels (*ibid.*) - as an example. When we learn about someone charging a relative or a friend in court we

may be somehow astonished, or at least feel a bit surprised. Conversely, we can overall empathize with a parent forgiving his son for a serious crime despite the law breach, or with someone standing by a friend who behaved completely inappropriately, for instance in the workplace. The reason beyond the “despite-all sympathy” lies in the fact that we acknowledge that there is something morally special about family and friends. This special moral status of friends and family members is such that we treat them differently than how we treat strangers. It is not a matter of being nice - and even nicer than to stranger - to people we like. Familial and friendly relationships entail reciprocal duties and responsibilities, which are integral parts of what being a friend or a family member actually means. The familial and friendly bonds consist in feelings of *affection* and *love* toward the loved ones, who therefore become subjects of our special consideration.

The first explanation might be that such relationships provide mutual material assistance and support. However, there seem to be some benefits going far beyond it. At a closer look, deeper psychological issues come into play at two different levels. On the one hand, by sharing our successes and achievements we experience a status of happiness that would not be so significant without someone to share the joy with, and at the same time the understanding of the loved ones is a source of major relief during hard times. On the other hand, our self-esteem largely relies on friends' and family members' returning of our affection, which confirms our value and worthiness as persons. Nevertheless, given the mutual nature entailed in friendly and familial relationships, they require the possession of those qualities enabling us to be a friend. *Loyalty* is certainly at the top of the list of the qualities (virtues) we need in order to be a friend to someone. Family members and friends should be able to count on each other despite the hard times, to expect forgiveness of eventual offences, as well as to

refrain from harsh judgments.

Of course, virtue ethics proponents acknowledge that we also have duties to other people, and even to strangers. However, these duties are different in that they are associated with different virtues and different levels of human relationships and interactions. Taking as examples two virtues related to principles discussed above (see Chapter 3.3.3. *Principlism*), in light of virtue ethics *beneficence* does not require the same degree of concern for strangers that it requires for family and friends, and *justice* applies differently within familial and friendly contexts, with different considerations regarding the meaning of impartial treatment for all. Virtues are those traits of character needed to conduct a good life. Because human nature is inherently rational and social, virtues are ultimately those traits required to interact successfully in the private as well as in the public sphere of life.

3.5.2. Applying virtue ethics to bioethics

As shown above, different kinds of human interaction might imply different virtues as well as different values and goals. While the list of virtues proposed by Rachels is not exhaustive, it aims at covering the major characteristics human beings might be required to apply in common life relationships. However, some of the professional roles we endorse during life – for example being a teacher or a medical doctor – require specific intellectual and moral characteristics to successfully behave and interact within the professional environment. In the clinical context, not all of the above-mentioned virtues are required to achieve the ends of medicine, yet some specific virtues appear to be of fundamental importance in establishing an effective relationship between patients and health care professionals (Holland 2011).

In the past few decades, a growing body of bioethical literature adopted virtue-based approaches to specific issues such as euthanasia (Foot 1977) (Gardiner 2003),

abortion and assisted reproduction (Hursthouse 1991). For example, Edmund Pellegrino (Pellegrino 1995) proposes a list of virtues rooted in the specific professional traditions of medicine and nursing. The list is intended to set out the most essential virtues defining a “good” clinician, a “good” nurse, and broadly any “good” health care professional. The seven major virtues Pellegrino identifies are: fidelity to trust and promise, benevolence, effacement of self-interest, compassion and caring, intellectual honesty, justice, and prudence. The seven virtues are mutually reinforcing and no priority order can be established among them, being all entailed by the end of the healing relationship itself (*ibid.*).

More broadly, clinicians and health care professionals have further developed accounts of virtues for clinical setting claiming that practical wisdom (*phronesis*) is closely related to traditional clinical judgment (Kaldjian 2010). Therefore, they argue, virtue ethics represents a more feasible theory than principle-based approaches to tackle the complexity of concrete clinical decision-making (Kaldjian, Weir and Duffy 2005) (Holland 2011). By focusing on wisdom and good judgment, virtue-based ethics can hold together the wide range of clinical goals, options and goods, and thereby constitute a moral guide for health care professionals (Kotzee, Ignatowicz, and Thomas 2017). Finally, by emphasising the concept of *eudaimonia*, virtue ethics is an excellence-oriented approach that serves better the healing goal of medicine than the principle-based ones, which are blamed to only require a minimum standard of moral actions that can be achieved by mere compliance to rules (Barilan and Brusa 2013).

There are two main critiques commonly directed towards the application of virtue ethics in bioethical contexts. First, advocates of principle-based approaches charge virtue ethics with not providing a concrete guide to medical practice and

therefore as not being able to practically solve concrete ethical problems. From this point of view, virtues provide the agent with motivation to realize what has already been judged right according to principles or rules (Oakley 2009). Second, without a set of principles to rely on, and from which to derive moral rules, virtue ethics provides little normative strength and therefore leaves room for arbitrary decisions among different courses of actions (*ibid.*).

3.6. Care ethics

In line with virtue ethics approach, the ethics of care (or care ethics) represents another alternative to traditional moral theories. On the basis of experience, reflection and discourse, the ethics of care develops an understanding and theorization of values, which are considered most basic and most comprehensive in human life. Hence, the common moral experience of human beings constitutes the starting point of ethical theorizing and models of approaching moral issues. Although there are similarities between virtue ethics and the ethics of care, the major distinction stands in the focus on disposition and character traits of the first, while the second emphasises the importance of relations (Held 2006). Based on this fundamental distinction, it is possible to consider the ethics of care as a distinct comprehensive moral theory having some similarities to virtue ethics. The basic feature of care ethics is, in contrast with deontological and consequentialist moral theories, the acknowledgment of the fundamental importance of dependency and response. In this respect, care ethics involves a shift in moral perspective and therefore a change in the focus on moral actions from what is right, to how to respond to the needs of others (Manning 2009).

The ethics of care is rooted in the wider constructive phase of the feminist thought and rethinking of the fields of enquiry themselves, which took place in the US

and Europe in the late 1960s. The major feature of feminism is the revolutionary character of the movement that aimed (aims) at overturning the so-called hierarchy of gender (Held 2006). So far, the most important achievement of feminism has been the establishment that women's experience is not only important and relevant in the social and political context, but also interesting from the philosophical (Diprose 2000) and especially ethical viewpoint (Noddings 2010). Interestingly, the feminist moral inquiry begins with experience, which has not to be interpreted as mere empirical observation, but as the lived experience of feeling, thinking and acting (Kriegel 2007).

Virginia Held (Held 2006), one of the most prominent proponents of feminist thought, roots the beginning of care ethics in the essay by Sara Ruddick *Maternal Thinking* published in 1980 (Ruddick 1980). In this work Ruddick analyses the practice of mothering, the kinds of thinking it gives rise to and the moral values and standards that derive from it. She argues that the aim of mothering is to preserve life, foster growth and help children to develop into acceptable persons. While mothering can be an ambivalent practice, sometimes characterised by hostile feelings toward children, the commitment and goals of mothering should provide standards to heed (*ibid.*). In 1982 Carol Gilligan's *In A Different Voice* provided a new impetus to the growth of care ethics by hypothesizing different ways in which men and women interpret, reflect on, and talk about moral issues and problems (Gilligan 1982). Gilligan argued that women are more inclined to refer to moral issues in terms of actual relationships and context, instead of appealing to general and abstract rules and principles. Although Gilligan's work did not provide strong empirical evidence, it rather presented a plausible alternative perspective on which further studies, inquiries and theorizing relied (Held 2006). Two years later, in 1984, Carol Noddings's

Caring brought forward the feminist outlook of ethics by theorizing a phenomenological account of caring activities and focusing on relation as a fundamental feature of care (Noddings 1984).

3.6.1. Features of the ethics of care

The advocates of the ethics of care generally endorse the ontological assumption that the more the self is connected and related to others, the better the self is (Fielding et al. 2007). This presupposition is strongly in contrast with the traditional conception of moral agents as rational subjects who, by engaging in a purely rational moral deliberation, abstracting themselves from particular circumstances, and invoking general abstract principles, can arrive to a proper ethical judgment. Traditional ethical theories are criticized by proponents of the ethics of care for building the image of independent, rational and autonomous individuals. Indeed, the ethics of care is built upon the epistemological presupposition according to which particular, concrete and emotional knowledge, as well as partial viewpoints, better expresses people's experience of life and of the world (Tronto and Fischer 1990) (Tong 1998) (Held 2006).

Care ethics scholars claim that the conception of person as a rational, autonomous and self-interested agent endorsed by the traditional theories has been directly imported from the liberal political theory. According to this line of critiques, the liberal conception fosters the wrong idea that society is composed of a sum of unrelated, independent, mutually indifferent individuals who are assumed to be equal (Held 2002). Moreover, traditional moral theories have focused on "public life" as relevant to morality, while ignoring the relevance and moral significance of "private" domains of life such as family and friendship. The moral agent was hence conceived as an abstract and fully rational subject, potentially choosing to associate with other

individuals. Traditional moral approaches have then developed universal, rational, abstract and general accounts of morality systematized in principle-based theories – mainly deontological and consequentialist theories, of which principlism is a derivation. The liberal conception provides an idea of person suitable for interactions among strangers, such as political, economic and legal efforts, yet running the risk of shaping individuals' moral life in so universalistic terms that it prevents them to take into consideration specific circumstances and others' actual interests.

By contrast, scholars and advocates of the ethics of care endorse a *relational conception* of person, as inherently interdependent and relational, both at the ontological and epistemic level (Diprose 2000). Right from her birth, every person begins as a creature dependent on those caring for her. The whole human life, and especially childhood and old age, is characterised by interdependency. Also the very possibility of thinking of ourselves and acting as independent individuals depends on social and relational networks. Such relations are not only necessary to foster human growth, but they are also an important part of what constitutes one's *personal identity* (Feary 2003) (Kriegel 2007). The emphasis on the relatedness of persons calls for the acknowledgment that several of our moral responsibilities come from being embedded in specific familial and social context. In particular, the concept of *equity* is extremely difficult to apply in “private” domains of life, which are by nature characterised by power imbalances. This is especially evident within familial contexts: relations between family members are marked by power imbalances at the physical, cognitive, moral, as well as economic and political level. These constitutive inequalities are all the more obvious when we consider relationships between parents and children, the latter being not only unequal with, but also and most significantly dependent on the firsts for many years.

Interestingly, the dependency of children on parents is twofold. First, children are dependent in their physical needs to survive and grow such as nourishment, warmth and protection. Second, children depend on parents for their psychological needs, which are as necessary to a healthy survivorship and growth as the physical ones. In fact, providing children with adequate nourishment, shelter and warmth, could not possibly be enough to develop those psychological capacities needed for human flourishing (Noddings 2010). The development of intellectual and moral capacities calls for something beyond providing physical and material sustenance. Activities such as holding, interacting with children and responding to their needs are required. Moreover, for children to become adults capable of successfully living – flourishing – in a specific historical and social context, language and cultural practices need to be taught as well (Noddings 1984).

By taking the parental relation as a model, and especially the maternal one, we can provide an initial sketch of what *caring* is: to care means to take responsibility for those who depend on us, both at the physical and at the psychological level. Caring is therefore a practice and a value, in that the fundamental emphasis of moral experience is put on the importance of understanding of, meeting and attending to the needs of those subjects we take responsibility for (*ibid.*). Human beings are intrinsically dependent one on another, especially in the early and elderly years of life. The moral claim for care of those dependent on others for their needs is of paramount importance. Moreover, developing caring relationships is considered of high moral value, in that caring relationships enable human being to live, progress and flourish. Care ethics therefore requires individuals to take responsibility for others embedded in such relationships, while more individualistic approaches may require only not to interfere with others' projects and life-plans (see Chapter 3.3.2.

Deontology). The claim for care and the moral obligation of caring hence appear to be compelling regardless of more abstract moral principles, such as justice. Care ethics advocates blame traditional ethics' emphasis on autonomy, independence and rationality for not accounting for these intrinsic and fundamental aspects of human life (Held 2006).

The ethics of care also values the role of emotions in moral deliberation rather than rejecting them. This feature is strongly in contrast with most of traditional moral theories, and especially with deontology and utilitarianism, which call for a rational approach to moral reasoning. The refuse of rationalist approaches nevertheless does not imply a complete acceptance of all ranges of emotions. Empathy, sympathy, sensitivity and responsiveness are highly valued by care ethics in that they are considered the kind of *moral emotions* that need to be cultivated. Emotions play a double role in moral deliberation: on the one hand, they serve as guides to better ascertain what actions are morally required; on the other hand, they help the implementation of rational dictates. Emotions are therefore *epistemic guides* in moral experience and may contribute to the appropriate evaluation of the moral right and wrong (*ibid.*). Even those emotions traditionally considered as negative can act as component of a proper moral judgment. For example, anger might be a very useful component of moral indignation in the case of assessing unjust or inhuman actions (*ibid.*).

In other words, the ethics of care acknowledges and recognises an important role in moral reasoning for those relational feelings and emotions that in concrete circumstances enable people to understand what needs and interests are at stake. Of course, raw emotions shall not guide morality and, in general, emotions should be cultivated and reflected upon. In this respect, the kinds of feelings that should be

discarded from moral judgment of actions overlap with those typically rejected also by traditional rationalistic ethical theories for they interfere and possibly undermine moral duties or norms (Fielding et al. 2007).

As already mentioned, the ethics of care strongly criticizes the universalistic and abstract approach to morality of the traditional ethical theories, and especially the priority given to impartiality in moral reasoning. Indeed, as dependency and caring relationships are recognized as the fundamental human features, moral claims of particular others may still be valid even though they conflict with more abstract universal norms. However, advocates of care ethics argue that such conflicts could be prevented if universal norms come to incorporate relational and care norms (Held 2006).

Finally, the ethics of care does not seek to dismiss universal rules from any domain. On the contrary, it acknowledges the importance of universalization of norms and rules in domains such as law, but it rejects the adoption of such an approach in other contexts where they appear inappropriate. In familial and friendly relationships, for instance, usually there is no sharp conflict between the interests of those involved, for interests are closely intertwined. Moreover, in this kind of relationships, individuals are not acting for the sake of humanity, yet they are committed in promoting and preserving actual relations with particular others. Therefore, a universalistic appeal to the principle of justice does not seem suitable to provide a guide for concrete action within familial and friendly relationships²³.

²³ A commonly shared experience among children is that of being told by adults to “eat everything on the plate for the sake of those starving”. While this common rebuke clearly has the educational aim of teaching the value of food, the appeal to a somewhat kind of justice does not seem to hold on children, who often reply that they are not hungry or just dislike the meal. It would be interesting to test different approaches more closely related to children’s daily experience and therefore eventually more effective, such as inviting them to help cooking or cleaning the vegetables in order to understand the

3.6.2. Defining care

While the features of care ethics provide insights into the approach to moral experience and morality, the concept of *care* still needs to be defined. Because of its dependency on contextual issues and considerations, care is an elusive concept and several descriptions of it have been provided. In general, the ethics of care adopts a conception of care as a practice and a value – like justice. Therefore, care needs a theorizing to provide valid norms, which serve to evaluate practices of caring. In other words, not just care itself, but an *ethics of care* is needed, meaning that the different aspects and expression of care – as well as of caring relations – have to be subjected to moral scrutiny and moral evaluation.

Joan Tronto defined *care* as those kinds of «activity that includes everything we do to maintain, contain, and repair, our “world” so that we can live in it as well as possible» (Tronto and Fischer 1990). In order to further specify this broad definition, Tronto listed four sub-elements of care, which have to be interpreted at once as *stages, dispositions* and *goals*: 1) attentiveness, which is the propensity to become aware one self's and others' needs; 2) responsibility, which refers to the willingness of meeting of and responding to needs; 3) competence, which regards the possession of skills to choose the best means to provide successful and good care; and 4) responsiveness, which entails the capacity to consider the others' position as they experience it (Tronto 1994).

Hence, similarly to the virtuous moral subject described by virtue ethics, the good carer seeks to flourish by enhancing and promoting her own intellectual and emotional, as well as social capacities. Care calls for the establishment and nurturing

labour behind a dinner, or maybe explore and understand their tastes, or perhaps just to remark that food is energy to play, to draw, to read and to run – in other words, to *flourish* as a kid (Montessori 2007).

of a relation first with oneself, and then with others: to care for oneself is a requisite in order to be able to care for others. Furthermore, among the four sub-categories, attentiveness and responsiveness can – and should - be trained as the fundamental aspects of human life; while the acquisition of competence skills can be achieved through specific training with respect to the particular circumstances of caring in which the subject is committed; and finally taking responsibility for those in need of care represents the moral duty each agent ought to observe (Held 2006) (Tronto 1994). Therefore the concept of care has a moral normative power in that it specifies duties and obligations that can be generally defined as *taking responsibility for those in need by engaging in a caring relationship that aims at understanding and responding to particular needs in the best possible way*. In this sense, the concept of care resembles the deontological duty of respect for autonomy, to which the agent is called to provide a concrete content.

However, the sub-elements of *care* move a step forward by determining the ways to understand one's moral role and therefore define means of moral actions depending on specific circumstances in which the caring relationship takes place. To properly take care of a new-born - who does not verbally express her needs - requires the development of acute attentiveness and punctual responsiveness, as well as the acquisition of competences regarding nutrition and nurturing. While taking care of a friend requires the building of an affectionate relationship, the development of relational skills is based upon trust and intimacy, which enables each other to flourish. Finally, care ethicists argue that the same model of *care* can also be effectively applied to professional relationships and specifically to the health care field, which by nature entails a dependent relationship between health care providers and patients (Tong 1998) (Donchin 2001).

3.6.3. The ethics of care in bioethics

The ethics of care represents another approach that seeks to provide an alternative to the principle-based methodologies and it has been applied mainly in nursing and rehabilitation contexts (Manning 2009). Nowadays medicine deals more and more with chronic illness, rehabilitation and prevention, whose goal is by nature different from the goal of medicine dealing with acute conditions (Donchin 2001). Indeed, the goal of chronic and preventive medicine is either reducing the progression of a disease and improving physical functioning and quality of life, or reducing morbidity and mortality from a given condition by means of *early detection* and treatment of asymptomatic individuals who developed risk factors for the given condition; whereas, in the context of acute illness, the goal of medicine is to cure and heal sick individuals (see Chapter 1.1. *Prevention is better than cure*). On the basis of such goal-of-medicine distinction, Donchin argued that traditional ethical theories and autonomy conceptualization seem more suitable to the cases of acute illness, in which the goal is clearly determined and the encounter between physician and patient mainly revolves around the decision to be taken among different treatment options (*ibid.*). Instead, in the context of nursing practice and preventive medicine, care ethics provides a more useful guidance in that it acknowledges the importance of listening, understanding the needs, and accounting for patients' self-conception and personal goals (*ibid.*) (Manning 2009).

Furthermore, in addressing political and bioethical issues, Diemut Bubeck provides a definition of care as «the meeting of the needs of one person by another person, where face-to-face interaction between carer and cared-for is a crucial element of the overall activity and where the needs is of such nature that it cannot possibly be met by the person in need herself» (Bubeck 1995, p. 129). Caring for

someone is therefore different from providing a service, the latter not involving a dependency state on someone else. It is worth noting that, although care ethics recognises an important role of emotions in moral deliberation, there is nevertheless no need for emotional bond between the carer and the cared-for. In fact, care can be provided in public contexts, such as public health care services, which do not require nor entail any specific affective or emotional connection to be properly carried out. Finally, health care professionals have deliberately chosen to have a formal role in health care practices. Medical professional roles inherently entail taking responsibility for patients in need and engaging in caring relationship. Healing is a part of the job, which however implies many other activities as ways of meeting patients' needs in a broader sense, from psychological well-being, to emotional understanding, from inclusion of individual preferences and beliefs, to relatives' involvement in clinical decision-making (Tong 1998). Therefore, by cultivating caring skills, health care providers can expand opportunities to strengthen patients' capacity and awareness of their agency, as well as encourage them to relate with others in those ways that support their goals (Manning 2009).

The range of critics to the application of care ethics within health care context is similar to the one generally moved toward virtue ethics (see 3.5.2. *Applying virtue ethics to bioethics*). More specifically, given the absence of general principle to rely on and appeal to in cases of conflicts or dilemmas, advocates of principle-based approaches charge care ethics with not being able to practically solve concrete ethical problems – in other words, with not providing a concrete guide to medical practice and with leaving room for arbitrary decisions (Oakley 2009). Cost-benefit analysis employed by consequentialism as well as appeal to deontological rules called by principlism advocates rely on what they consider more objective concepts and

approaches that are not only useful, but also needed while facing concrete problems. In response to such critics, advocates of the ethics of care argue that their moral epistemology better tackles concrete problems and that the concept of care has a normative power in moral deliberation. Therefore, some moral rules can be derived from the general concept of care, which thereby provides guidance in concrete problems resolution.

3.7. Summary

The many complexities of breast cancer screening programs range from public health considerations on what good is to be pursued, to individual decision-making under uncertainty, from the establishment of reliable scientific trials, to the acknowledgment of individual women preferences, values and personal goals. The specifically interdisciplinary nature of bioethics, which crosses the boundaries of philosophy, ethics, medicine, biomedical sciences, and public policy, represents a promising approach to the ethical analysis of breast cancer population-based screenings. Bioethics is usually considered a form of applied ethics, in that ethical theories and frameworks are applied to the issue at stake. The most commonly used methodologies can be grouped into principle-based and non-principle-based methods. The principle-based methods are considered dominant in bioethics and include *consequentialism*, *deontology* and *principlism*. As shown, these approaches share the adoption of general moral principles from which to derive moral rules and moral considerations as concrete guides for action. In general terms, among principle-based methodologies, there are two opposite conceptions of moral principles and considerations. On the one hand, the *absolute* conception, which holds that a moral principle is a universal claim, for any action or decision of a certain kind is right or wrong on the basis of its adherence to the moral principle in question,

which has to be assessed through rational judgment (*deontology* and *consequentialism*). On the other hand, the *prima facie* conception holds that more than one moral principle can be applied in certain circumstances (*principlism*). Therefore, the right action has to be assessed by looking at all the morally relevant aspects of a particular case and choosing the right principle through practical judgment. In case of a conflict between different *prima facie* duties, principles need to be *applied, balanced* and *specified* in order to decide which one has the priority over the others. Beyond the differences in deducing rules for action, the three methods propose rational, abstract and general accounts of morality systematized in principle-based theories from which rational moral agents derive guidance and justification for actions on the basis of their adherence to general moral principles – *deontology*; maximization of positive consequences and effects – *consequentialism*; or a balanced mix of the two – *principlism*.

On the contrary, *virtue ethics* and the *ethics of care* draw attention to the moral agent and his/her character, disposition, capacity of moral judgment, and emotions. Beside this fundamental feature, the major distinction between the two approaches stands in the focus on disposition and character traits of *virtue ethics*, while the *ethics of care* emphasises the importance of relations, dependency and needs. In this respect, *care ethics* involves a further shift in moral perspective in that the focus of moral actions is on how to respond to the needs of others. In the past few decades, a growing body of bioethical literature has adopted virtue-based and care-based approaches to specific issues and additional theorizations have been proposed. Advocates of virtue ethics have mainly focused on listing the virtues defining a “good” health care provider and on promoting the feasibility of practical wisdom as a moral guide in health care settings, for it can hold together the wide range of clinical goals,

options and goods. On the other hand, proponents of *care ethics* claim that the adoption of *care* as a practice, value and disposition provides the specification of what professional moral roles require in terms of meeting the needs of others.

The next Chapter will analyse how different methodologies face and conceptualize moral questions and concerns arising from population-based mammography screening programs, and aims to provide a suitable ethical framework.

CHAPTER 4

The ethics of mammography screening

4.1. Introduction

Population-based screening programs entail many complexities, combining considerations of economics, ethics, effectiveness and equity. Ethical issues emerge at all stages of population-based screening programs, from establishing a new screening procedure, to participants' recruitment and actual testing and monitoring of the program. Hence, arising ethical considerations and analyses are of interest to citizens, health care professionals, and policy makers. The Chapter ahead, taking advantage of and systematically applying the theoretical elements presented in Chapter 3, aims at providing an ethical analysis of mammography screening from two different viewpoints. First, features of public health are presented and an overview of public health ethical issues is outlined. Specifically, the arguments focus on the moral justification of screening programs and particularly mammographic ones, highlighting the intrinsic tension between the public and the individual perspective on health.

The second part of the Chapter focuses on the individual perspective and specifically on patient-physician relationship models, which are analysed with regard to mammography screening decision-making process, which represents a concrete case of complex clinical decision-making. Features and elements presented in Chapter 2 are implemented and scrutinized. Particular relevance is put on the statistical nature of scientific evidence and the uncertain balance between benefits and harms of

screening, which challenge physicians in delivering a complete and understandable information. Following the age-group division endorsed by most Western countries' guidelines, the ethical analysis addresses especially women aged 40 to 49, who face the biggest uncertainty. Throughout the paragraphs, ethical principles, perspective and theories presented in Chapter 3 are applied to the case at stake and critically analysed.

4.2. A public health perspective on mammography screening

The object of public health inquiry is population, and not individuals, for public health is by nature a public and communal good. The promotion of public health implies a core commitment to prevention, which can be categorised as *primary*, *secondary* and *tertiary* depending on the aim of the intervention itself (see Chapter 1.2. *Prevention is better than cure*). At the population level, the benefits for an individual cannot be discerned from those for another, in that public health policies endorse epidemiological and statistical approaches for identifying and designing the interventions. As a consequence, benefits and burdens of public health interventions often fall in a non-uniform manner on population sub-groups as well as on individuals in target-populations. In this respect, preventive population-based programs such as mammography screening raise a preliminary set of questions about the consideration of persons and individual lives as numbers.

Moreover, all public health policies aim at advancing good health outcomes and avoiding or preventing bad outcomes, to which, given the purely outcome-oriented approach, *consequentialism* is often invoked to provide moral justification and foundation (see Chapter 3.3.1. *Consequentialism*). However, in public health ethics discourses, consequentialist arguments are usually constrained by additional deontological concerns regarding individual autonomy and rights, as well as ulterior

justice-based claims for fair distribution of benefits and burdens (Childress et al. 2002). Therefore, public health interventions are mostly justified by a mixed set of moral considerations and rules derived from different ethical theories that come into the assessment of what constitutes the greatest good to pursue. Such principles and rules are traceable to the ethical theories of *deontology* and *principlism*. Yet, traditional moral principles are designed for clinical practice and mainly focus on patient-physician relationship and thus they need to be adapted to provide a useful tool for public ethics inquiry. Advocates of principle-based approaches argue that the universalistic claim of general ethical principles allows for their application in a wide range of circumstances including public health ethics and bioethics (Beauchamp and Childress 2013).

4.2.1. Public health ethics and screening

In contemporary public health ethics discourses there is no theoretical agreed-upon framework, but there are three most often invoked positions (Roberts and Reich 2002): 1) *consequentialism*, which states that actions and decisions should be judged on the basis of their consequences, especially on the effect on the sum of individual wellbeing; 2) *liberalism*, which focuses on rights, opportunities and responsibilities of individuals; and 3) *communitarianism*, which calls for a vision of an adequate social order in a particular community and for the endorsement of those virtues needed to maintain such an order.

Because of the emphasis posed on the balance between benefits and harms, *consequentialism* - and specifically *utilitarianism* - is often applied when reasoning on the ethics of screening, both for assessing its ethical appropriateness as a population-based program, and for evaluating its acceptability at the individual level (Juth and Munthe 2012) (Roberts and Reich 2002). All screening programs serve the objective

of offering either the benefits of prevention or the *early detection* of the condition in question. The underpinning rationale of population-based programs is that screening should help optimizing the population health. Therefore the principles for ethical analysis necessarily refer to the field of public health ethics, which significantly differ from the context of traditional medical ethics. However, as mentioned above, a mixed set of moral consideration usually informs the final assessment of the moral justifiability of a given intervention. Considerations and rules derived from *deontological* and *principlistic* ethical theories constrain the assessment of what constitutes the greatest good often leading to a tension between improving and promoting the public good and protecting individual rights, goals and preferences. In order to solve this intrinsic tension, Childress and colleagues (Childress et al. 2002) have tried to sketch out an account of public health ethics by listing a set of general moral considerations, each of which refers to a traditional ethical principle, that are outlined in **Table 5**.

Table 5 - Moral considerations and related general principles

Moral consideration	Principle
Producing benefits	Beneficence
Avoiding, preventing, and removing harm	Beneficence Non-maleficence
Producing the maximal balance of benefits over harms and other costs	Utility
Distributing benefits and burdens fairly	Distributive justice
Ensuring public participation, including participation of affected parties	Procedural justice
Respecting autonomous choices and actions, including liberty of action	Autonomy
Protecting privacy and confidentiality	Autonomy
Disclosing information and speaking honestly and truthfully	Transparency
Building and maintaining trust	Accountability

These general moral considerations are not *absolute*, but rather *prima facie*. The

prima facie nature calls for the acknowledgment of a possible need to balance general moral considerations when conflicts between them may arise²⁴. Childress and colleagues also propose a methodology to be applied for solving possible conflicts. The methodology provides five “justificatory conditions” for determining when, in certain circumstances, the promotion of public health goals overrides other values such as individual liberty or justice. The “justificatory conditions” are: effectiveness, proportionality, necessity, least infringement, and public justification (Childress et al. 2002, p.173).

Public health moral reasoning often requires to balance community and individual values and goals, but with a key theme of benefitting the population as a whole by promoting and protecting community health. While traditional medical ethics puts the emphasis on individual rights and principles such as autonomy and non-maleficence, public health ethics rather focuses on collective values and principles. Therefore, in public health ethics discourse, among the above principles, the principle of *utility* often has priority over the others (Newson 2011) (Delatycki 2012) (Bradley 2000).

4.2.2. The principle of *utility*

Moral reasoning involves reaching a decision about ethical issues by engaging in rational analysis. Such deliberations may be justified on the basis of the application of ethical theories to concrete circumstances. As seen in Chapter 3, *deductivism* is a common approach for ethical justification of decisions and actions, which holds that

²⁴ In general terms, there are two opposite conceptions of moral principles and considerations. On the one hand, the *absolute* conception, which holds that a moral principle is a universal claim, for any action or decision of a certain kind is right or wrong on the basis of its adherence to the moral principle in question. On the other hand, the *contributory/prima facie* conception, which holds that more than one moral principle can be applied in certain circumstances (Beauchamp and Childress 2013). Therefore, the right action has to be assessed by looking at all the morally relevant aspects of the particular case and choosing through practical judgment. In case of a conflict between different *prima facie* duties, one usually has priority over the others (Beauchamp and Childress 2013) (Dancy 2013).

the deliberation process should deduct the final judgment from one or more general moral principles. Such principles might be expression of a comprehensive ethical theory such as *deontology* and *utilitarianism*. Broadly speaking, the first claims that actions are good or bad – right or wrong – regardless of their practical consequences. The latter, instead, calls for the maximization of beneficial consequence as justification of any action, therefore refusing any *a priori* moral evaluation of actions²⁵.

Although the principle of *utility* in its traditional formulation is ascribed to the *deductivist* approach in moral reasoning, in which it is the ethical principle from which all other principles are derived, it can also be applied in *non-deductivist* approaches such as *principlism* (Coughlin 2008), which requires to balance different principles in order to solve concrete ethical issues. As shown above, indeed, there might be a set of considerations of moral relevance in certain circumstances, such as in public health decision-making and policy-making regarding population-based screening programs. As the good of the community is considered the aim of public health, in case of conflicts between moral considerations, the one referring to the principle of utility comes to weigh more in moral deliberation (Juth and Munthe 2012). Therefore, whatever approach might be chosen in moral reasoning – either a *deductivist* or a *non-deductivist* one – the aim of public health inherently calls for the prioritization of *utility* over other considerations or principles (Troop 2000). The moral rightness of actions and policies is therefore determined by the extent of maximization of aggregate and/or collective benefits. While there are different definitions, in contemporary public health ethics “benefits” shall be interpreted as

²⁵ For more on the issue see: Copp D. (2007), *The Oxford Handbook of Ethical Theory*, Oxford University Press.

both the fulfilment of the interest of the population/community and of the individuals involved in the policy²⁶.

4.2.3. Applying, specifying and balancing principles

The application of the traditional principles and concerns of beneficence, autonomy and justice helps connecting the dualistic nature of population-based screening programs. However, as already mentioned, medical ethics primarily focuses on individual rights, duties and responsibility. In this respect, the principles of *beneficence*, *non-maleficence*, *autonomy* and *justice* are commonly adopted to assess and guide clinical practice. Although public health ethics does not completely dismiss individualism, within population-based screening programs context, the focus tends to be placed on the collective effort of promoting health (Newson 2011). This juxtaposition of focus is mirrored in the ethical concerns regarding screening, where dilemmas between divergent ethical demands may arise. Therefore, a brief outline of the most significant traditional values and principles and their role and application in screening practice is presented.

In order to properly engage in an ethical deliberation under the light of the *principle of utility* it is nevertheless necessary to specify the content, extent and meaning of other moral principles relevant to the discussion. Therefore, somewhat roughly, the moral concerns and principles identified by Childress and colleagues (Childress et al. 2002) can be further grouped into three general categories, each of which – again - refers to one traditional ethical principle. Indeed, according to Juth and Munthe there are three kinds of goals or values that can provide the rationale for introducing and assessing the ethics of screening programmes (Juth and Munthe

²⁶ The definition of benefits as fulfillment of preferences refers to the *preference utilitarianism*, as different from the *classic utilitarianism*, which endorses a hedonistic definition of benefits as pleasure or absence of pain. For more on utilitarian ethical theory see: Singer P. (2011), *Practical Ethics*, 3rd edition, Cambridge University Press, New York.

2012).

First, the program should in general terms improve the physiological health and/or the psychological wellbeing of the individuals in the screened population. These kinds of concerns relate to the *principle of beneficence*. Second, as far as possible within a population-based program, there should be room for autonomous actions and choices of participants, as well as respect for their privacy and confidentiality. This second kind of considerations includes the *specifications* of the more general *principle of autonomy*. Third, the call for a fair distribution of benefits and costs among participants, and the acknowledgment of the importance of ensuring public participation in policy-making refer to the *principle of justice* either in its distributive or procedural expression.

In traditional health care ethics the *principle of beneficence* implies a moral obligation to act for the benefits of patients (Beauchamp and Childress 2013). It usually relates to the *principle of non-maleficence*, which in turn calls for the duty not to harm the patient by means of clinical procedures. As already said, for a screening program to be ethical, it should produce a substantial benefit. In this respect, Holland suggests a two-part ethical “benefit criterion”, which determines at the same time the beneficial effect and for whom it is intended (Holland 2007). On the basis of the “benefit criterion”, screening should benefit the participants by means of allowing earlier and more effective treatment for the screened-for disease.

Yet, the benefit of screening can be further divided into two components, one physiological, and the other psychological. From the physiological viewpoint, reductions in morbidity and mortality, as well as better prognosis due to early treatment, represent the more uncontroversial rationale for screening programs (Juth and Munthe 2012). Whereas things get a bit more complicated for what

concerns the assessment of the psychological benefits of screening, which are usually referred to as the reduction of anxiety, worries and uncertainty about the future. However, screenings run the risk of creating more psychological burden than they reduce, for people invited to participate in the program had no prior worry or suspicion of being at risk (Dawson 2011). Therefore, in order for any screening to be ethically justified on the basis of the *principle of beneficence*, it primarily has to improve physiological wellbeing or health (Bradley 2000).

A major ethical problem arises from the possibility of *false test results*, which inevitably imply some psychological as well as physiological harm to individuals. As screening tools lack either in *sensitivity* or in *specificity*, the rates of false test results might actually be significant. If on the one hand there is no doubt that a *false negative* result, by erroneously reassuring and possibly delaying diagnosis, represents harm, regarding *false positive* results some further clarifications have to be provided. Hence, the extent of harm does not seem to be of great entity. *False positive* results are usually ruled out throughout further investigations, in the end resulting in a few days of anxiety and relatively non-invasive diagnostic tests - such as needle aspirated biopsy or blood test (see Chapter 1.5. *General harms of screening*). The potential benefits of *early detection* still appear to outweigh the low costs of *false positive* results' consequences (Juth and Munthe 2012) (Bradley and Burls 2000).

In traditional health care ethics the *principle of autonomy* implies the duty for clinicians to respect *patient's autonomy* in making choices about her health in a broad sense, and especially in accepting or declining any medical procedure (Beauchamp and Childress 2013). The principle of autonomy can be interpreted in two different ways. First, it may imply the negative duty of not interfering in individual's decision-making (Engelhardt 1996). In this respect, no medical procedure can be imposed on

patients without their voluntary consent. Informed consent hence appears as a precondition for assuring an ethical delivery of screening. In the context of screening, such a conception of the principle of autonomy calls for the restriction of the public health perspective by avoiding the coercion of or pressure on people in undergoing tests or participating screening programs²⁷. Therefore, individuals of the target population are usually invited to screening by means of invitation letters or clinicians recommendation/suggestion to be screened.

Second, a more proactive manner of interpreting the principle of autonomy implies the duty to promote individual autonomy. Respect for patient's autonomy hence requires enabling patients to promote their own health and thereby become more autonomous (O'Neill 2004). Consequently, health care providers and policy makers have the duty to empower patients to make informed decision about treatment options, diagnostic and screening tests, and therapeutic plans. This view of autonomy also entails the acknowledgement of personal values, beliefs and ideas concerning what is valuable in life, and how health management should be interpreted in order to promote individual autonomy. In this respect, mammography screening may become a means for exercising women's right to autonomous choices regarding one's health status and prevention of diseases (Juth and Munthe 2012).

Finally, because of the public nature of population-based programs, the *principle of justice* is often mentioned and analysed in the context of screening (Shickle and Chadwick 1994) (Paul et al. 2008) (Juth and Munthe 2012) (Plutynski

²⁷ Mandatory screenings are difficult to justify, and usually are performed exclusively for infectious diseases (such as tuberculosis, HIV, or hepatitis B) at public sampling points such as the admission to clinics and/or hospitals. The rationale behind the justification of mandatory screening is that the result might have a strong impact on the individual health status and on professional or public health. The subjective right of making autonomous decisions about whether to undergo the test is therefore transcended by the need to prevent the spread of an infectious condition or reduce the risk of contagious for health care providers (Dawson 2011).

2012) (Parker, Rychetnik and Carter 2015). Broadly speaking, justice can be defined as the idea that similar cases should be treated similarly (see Chapter 3.3.3. *Principlism*). On the basis of this definition, *justice* requires that, if a screening test is proposed due to its potential to offer benefits to some individuals, it should be offered to all those who might gain the same benefits from the screening procedure. However, the direct appeal to the *principle of justice* works only in the cases in which the equal opportunity of access regards what is an obvious and clear good to achieve, and therefore the program implementation is justified (Juth and Munthe 2012). Thus, in the case of mammography, the target population of screening program should include all women for whom scientific evidence shows a benefit of undergoing routine tests.

As shown in Chapter 2, the target population of most national mammography programs is defined as all «asymptomatic women aged 40 years or older» at average risk for breast cancer (Siu 2016, p. 280). Yet, scientific evidence proves that routine screening implies a risk of harms of significant *magnitude* and *relevance* – especially for women aged 40 to 49. The definition of what constitutes an obvious and clear good relies on the assessment of balance between great benefits and eventual mild and few side effects for the individuals. Therefore, it has been argued that justice-based considerations should represent additional arguments when preliminary considerations of *beneficence* and *autonomy* already point in favour of screening, for promotion of individual autonomy and wellbeing seems more plausible to justify the introduction and implementation of population-based mammography screening programs (Juth and Munthe 2012).

4.3. Bioethics in mammography screening

The main research question of my PhD project regards how women – and especially women aged 40 to 49 years for whom evidence about the net benefit is uncertain – decide whether to participate mammography screening programs. As shown in Chapter 2, such decision is generally delegated to individual women and therefore results from a concrete clinical decision-making process within a particular medical encounter. The decision-making process therefore takes place within a concrete relationship between an individual woman and her physician – mostly general practitioner and/or gynaecologists. Therefore, in trying to address the issue regarding mammography screening choices, I conducted a review of the literature on oncological clinical and preventive decision-making, which has lately received a growing attention from researchers (Hunink et al. 2001) (Briss et al. 2004) (Rimer et al. 2004) (Barnato et al. 2007) (Hoffmann et al. 2010) (Pravettoni and Gorini 2011) (Biesecker, Schwartz and Marteau 2013) (Wardle et al. 2015).

The review and analysis of such literature reveal a shared-by-all identification of two main drivers of decision-making in the context of mammography screening: evidence-based information about benefits and harms, and individual preferences and values. The two themes are closely intertwined and recur both in literature focusing on experts' perspective and duties and in literature regarding patients' rights and empowerment. From the broad viewpoint on clinical decision-making as driven by information and values, it is possible to articulate three major areas of ethical interest regarding mammography screening issues from which to analyse the issue and try to provide a comprehensive picture:

- 1) Physicians understanding of evidence and guidelines;

- 2) Respecting autonomy: informed decisions and communication of complex probabilistic information to lay people;
- 3) Respecting autonomy: incorporating patients' values in clinical decision-making.

Next paragraphs provide an ethical analysis of the mammography screening following each of the three sub-categories. The proposed ethical analysis combines together all the elements presented in previous Chapters, and in particular it takes full advantage of the methodologies outlined in Chapter 3. By applying different ethical frameworks and concepts, the analysis highlights possible concerns as well as critics arising from the adoption of one method over another. The focus is placed on the different possible kinds of relationship between women and physicians, each of which implies different decision-making processes and therefore different communication modalities. Such different approaches to clinical decision-making are critically evaluated with regard to mammography screening, especially for women aged 40 to 49.

4.3.1. Deciding what to do: delivering benefits, avoiding harms

As seen in Chapter 2, in Western countries up-to-date scientific evidence informs mammographic screening recommendations on which population-based programs rely for delivering an effective and safe practice. In the past few years, the reports of new data from systematic reviews and meta-analyses (Gøtzsche and Jørgensen 2013) (Marmot et al. 2013) resulted in an adjournment of most guidelines, which physicians are expected and required to follow. Therefore as a preliminary and allegedly naïve deontological consideration, physicians have the professional duty to keep themselves current on the latest released guidelines, just as on all the new clinical protocols.

While this consideration may seem somewhat trivial, it actually is of fundamental importance for those physicians who are the first encounters for women eligible for mammography screening - such as general practitioners (GPs) and gynaecologists who receive and reply to generic questions on patients' health status and preventive options. Indeed, from the *principle of beneficence* physicians should derive the general rule of acting for the benefit of patients, which obviously implies having specific professional skills - in this case awareness and knowledge on up-to-date protocols and guidelines. Moreover, keeping themselves updated on guidelines enables physicians to offer mammography screening to all individual women who might benefit from testing, thus fulfilling the fundamental *principle of justice* claim of treating similarly the similar cases (see Chapter 3.3.3. *Principlism*).

Nevertheless, as in the case of mammography screening and especially for women aged 40 to 49, it is not always possible to objectively assess what constitutes a benefit for patients. Different options could entail both potential benefits and harms or a significant level of uncertainty regarding interventions' outcomes, therefore resulting in the possibility of a conflict between the *principle of beneficence* and the *principle of non-maleficence*. In these cases, the evaluation of the moral appropriateness of the intervention would require moving forward from a mere application of principles, and entails further *specification* and *balance* of principles in order to successfully determine which action is morally appropriate in concrete and specific circumstances (see Chapter 3.3.3. *Concrete case analysis through principle-based methodologies*).

By *specifying* principles, physicians would restrict the scope and range of general principles to concrete circumstances. In the case of mammography screening, the *principle of beneficence* would thus generate rules regarding the delivery of

benefits such as reduced risk of *mortality* from breast cancer, eventual decrease in *morbidity*, reassurance, and opportunity to access to a wider range of therapeutic options. Each of these *specifications* provides a guide towards the advice for screening on the basis of the *principle of beneficence*. On the other hand, by *specifying* the *principle of non-maleficence*, physicians would derive rules requiring the avoidance of harms such as general inconveniences of getting tested and anxiety while waiting for the test result, but especially those rules would call for the avoidance of *false positive* results, *overdiagnosis* and *overtreatment*. Thus, *specifications* of the *principle of non-maleficence* generate rules for advising against participating in the screening. Again, the impasse does not seem to dissipate, for the conflict between the two principles persists.

One possible solution could be based on the adoption of the *principle of double effect* (PDE)²⁸, by which physicians can evaluate advising for screening as the best action to perform. The PDE justifies performing an action that the doctor foresees to produce a possible good effect and a possible bad outcome (Beauchamp and Childress 2013). Notably, possible harmful outcomes such as *false positive* results and *overdiagnosis* are not merely unwanted: they are unintended even if foreseen. However, it has been argued that the *principle of double effect* is unhelpful in solving physicians' eventual moral dilemma of whether to recommend screening or not, in that it would justify the harm caused by both recommending and advising against mammography (Shickle and Chadwick 1994). Therefore, in order to establish a

²⁸ «The principle of double effect (PDE) is often pleaded to justify the permissibility of an action that causes harm as a side effect of promoting a good end. In medical ethics PDE is often mentioned in discussions on palliative care, which aims at pain relief but may also cause respiratory failure. For the action being permissible four conditions have to be verified at the same time: 1) the action's object is good or at least indifferent; 2) the intended effect is the good and not the evil one; 3) the good effect is not produced by means of the evil one; 4) there is a proportionately reason for permitting the evil effect» (Ferretti 2016, p.111). For more information on the PDE see McIntyre A., *Doctrine of Double Effect*, The Stanford Encyclopedia of Philosophy (Winter 2014 Edition), in Zalta E.N. (ed.), available at: <http://plato.stanford.edu/archives/win2014/entries/double-effect/> (last accessed on 10.13.2017).

course of action, physicians would need to *balance* principles aiming at prioritizing one of them over the competing other, meaning which duty among providing benefits and avoiding harms outweighs the other, with no direct call to the general principles.

This process consists in the *intuitive* balancing of moral considerations, which takes into account further elements such as the *magnitude* of benefits and harms, but also their *relevance*. Although *balancing* often results in the resolution of conflict (Beauchamp and Childress 2013), it also introduces a new element of concern. As seen in Chapter 3, by leaving room for individual subjective intuition in the conflict resolution process, *balancing* involves an arbitrary element in moral deliberation, which might undermine the appropriateness of moral judgment (Clouser and Gert 1990). As a matter of fact, a recent study demonstrated that experts' – including physicians, policy makers, programs managers and researchers - support for mammography screening is largely affected by how they conceive, *specify* and *prioritize* general deontological principles (Parker, Rychetnik and Carter 2015).

These preliminary considerations reveal the complexity physicians would have to face to eventually justify either advising for or against mammography screening on the basis of the *principle of beneficence* and/or the *principle of non-maleficence* alone. Even through principles' *specification* the doubts persist, and the *balancing* process inherently entails an intuitive arbitrary element. Therefore, this way of reasoning would work only if a *paternalistic* model of decision-making is endorsed. In the *paternalistic* model, physicians dominate the encounter with patients and decide on the basis of clinical knowledge and personal judgment what is *the best interest* of patients (Emanuel and Emanuel 1992). In extreme cases, physicians would only inform patients about the interventions that will be performed; while in less extreme cases physicians would disclose selected

information and encourage patients to consent to what they have already determined as the best option. In the paternalistic model of clinical decision-making patients' role is therefore reduced to providing consent (*ibid.*).

As clearly appears - beyond consent to treatment - there is no space for patients' *autonomy* in that physicians decide what is patients' *best interest* in terms of health and well being. Therefore, the general moral principles guiding the *paternalistic* model of decision-making are *beneficence* and *non-maleficence*, from which deriving rules balanced through physicians' personal and professional judgment of what constitute patients' greatest good and what risks are worth taking in order to achieve it. However, the *paternalistic* model is highly criticized for being inappropriate in most circumstances and strongly rejected in favour of models ensuring an increased role of patients in clinical decision-making. Indeed, a growing attention has been given to enhance and support informed choices rather than on finding ways of maximizing recruitment and uptake to population-based programs (Raffle 2001).

4.3.2. Respecting autonomy: towards informed decision-making

The classification of recommendations in *strong* or *weak/qualified*, as well as the establishment of an *eligible* but not-invited to screening age group requires a deep understanding of the meaning of guidelines on the side of physicians (see Chapter 2.6. *Recommendations, guidelines and mammographic screening programs*). The very rationale of such classification calls for a direct and proactive involvement of physicians in discussing with individual women the benefits and harms of mammography. This fundamental requirement, which is acknowledged by all Western countries guidelines, relies on the *principle of autonomy* that above all aims at preventing possible interferences by providing rules to guide the exchange of

information and to guarantee patients' autonomous choices (see Chapter 3.3.2. *Deontology*). Following this line of moral reasoning, clinicians' primary duty is to provide patients with all the information they need to take an informed decision (Engelhardt 1996).

Reaching an informed choice is different from achieving an informed consent in that it requires the disclosure of treatment and/or intervention options and it is not limited to the mere consent to treatment. Indeed, the informed decision-making model is based on the recognition of the intrinsic information asymmetry between patients and physicians (Charles, Gafni and Whelan 1997). Both parties bring some knowledge in the decision-making process, yet the kind of knowledge differs in a significant manner, and yet they need to be combined. Physicians possess the *theoretical medical knowledge* regarding the effectiveness of treatment options in improving *health status*; while individual patients possess the *evaluative knowledge* regarding how eventual improvements in health status impact their *wellbeing* expressed in the form of preferences for treatment (Joosten et al. 2008). In order to enable patients taking a decision consistent with his/her preferences – and therefore *valued* by patients – physicians should improve patients' knowledge about treatment options and possible risks.

The ideal informed decision-making process therefore revolves around the communication of the best evidence-based information about benefits and risks of different options on the basis of which patients may choose the option more consistent with and better mirroring their goals, values and preferences (Charles, Gafni and Whelan 1997) (Briss et al. 2004). In contrast with the *paternalistic model*, physicians are required to withhold recommendations and expression of personal preferences (Joosten et al. 2008). These deontological requirements derive from

endorsing the *principle of autonomy* in its traditional conception, of which derived rules mainly regard the negative duty of non-interference with others' decisions and choices, and the positive duty to provide all the information needed to enable patients making an autonomous decision (see Chapter 3.3.2. *Deontology*).

4.3.3. Understanding options: statistical information and communication

Yet, for physicians to provide complete information in the context of mammography screening, they should firstly manage themselves statistical information, for the scientific evidence on population screening is by nature probabilistic. It is important to emphasise that requiring physicians to understand and manage statistical information does not mean they should go through the scientific evidence and pursue a full-scale statistical examination. Not only it would be unreasonable, but it would also be unfair – and perhaps dangerous. There are agencies taking advantage of professional statisticians and epidemiologists that are called to evaluate the available scientific evidence by performing systematic reviews and meta-analyses for which they hold responsibility and on which policy makers rely for evaluating the feasibility and moral permissibility to establish, implement, or eventually update public health interventions (see Chapter 2).

On the basis of the latest up-to-date evidence, policy makers have evaluated that for women aged 40 to 49 it is not acceptable to endorse a one-size-fits-all approach, in that the evidence is either insufficient or low to objectively assess the individual net benefit of routine screening (see Chapter 2.6. *Recommendations, guidelines and mammographic screening programs*). The assessment depends on the values and preferences each individual woman places in determining what constitutes a worthwhile benefit and what constitutes a great harm (Canadian Task Force on Preventive Health Care 2011) (Oeffinger et al. 2015) (Lauby-Secretan et al.

2015) (Siu 2016). Therefore, the extent of statistical knowledge physicians need to manage is limited to those skills needed to entail an adequate communication of information with patients. Indeed, informed decision-making requires that both physicians and patients understand the benefits and harms of treatment and intervention options (Charles, Gafni and Whelan 1997).

Unfortunately, psychologists have extensively studied our understanding of probability and found that we systematically tend to misinterpret statistical information due to cognitive shortcutting heuristic strategies and related systematic biases (Gorini and Pravettoni 2011), and in particular that individuals find very problematic understanding risk in probability and percentage format (Schwartz et al. 1997) (Gigerenzer et al. 2008). Such difficulties commonly affect patients, physicians, and policy-makers therefore representing a form of “collective statistical illiteracy”, which can have significant and serious consequences for health and wellbeing (*ibid.*).

For example, despite the centrality of probability in breast cancer screening context, an empirical study by Gerd Gigerenzer and colleagues reported an alarming possibly everyday-life situation (*ibid.*). The study was specifically designed to test physicians’ statistical literacy on common practice procedures. Researchers provided 160 gynaecologists with the statistical information relevant for calculating the chances that a woman receiving a positive mammography result actually has breast cancer²⁹. Surprisingly only 21% of gynaecologists found the correct answer among the proposed ones. Gigerenzer and colleagues argue that the misunderstanding lies in the way statistics is framed: when information is presented in terms of *conditional probabilities* it is hard to grasp for the vast majority of people, including health professionals. As an effective solution, researchers suggested translating probabilistic

²⁹ The information provided was the prevalence of the disease among the population (1%), the *sensitivity* of mammographic tool (90%), and the *false positive rate* (9%) (Gigerenzer et al. 2008, p. 55).

information into *natural frequencies*, which facilitate computation. The problem was hence reframed in *natural frequencies* format³⁰. By presenting exactly the same information in *natural frequencies* format, the percentage of gynaecologists correctly answering the question rose up to 87% (*ibid.*).

While the study showcases a major difficulty that might severely undermine the informed decision-making process, it also proposes a realistic and somewhat easy solution by focusing on user-friendly formats of statistical framing. Taking as an example the issue presented by Gigerenzer and colleagues, **Figure 3** (adapted from Gigerenzer *et al. Psychological Science in the Public Interest*, 2008) illustrates how the probability of a *false-positive* result in mammography screening can be presented to patients in order to help them understanding both the meaning and magnitude of *false positive* results.

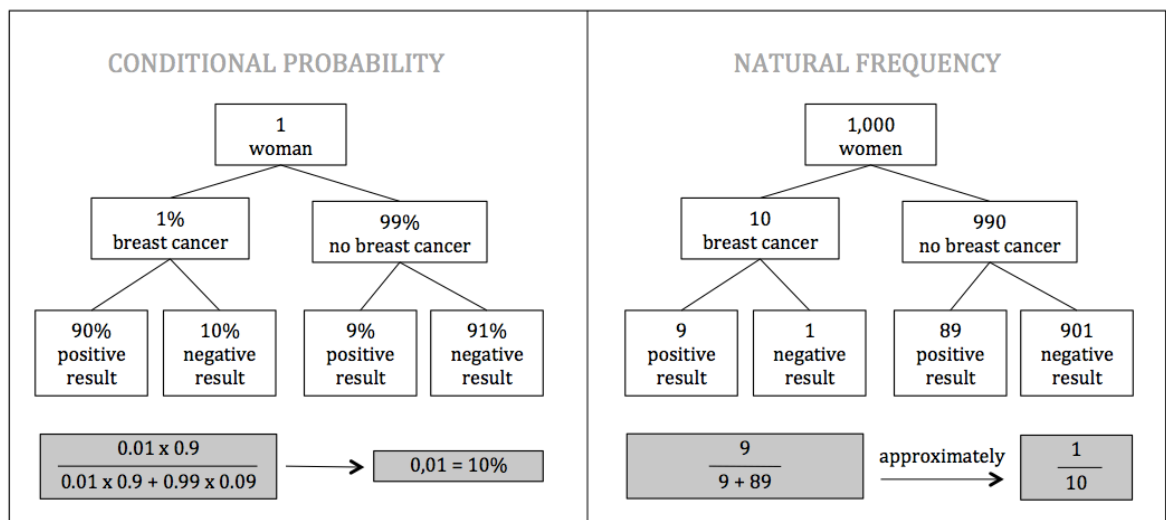


Figure 3 - Statistical information on false positive results in conditional probability and natural frequency formats

³⁰ The information provided in *natural frequencies* format was as follows: 10 out of 1,000 women have breast cancer; of these 10 women who have breast cancer, 9 test positive at mammography screening; of the remaining 990 women who do not have breast cancer, 89 nevertheless receive a positive result. On the basis of the provided information, the correct answer is that approximately 1 woman out of 10 receiving a positive result actually has breast cancer, or that the probability of actually having breast cancer of a woman receiving a positive test result is about 10% (*ibid.*).

4.3.4. Choosing the best option: information and preferences

In order to enable patients to make a fully informed decision, it is imperative for physicians both to achieve/improve basic statistical knowledge - especially with regard to everyday clinical practice's procedures -, and to manage communication formats such as percentages, natural frequencies (Gigerenzer et al. 2008), base rates and proportions (Visschers et al. 2009), absolute and relative risk reduction (Schwartz and Meslin 2008), graphic risk presentation (Dolan and Iadarola 2008) risk ladders (Petrova et al. 2015), as well as adopting a plain language for the explanation of probability (Fagerlin, Zikmund-Fisher and Ubel 2011). These statistical skills are essential to inform women about the possible benefits and harms of mammography screening, in that *mortality reduction*, *false positive* results, and *overdiagnosis* are by nature expressed in probabilistic format (see Chapter 1 and Chapter 2). Moreover, a complete communication aimed at informed decision-making about breast cancer screening should also include information about alternative screening modalities such as CBE, breast ultrasound, magnetic resonance imaging (MRI), and digital tomosynthesis³¹ (Lee and Peters 2013), as well as the explanation of eventual detection of *in situ* pre-malignant lesions - DCIS and LCIS³² - and the possible alternatives of their clinical management (Bulliard and Chiolero 2015) (see Chapter 2.3. *Available treatments for breast cancer*).

Nevertheless, several studies have demonstrated that, although women positively value receiving information about possible screening outcomes, they often

³¹ «This relatively new breast cancer screening method uses multiple X-rays images to create 3-dimensional picture of the examined breast. Currently available research results are promising and it is thought that this screening modality might overcome the disadvantages posed by mammography screening» (Ferretti, Linkeviciute and Boniolo 2017, p. 40).

³² It has been suggested that the terms "ductal carcinoma *in situ*" and "lobular carcinoma *in situ*" should be replaced respectively with the new terms "ductal intraepithelial neoplasia" (DIN) and "lobular intraepithelial neoplasia" (LIN) in order to reduce patients' confusion regarding the prognosis, and to limit the adverse psychological effects associated with DCIS and LCIS diagnoses (Pravettoni et al. 2016).

find it difficult to understand not only statistical information, but can also get confused by some of the major features of mammography screening (Klein and Stefanek 2007) (Toledo-Chàvarri et al. 2017). Among other difficulties, communicating *overdiagnosis* appears particularly challenging, in that it represents a new and counterintuitive concept to many people (Hersch et al. 2013) (McCaffrey et al. 2016), and it can only be described at the population level (Forbes and Ramirez 2014). Such difficulties in understanding may even lead patients to ask physicians' recommendation when considering whether to participate in the screening (Metsch et al. 1998), or even to explicitly delegate the responsibility for decision to physicians (Charles, Gafni and Whelan 1997).

In complex clinical situations where probability and uncertainty represent the only available information, the *informed decision-making* model might fail in its very intent of enabling patient to make decisions consistent with their preferences and values. Providing patients with the best possible scientific evidence might not be sufficient to guarantee a fully informed decision, and patients may even opt for delegating treatment choice or relying on physicians' evaluation of options. The traditional conception of the *principle of autonomy* as the guarantor of autonomous individuals' choices does not generate any *positive duty* to enhance decision-making. Therefore, when patients fail/are incapable of deciding which intervention option is the best according to their goals and values, the *informed decision-making model* runs the risk of reaching a decisional impasse or paradoxically even of turning into a soft *paternalistic model*, where physicians are eventually called to judge what is the best interest of patients. People are not as rational and autonomous as depicted by traditional ethical theories; on the contrary, emotions and cognitive aspects challenge the complete adherence to the *informed decision-making model* requirements.

As highlighted by virtue ethics and care ethics proponents, emotions and character play a central role in human life, and cannot be ignored nor in moral reasoning, nor in clinical decision-making (see Chapter 3). From the virtue ethics viewpoint, physicians should possess specific intellectual and moral characteristics enabling them to successfully behave and interact within the professional environment. While the former entail the duty to understand and manage statistical information – as for traditional ethical perspectives –, the latter call for the development of those relational skills needed to establish successful relationships with patients and colleagues. Yet, a definition of successful relationships is not provided and the list of virtues defining a “good” physician³³ does not directly relate to problem of information and communication. As seen in Chapter 3, the major critic of virtue ethics regards the little normative strength of the theorization of character and disposition, which leaves room for arbitrary decisions among different courses of actions (Oakley 2009). Again, by introducing an arbitrary element in the evaluation of different clinical options, the adoption of a virtue-based approach within the *informed decision-making model* of patient-physician relationship risks to fail the very rationale of the model.

4.4. Summary

Mammography screening programs combine two major levels of ethical concern and interest. First, the public nature of population-based screening implies the adoption of a public health ethics perspective in analysing the moral acceptability of mammography as a nation-wide intervention. On the basis of the outcome-oriented character of screening programs, *consequentialism* is often invoked to provide moral justification and foundation for the introduction and/or implementation of

³³ Pellegrino identifies seven virtues essential to define a “good” health care provider: fidelity to trust and promise, benevolence, effacement of self-interest, compassion and caring, intellectual honesty, justice, and prudence (Pellegrino 1995); see Chapter 3.5.2. *Applying virtue ethics to bioethics*.

mammographic screenings. However, the consequentialist approach is usually constrained by *deontological* and *principlistic* considerations and rules in defining what constitutes the greatest good for the population, often unveiling the intrinsic tension between improving and promoting the public good and protecting individual rights, goals and preferences. Therefore, notwithstanding the fundamental *consequentialist* approach of public health, the proposed ethical analysis includes consideration of traditional ethical principles – such as *autonomy*, *beneficence*, *non-maleficence* and *justice* – that contribute to constraining and defining the greatest good in mammography screening programs. The analysis takes advantage of the methodologies presented in Chapter 3 and in particular derives, applies, specifies and balances concrete moral rules and general principles. Rules derived from the *principle of beneficence* require that screening should benefit participants by means of allowing earlier and more effective treatment for the screened-for disease, and thereby improving physiological wellbeing. On the other hand, rules derived from the *principle of non-maleficence* require the avoidance of both great harms – especially *false positive* results and *overdiagnosis* -, as well as of mild harms - such as the inconveniences of getting tested and anxiety while awaiting for the test result.

Given the possibility of great harms due to mammography screening, and the uncertainty of the magnitude of benefits, further specification of the *principle of autonomy* are presented, specifically regarding the right to choose and autonomously decide whether to participate in the screening program. For example, mammography can be considered as a means of exercising women's right to autonomous choices regarding one's health status and prevention of diseases. Finally, by specifying the *principle of justice*, it is possible to derive concrete rules regarding the equal opportunity of access to mammography for all women for whom scientific evidence

shows a benefit for undergoing routine tests. The first part of the present Chapter therefore outlines the major arguments used in public health ethics discourse to justify the introduction and implementation of population-based mammography screening programs.

As shown in Chapter 2, although most current Western countries' guidelines and recommendations establish slightly different age-group classifications and screening intervals, they all share a fundamentally individualized approach to screening for women aged 40 to 49, who are *eligible*, yet do not receive any formal invitation to participate the program. The decision-making process, thus, takes place within the concrete relationship between women and their physicians, especially general practitioners and gynaecologists. The ethical analysis of mammography from an individual perspective refers to the field of bioethics, and specifically takes into account the peculiarity of the kind of relationship women and physicians might engage in and the subsequent different decision-making processes, from the *paternalistic model* to the *informed model*. In addressing the issue, the emphasis is put on the role of physician within the medical relationship.

The ethical analysis employs the theoretical concepts and elements presented in Chapter 3 to critically evaluate the adoption of one approach over the competitor ones. First, the question regarding the moral legitimacy of advising for or advising against mammography screening is evaluated from a *paternalistic* viewpoint. In this respect, the *principle of beneficence* and the *principle of non-maleficence* play the central role in moral reasoning. Nevertheless, the Chapter shows how this approach fails to provide the concrete and objective guide to action. Given the impossibility of reaching an objective conclusion and the need for an *intuitive balancing* between opposite moral rules' demands, the *paternalistic model* does not seem appropriate to

successfully address the issue. Therefore, the *principle of autonomy* is introduced as the core ethical element to the patient-physician relationship implying to kinds of duties for physicians: 1) the negative duty of non-interference with patients' decisions and choices; and 2) the positive duty to provide all the information needed to enable women making an autonomous and informed decision. In the context of mammography, hence the *informed decision-making model* acknowledges that the assessment between benefits and harms of screening depends on individual preferences and values regarding what goal to achieve. While physicians are required to withhold recommendations and expressions of personal preferences in order not to influence or interfere with women's decision-making, they must provide the best possible evidence-based information about benefits and harms. However, understanding and communicating statistical information can be really challenging, and there is a wide consensus on the need to manage different communication formats. Moreover, cancer-related emotions and cognitive aspects challenge the *informed decision-making model* in that they can lead to delegate the decision and responsibility to physicians. Therefore, while adopting the *informed decision-making model* implies the recognition of the fundamental autonomy of women, nevertheless the complexity of information to be provided, as well as some psychological and emotional characteristic features of the oncological field might prevent women reaching a truly *informed decision* regarding whether to participate mammography screening.

CHAPTER 5

A different approach

5.1. Introduction

The Chapter ahead outlines how the endorsement of care ethics provides a strong normative guidance in the context of mammography screening decision-making. As seen in Chapter 3, the traditional conception of morality has been criticized for conceiving moral agents as equal and fully rational subjects. Such a conception shapes individuals' moral life in so universalistic terms that it runs the risk of preventing them to take into consideration specific circumstances and others' actual capacities, interests and needs. On these bases, traditional theories have been applied to prevent possible interference and coercion due to the intrinsic power imbalances within the medical encounter, nevertheless focusing on providing information and knowledge as the fundamental - yet unique - means of respecting patients' autonomy and self-determination.

In contrast, care ethics highlights the fundamental importance of dependency, acknowledges the need to address the characteristic intrinsic power imbalance of patient-physician relationship in a way that truly involves patients as both rational and emotional individuals (see Chapter 3.6.1 *Features of the Ethics of Care*). Therefore, by adopting a wider viewpoint on people's experience of life and significant choices, the ethics of care recognises that individual decision-making is shaped together by theoretical and emotional knowledge, both of which can – and should – be recognised and enhanced in patient-physician relationships. Moving a

step forward, much of the theoretical work of care ethicists includes the definition and conceptualization of *caring relationships* as the core issue of human moral experience, as either carer or cared-for. The “good” carer engages in relationships with the aim to understand and respond to particular needs in the best possible way. In health care, meeting needs is not limited to fill a gap in clinical knowledge and to propose treatment alternatives. Patients’ needs go far beyond understanding clinical information, and often include some kind of dependency on health care providers – being it functional, technical, material, emotional, or even social (Twomey 2012). The emphasis is thus put on the importance of listening, understanding the needs, and truly accounting for patients’ self-conception and personal goals. This approach calls for moving on from a conception of patient-physicians relationship limited to information exchange and autonomous decisions in favour of a *shared decision-making model*, which strengthens patients’ awareness and thereby empowers their capacity for agency (Barry and Edgman-Levitan 2012).

First and foremost, the Chapter outlines what is the *shared decision-making* (SDM) model of patient-physician relationship, how it practically enables patients for making truly informed and value-based choices, and thereby accounts for a full respect for individual autonomy. The intrinsic fundamental role of the *partnership* between patients and physicians is described in details, and a concrete methodology for the application of SDM is provided. Then, patient decision aids (PtDAs) are presented as effective tools to help patients understand the relevant information regarding clinical options and incorporate their personal values in the decision-making process. Indeed by providing up-to-date and user-friendly information, PtDAs have been proven beneficial in SDM. However, PtDAs do not replace the medical encounter, which still remains the ideal place where to take

clinical decisions. Hence, once patients are informed and their values and preferences have been elicited by PtDAs, physicians are able to engage in a discussion aimed at reaching a fully personalised decision. Nevertheless, not only the SDM model requires specific attitudes toward patients' empowerment, but it also requires a deeper and particular knowledge regarding what patients care about, how they reason and which personal features inform their choices. In order to provide physicians with a piece of knowledge on women's decision-making, a review and a critical analysis of the literature on women's experience of breast cancer are presented and the four major identified themes are hence applied to the mammography screening context for women aged 40 to 49. Finally, on the basis of the literature review's analysis, a qualitative empirical study is proposed in order to investigate the role of mothering and of significant relationships in women considering whether to uptake routine mammography screening.

5.2. Respecting autonomy: towards shared decision-making

Shared decision-making model (SDM) has been defined as an «approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences» (Elwyn et al. 2012, p. 1361). SDM is based on the recognition and acceptance that self-determination is a desirable goal of health care, and therefore SDM aims at conferring agency to patients by providing information and supporting clinical decision-making process. Physicians hence have the duty to provide high quality information – as in the case of *informed decision-making* – and to support and help patients to deliberate about their

options in order to reach a decision consistent with their values and preferences³⁴ (Charles, Gafni and Whelan 1997). The kind of relationship between health care providers and patients, therefore, moves a step forward from the pure exchange of information, toward the development of a *partnership* in which physicians' *theoretical knowledge* and *clinical preferences* are combined with individual patients' *preferences* and *needs* with regard to their particular lifestyle and values (Joosten et al. 2008). In order to engage in a proper SDM, four key characteristics have to be met: 1) there must be at least two participants involved – patient and physician – but patient's relatives and friends may also be involved; 2) both parties share information and therefore engage in a two-side communication; 3) both parties participate in deliberating on the treatment/intervention to uptake; and 4) an agreement is reached between patient and physician regarding the treatment/intervention to be implemented (Charles, Gafni and Whelan 1997).

SDM appears of particular importance when more than one treatment option or screening is available and the outcome of intervention is uncertain (O'Connor, Légaré and Stacey 2003) and thus patients may find it difficult to make a choice and eventually may even face a *decisional conflict* (Gorini and Pravettoni 2011). Firstly, decisional conflicts may arise from the inherent complexity of the available information regarding the intervention - such as statistical data on benefits and harms – which is mostly adaptable only in its presentation format (see Chapter 4.3.3. *Understanding options: statistical information and communication*). Secondly, the uncertainty about which option to choose may arise from modifiable factors such as inadequate or lacking knowledge, unclear values and preferences, and inadequate support in the process of decision-making.

³⁴ In this sense, *shared decision-making* represents a mixed approach combining both the *interpretive* and the *deliberative models* proposed by Emanuel and Emanuel in which values are explored, elucidated and discussed in relation to the set of available clinical options (Emanuel and Emanuel 1992).

Therefore, SDM aims at providing patients with information and with a way of reasoning about treatment/intervention options that helps in focusing on key issues and evaluating relevant options (Charles, Gafni and Whelan 1997).

Elwyn and colleagues have suggested a three-step model to accomplish a good SDM in clinical practice through physicians' active support in patients' deliberation (Elwyn et al. 2012). As a preliminary step, physicians should engage in a talk regarding the available *choices*, by listing and offering choices and emphasizing the scientific and clinical uncertainty and the importance of individual's preferences and values. Talking about *choices* aims at ensuring that patients are aware that different yet reasonable options are available for the clinical condition at stake. Then, physicians should engage in a talk regarding the *options* by describing the practical features and providing detailed information of each option, especially regarding possible benefits and harms. Finally, physicians and patients should undertake a *decisional* talk by mainly focusing on patients' preferences and mutually supporting the decision-making process in order to decide what is the best decision for individual patients (*ibid.*). The first two steps of SDM overlap with the requirements of the *informed decision-making* model, while the third step is the fundamental characteristic differentiating SDM from other decision-making models. Indeed, by clarifying values, preferences and needs, and by guiding and coaching patients in the decision-making process, SDM constitutes an effective way of addressing the modifiable factors of *decisional conflict* (O'Connor, Légaré and Stacey 2003).

Among the *needs* patients may express in SDM, it is important to highlight the possible need to overcome cognitive difficulties in understanding statistical evidence and therefore in applying it to inform their personal choices, as well as psychological and emotional factors influencing both patient-physician

126

communication and the decision-making process (Barry and Edgman-Levitan 2012). Clinical decisions tend to be informed by scientific and factual evidence on benefits and risks of the intervention, but at the same time they are strongly influenced by emotions and feelings, especially in oncological settings (Pravettoni and Gorini 2011). Moreover, psychosocial outcomes such as anxiety, anticipated regret, perceived risk, and worriedness are actually a matter of personal evaluation in balancing benefits and risks of screening and should be also taken into account (Pace and Keating, 2014). Therefore, for physicians to encourage patients sharing information regarding what they care about and what personal life plans and goals they strive for, what they need, how do they perceive and elaborate clinical information, how emotions affect and influence the decisional process, some competences on the side of physicians are required. As a starting and preliminary key point of SDM, physicians should possess the relational and professional ability of building a partnership with patients, which implies mutual responsibilities, requires attention and discussion about the relationship itself that should be dynamic and adaptable to changing circumstances, and takes time to develop (Towle and Godolphin 1999). Building a partnership means that physicians take responsibility for answering patients' questions, understanding specific individual needs, addressing specific concerns regarding the intervention, as well as responding to patients' ideas and expectations (King and Moulton 2006).

Once the partnership has been built, physicians have the chance of establishing and reviewing patients preferences regarding their role in decision-making, such as taking risks and/or involving significant others in the process. Most importantly, in SDM patient-physician consultation revolves around understanding and evaluating evidence-based clinical options in light of individual patients' lifestyles and plans. Hence, physicians should possess communication

skills and relational capabilities for encouraging patients to share personal information aimed at incorporating life goals and values in the decision-making process itself (Towle and Godolphin 1999). In other words, SDM allows for truly taking into account individual patients' cognitive and emotional competences and eventually personalizing the way in which communication regarding effects of different options is framed. On the basis of information, physicians can effectively help patients reflect on and evaluate the impact of alternative decisions in light of personal values and life goals.

From the ethical viewpoint, SDM represents an effective means of respecting patient autonomy, but it moves a step forward from *informed decision-making*. Indeed, respecting autonomy in a broader sense requires promoting patients' self-determination, and goes beyond just not interfering with their decisions. Hence, by engaging in SDM physicians provide and discuss information in personalized ways and encourage patients to share their life-plans and goals, evaluate their preferences by incorporating personal values in the process of decision-making. In this respect, the ethics of care – as presented in Chapter 3 (see Chapter 3.6.3. *The ethics of care in bioethics*) – constitutes a suitable normative framework to SDM in that it requires engaging in activities such as listening, understanding the needs, and accounting for patients' self-conception and personal goals (Manning 2009) (Donchin 2001).

Moreover, by emphasizing the importance of responding to concrete individuals' needs, the ethics of care pursues the development and application of personalized communication strategies that truly take into account and address individual cognitive capabilities of understanding complex statistical information. Finally, the core feature of SDM is the partnership between physician and patient, which is the prerequisite for reaching a consensus regarding the medical

intervention to be implemented. Again, the ethics of care promotes specific and concrete relationships as the fundamental moral activity implying duties and obligations that can be broadly defined as taking responsibility for those in need by engaging in a *caring* relationship aiming at understanding and responding to particular needs in the best possible way. Hence, by focusing on responding to specific personal needs, the ethics of care expands the concept of medical goal from the mere healing to the broader enhancement of individuals' wellbeing.

Table 6 (adapted from *Joosten et al., Psychotherapy and Psychosomatics, 2008*) lists the three major models of patient-physician relationship and outlines the most important features of each model.

Table 6 - Paternalistic, IDM and SDM models of patient-physician relationship

	Paternalistic Model	Informed Decision-making Model	Shared Decision-making Model
Role of physician	Active: reports selected information to patients, decides the treatment based on the "best interest" of patient	Passive: provides all the information to patients, withholds recommendations, makes no decision	Active: provides all the information to patients, can recommend an option, decides together with the patient
Role of patient	Passive: accepts the proposal of physician, provides consent to treatment (informed consent)	Active: receives all information, forms his/her own judgment, chooses between all options without any influence from physician, decides on the treatment alone	Active: receives all information, forms his/her own judgment on treatment options' benefits and harms, discusses preferences with physician, decides on treatment together with physician
Information	One way: physician→patient	Largely one way: physician→patient	Two way: physician↔patient
Deliberation	Physician alone or with other health care providers	Patient alone (plus potential others)	Physician and patient (plus potential others)
Decision	Physician	Patient	Physician and patient
Moral principles	Beneficence Non-maleficence	Respect for autonomy	Respect for autonomy and Self-determination Care
Relationship	Paternalistic	"Contractual"	Partnership

In the context of mammography screening for women aged 40 to 49, SDM requires physicians to disclose all the high quality available information, and especially the inherent uncertainty of the balance between benefits and harms. In this respect, particular attention should be paid to the explanation of the general concepts of mammography screening, such as *mortality reduction*, *false positive* results and *overdiagnosis*. By engaging in a clear and explicit communication regarding benefits and harms, women have the chance of evaluating and discussing the *value* of options and thus make a truly informed choice. Whether a particular risk is worth taking or not, it rests on a decision that is inescapably the result of life plans, goals, values and beliefs of individual women. Indeed, in SDM the final decision depends on the evaluation of available scientific information, which is a matter of what patients consider the *right* option for them. In other words, the proportionality between the disvalue of possible harmful outcomes and the value of possible beneficial ends should be assessed by individual women who may have a personal view about what constitutes benefits and harms, and especially as to what extent risks are worth taking up or not.

5.2.1. Information and preferences in SDM: patient decision aids (PtADs)

As seen in Chapter 4, communicating information on benefits and harms of mammography screening might be a challenging task and some possible solutions to the issue have been proposed to overcome the communication difficulties, traditionally focusing on the presentation format of statistical data. However, critics of the conventional approach to breast cancer screening communication argue that public health messaging and campaigns have further complicated women's process of decision-making by delivering simplistic and overly positive, yet misleading messages (Gigerenzer 2014) (Wang et al. 2014). In the past decades – they claim – public health messaging and information materials have tended to

present mammography as an effective and safe mean of prevention (Reynolds 2012), as well as to emphasize benefits and minimize harms (Gummersbach et al. 2010). As a consequence, women commonly tend to overestimate the overall benefit of mammography (Domenighetti et al. 2003) (Hoffman et al. 2010) (Woloshin et al. 2012). Furthermore, decision-making regarding mammography screening is a process in which the tension between emotions and individual assessment between benefits and harm is particularly evident and makes it challenging to properly communicate the possible harms of screening (Vahabi and Gastaldo 2003) (Rosenbaum 2014).

Among different communication strategies that have been applied in the context of breast cancer screening, patient decision aids (PtDAs) appear to be particularly promising for enabling women making choices consistent with their values and preferences (McCaffery et al. 2016). PtDAs can be defined as «tools designed to help people participate in decision making about health care options», and specifically PtDAs «provide information on the options and help patients clarify and communicate the personal value they associate with different features of the options» (International Patient Decision Aid Standard – IPDAS)³⁵. PtDAs may be designed in various formats – such as booklets, webpages, and videos - and differ from usual health messaging materials for their detailed focus on options and possible outcomes of specific decisions (Stacey et al. 2017).

It is important to highlight that PtDAs do not advise for or against choosing one option over another, instead they help patients to make informed and value-based decisions together with their physicians. The patient-physician relationship keeps on playing the central role in decision-making, for within the medical encounter and consultation patients discuss options and preferences rising from

³⁵ Available at: <http://ipdas.ohri.ca/what.html> (last accessed on 10.13.2017).

PtDAs, and reach an agreement on the course of action to implement (International Patient Decision Aid Standard – IPDAS). In 2005 the IPDAS published the first *Criteria for Judging the Quality of Patient Decision Aids*³⁶, which currently constitutes the most commonly applied guide for developing PtDAs as reliable sources of health information that can effectively help in decision-making (IPDAS 2005). The document provides a checklist of features that must be included in PtDAs development and presentation in order to meet the IPDAS quality criteria. Concerning the contents, 4 major criteria should be met: the PtDA should 1) provide information about options in sufficient detail for decision-making³⁷; 2) present probabilities of outcomes in unbiased and understandable way³⁸; 3) should include methods for clarifying and expressing patients' values³⁹; and 4) should include structured guidance for deliberation and communication with physicians⁴⁰.

PtDAs meeting the IPDAS criteria have been proven effective in helping patients understand and absorb relevant and up-to-date information and scientific evidence and thereby develop and share informed preferences about options,

³⁶ IPDAS 2005: *Criteria for Judging the Quality of Patient Decision Aids*, available at: www.ipdas.ohri.ca (last accessed on 10.13.2017).

³⁷ Specifically, the information provided should describe the health condition, list the available options including the option of doing nothing, describe the procedure as well as the benefits and harms or side effects of each option, and include the chances of positive and negative outcomes of the intervention (IPDAS 2005).

³⁸ In particular, the probabilities of outcomes should be presented divided per age groups and using multiple formats such as words, numbers and diagrams that can be selected by users, and using both positive and negative information framing – *mortality reduction*, *survival rates*, and *death rates* (IPDAS 2005).

³⁹ Clarifying patients' values and preferences means that the PtDA should describe the procedure and outcomes to help patients imagine their likely physical, emotional and social experience of the intervention, as well as considering which positive and negative features matter most to individual patients, and finally suggesting ways of communication such preferences – for example by providing a final report listing all the contents presented in the PtDA (IPDAS 2005).

⁴⁰ In order to constitute a concrete guidance in deliberation, PtDAs should provide a step-by-step way of reasoning regarding the decision to be made. Furthermore, PtDAs can effectively facilitate patients' preferences by including tools such as reports or worksheets to discuss options with physicians (IPDAS 2005).

especially when they have not yet experienced possible outcomes (Barry and Edgman-Levitan 2012). In breast cancer screening context, PtDAs currently provide patients with reliable and up-to-date information about breast cancer and screening options in order to increase women's participation in the clinical decision-making process by making informed choices based on adequate knowledge of both the condition and options, and consistency between their preferences and available screening behaviours (Gorini, Masiero and Pravettoni 2016). Given the limited understanding of mammography screening features among the general public, it appears of fundamental importance to identify successful strategies of communicating not only the amount of possible benefits and harms, but also the basic concepts of screenings, particularly with regard to *false positive* results and *overdiagnosis* (Barratt et al. 2005) (see Chapter 4.3.4. *Choosing the best option: information and preferences*). **Figure 4** presents a flowchart of possible mammography outcomes, with graphical explanation of the concepts of *true negative*, *false negative*, *true positive* and *false positive* results (adapted from Nelson, Scholar Archive, 2011).

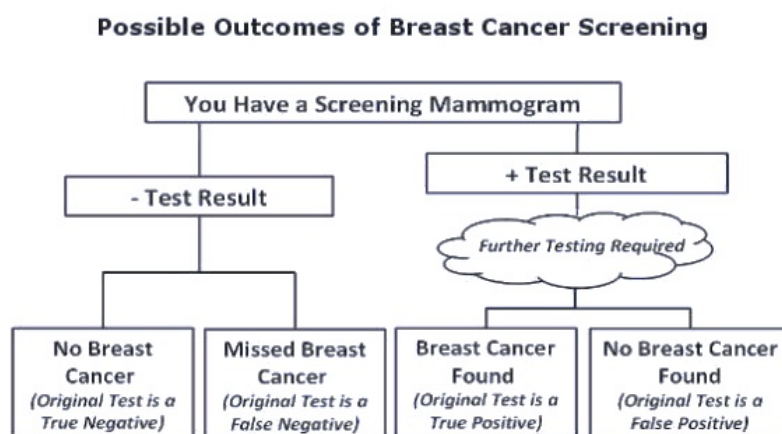


Figure 4 - Graphical explanation of possible mammography screening results

As shown in Chapter 4, people find it less difficult to understand statistical information in natural frequencies format, and infographics helps to further frame

the conceptual and statistical information in a user-friendly way. For example, **Figure 5** and **Figure 6** (both adapted from *Hersch et al., Lancet – Supplementary Appendix, 2015*) illustrate how information regarding *false positive* results and *overdiagnosis* can be framed in infographic and natural frequency formats. Moving a step forward in simplifying presentation formats, the YouTube video *Lazris & Rifkin's Risk-Benefit Characterization Theater*⁴¹ intends to explain the benefits and risks of routine mammography screening – for women of all age groups - without using any mathematical information. In general, it has been demonstrated that women considering mammography screening are less likely to undergo the test when provided with a PtDa including easy understandable information about *false positive* results and *overdiagnosis* (Hersch et al. 2015).

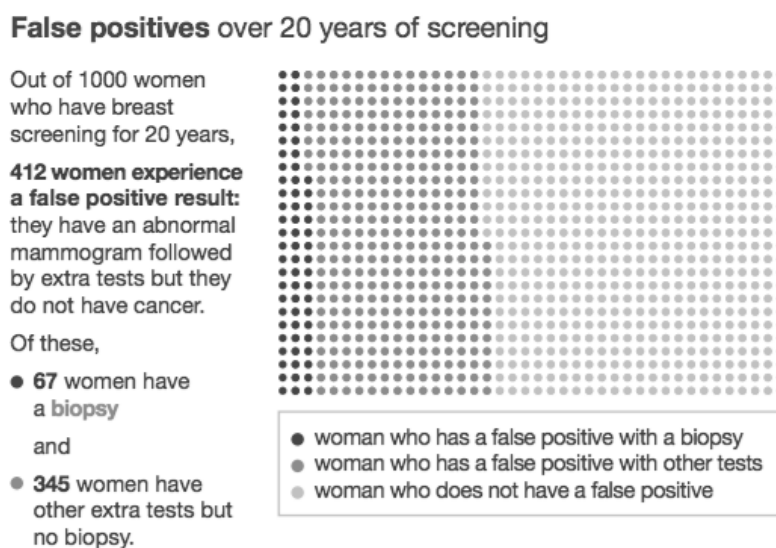


Figure 5 - Infographics and natural frequency format of mammography false positive results

⁴¹ Available at: <https://www.youtube.com/watch?v=UZIY6Q4m-MM> (last accessed on 10.13.2017).

Over-detection: an example

Imagine a woman called Maria who develops a small, slow-growing breast cancer in her 50s or 60s. The picture below shows two possible scenarios that could happen to Maria: Scenario 1 (top) is with screening, and Scenario 2 (bottom) is without screening.

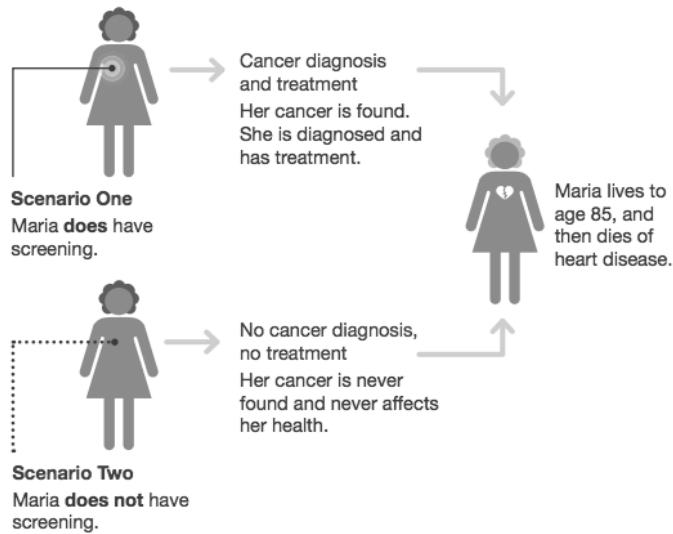


Figure 6 - Infographics representing mammography overdiagnosis

PtDAs have been proven beneficial by the Cochrane systematic review of trials (Stacey et al. 2017). In particular, PtDAs were proven effective in reaching an increased knowledge regarding intervention options and more accurate risk perception. Notably, PtDAs also lead to a greater number of decisions consistent with patients' preferences and values, a reduced level of patients' internal decisional conflict and therefore a fewer patients deciding to remain passive or undecided in clinical decision-making (*ibid.*). PtDAs have been shown to help patients overcome some of the modifiable factors of decisional conflict and thus to improve clinical decision-making (Ivlev et al. 2017). However, the evidence regarding the balance between benefits and harms of mammography screening varies among different age groups and, therefore, PtDAs should be differentiated according to such differences. In fact, for women aged 50 to 70, a routine screening is recommended by all Western countries guidelines (see Chapter 2.6. *Recommendations, guidelines and mammographic screening programs*) and PtDAs addressing this age group can rely on strong evidence on the net benefit of

mammography. Therefore, the information to be provided regards the general features of breast cancer and screening in order to enable women to make an *informed choice* about undergoing mammography. The choice to participate the screening program, however, is considered by policy-makers to be *reasonable* in that «most individuals in this situation would want the course of action» and therefore «most individuals should receive the recommended course of action» (Oeffinger et al. 2015, p. 1600).

5.2.2. Mammography screening PtDAs for women aged 40 to 49

As seen in Chapter 2, the evidence regarding benefits and harms of mammography for women aged 40 to 49 is insufficient to objectively assess the net benefit of routine screening. Thus, PtDAs addressing women younger than 50 years should first and foremost explicitly state the uncertainty of the effectiveness and safety of mammography, and that different choices regarding the uptake of the intervention are ultimately *reasonable*. Indeed, all guidelines acknowledge the fundamental role of personal evaluation of benefits and harms in assessing the net benefit of participating the screening program. The use of specific PtDAs is often recommended when the balance between benefits and harms of an intervention is uncertain (Barratt et al. 2004), as in the case of routine mammography for women older than 70 years (Mathieu et al. 2007) (Schonberg et al. 2014) and younger than 50 years.

Following the update of Western countries' guidelines, several studies have been focusing on the development on the basis of the IPDAS criteria and evaluation of specific PtDAs addressing women aged 40 to 49 to help them make an informed and value-based decision. For example, in November 2016 the USPSTF uploaded on YouTube the video *Mammogram Questions to Think about for Women Aged 40-*

49⁴², which is intended to help women understand the recent guidelines update, especially emphasising that the decision whether to begin routine screening is an individual one (see Chapter 2.6. *Recommendations, guidelines and mammographic screening programs*). Among the many PtDAs developed specifically for women in their forties, this study presents only those whose effectiveness has been evaluated through scientific studies:

- 1) The *Australian Mammography Decision Aid*⁴³, which was proven effective in increasing women's knowledge about benefits and risks of mammography, and in improving communication and discussion about preferences between women and their physicians (Mathieu et al. 2010).
- 2) The *Mammopad*⁴⁴, a web-based PtDA, which a pilot study (Scariati et al. 2015) and a RCT (Eden et al. 2015) demonstrated effective in reducing women's decisional conflict regarding whether to participate screening.
- 3) The *Breast Screening Decisions*⁴⁵, a web-based PtDA that was shown to support informed, individualized decisions about screening mammography and facilitate discussions about preferences between women and their physicians (Elkin et al. 2017).

Notably, a systematic review and meta-analysis of multiple PtDAs addressing different age groups – and including the three mentioned above -, reported that the use of PtDAs for screening mammography increases women's aged 40 to 49 reluctance to begin routine screening (Ivlev et al. 2017). While the majority of

⁴² The PtDA *Mammogram Questions to Think about for Women Aged 40-49* provides general information on breast cancer and routine mammography screening, its possible benefits and harms, with data framed in percentage, natural frequency and infographic formats. Notably, the video devotes an entire section to clarify the concepts and quantify the magnitude of *false positive* results and *overdiagnosis*, and finally suggests women to think about the received information and discuss it with their physicians. Available at: https://www.youtube.com/watch?v=6uGy720Cv_Q (last accessed on 10.13.2017).

⁴³ Available at: <http://www.mammogram.med.usyd.edu.au/> (last accessed on 10.13.2017).

⁴⁴ Available at: <http://www.mammopadforme.org/> (last accessed on 10.13.2017).

⁴⁵ Available at: <http://www.breastscreeningdecisions.com/#/> (last accessed on 10.13.2017).

cancer PtDAs has been criticized for low levels of individualization (Fagerlin et al. 2012) (Gorini, Masiero and Pravettoni 2016), all three PtDAs mentioned above can be classified as proper *personalized tools* in that they devote a section to individual health and breast cancer risk assessment⁴⁶, and a section to value clarification by considering personal ratings of pros and cons of options and individual women risk estimation (Pignone et al. 2012). When decisions have to be made under scientific uncertainty, personal values, beliefs and attitudes appear particularly significant in the decision-making process (O'Connor, Légaré and Stacey 2003)⁴⁷.

Regarding the clarification of personal values, specifically the *Australian Mammography Decision Aid* and the *Breast Screening Decisions* provide users with *ten-point rating* and *ranking scales* to rate feelings, concerns and risk perceptions related to mammography screening; while the *Mammopad* presents *discrete choice tasks* (or *choice-based conjoint analyses*) between alternative options regarding benefits and harms. Finally, the *Mammopad* and the *Breast Screening Decisions* provide a personalized final report containing a summary of information and the list of preferences women listed throughout the PtDA. Reports are explicitly designed to help women discuss preferences and concerns with their physicians, acknowledging the fundamental role of SDM in reaching truly informed and value-based decisions. Many researchers claim that further studies is necessary in order to assess whether the use PtDAs should precede the consultation with physicians, should be used during the consultation or should follow the encounter (O'Connor,

⁴⁶ Individual breast cancer risk assessment is a preliminary and necessary evaluation, for mammography screening current guidelines refer to those «asymptomatic women aged 40 years or older who do not have pre-existing breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation» (Siu 2016, p. 280). Indeed, the risk assessment is based exactly on these general risk factors.

⁴⁷ Notably, values appear to inform also experts' screening evaluation both at the epistemic level concerning how evidence should be created and used, and at the ethical level regarding what has to be considered good, right and important (Parker, Rychetnik and Carter 2015). See Chapter 4.3.1. *Deciding what to do: delivering benefits, avoiding harms.*

Légaré and Stacey 2003) (Fagerlin et al. 2013). Indeed, beside the helpful contribution of PtDAs in reducing the eventual *decisional conflict*, SDM still represents the most effective way of eliciting and clarifying patients' values and preferences regarding different clinical options (IPDAS 2005) (King and Moulton 2006) (Elwyn et al. 2012) (Pignone et al. 2012) (Elkin et al. 2017). PtDAs, hence constitute a good starting point from which physicians can engage in SDM by discussing with already informed patients about specific concerns and preferences by further taking into account particular life styles, personal goals and values (King and Moulton 2006) (Breitsameter 2010) (Thorne, Oliffe and Stajduhar 2013).

5.3. Incorporating values in shared decision-making

As seen throughout this work, physicians' requirement to provide patients with information is a feature common to both IDM and SDM. The fundamental difference between the two methods lies in the kind of relationship they entail. Within an IDM framework, respecting patients' autonomy entails that physicians' primary duty is to enable patients in making informed decisions by providing them with all the relevant clinical information about treatment options. At the same time, physicians should avoid expressing their own preferences regarding available options, in order not to interfere with patients' evaluations and preferences. The kind of relationship between health care professionals and patients resembles the *contractual* relation typical of economic and public domains: the encounter between two equal, rational and self-interested agents. Conversely, SDM requires the establishment of a *partnership* in which both physicians and patients bring information, share concerns and preferences, discuss options, and finally reach an agreement on the course of action to be implemented. In particular, through SDM patients have the opportunity to discuss options' features in light of their personal needs, life styles, and goals.

In health care, meeting needs is not limited to fill the gap in clinical knowledge and proposing treatment alternatives, nor just providing a PtDA and let patients decide alone. The “good” carer engages in relationships aimed at understanding and responding to particular needs in the best possible way. However, individualized complexity requires individualized interpretation, understanding and responsiveness, and sophisticated communication skills, which are influenced by physicians’ *attitudes* and *knowledge* (Thorne, Oliffe and Stajduhar 2013). Attitudes can be referred to as the character disposition and the endorsement of an ethical account of patient-physician relationship, which in SDM is inherently based on a strong conception of patient autonomy requiring the empowerment of his/her agency. On the other hand, knowledge is not just a matter of clinical knowledge, nor of technical knowledge regarding different statistics presentation formats. In light of the ethics of care, the concept of knowledge moves beyond, and embraces the capability of listening, understanding, encouraging and enhancing individual agency. In the context of mammography screening - which by nature addresses healthy and asymptomatic individuals -, scientific and clinical knowledge are clearly insufficient for physicians to engage in an effective partnership with women. Promoting women’s self-determination by means of routine screening requires a broader discussion and evaluation of general life plans, goals, as well as psychological and emotional attitudes toward the procedure and the disease. In other words, through the *SDM partnership* physicians should get to know individual women, how they reason, and what they care about (Hoffman et al. 2014).

As suggested by Elwyn and colleagues (Elwyn et al. 2012), a complete section of the process of SDM is devoted to patients’ values elicitation and clarification in order to reach a truly value-based decision. Indeed broadly

speaking, values are the rules by which people make decisions about what is right or wrong, they inform preferences and provide the rationale for the final uptake of one course of action over another – from daily life experience, to clinical DM -, and often individuals disagree about what is the right decision to be taken. This disagreement arises from the so-called “moral pluralism”, that is the acknowledgment that there are many different values irreducible to one super value (Engelhardt 1996). Values, and especially moral values, might have different sources: they might originate from culture or be rooted in religion, but they also might be grounded in personal experience or find their justification in laws and social rules, and finally, it has been argued they might be characterised by gender (Gilligan 1982) (Noddings 2010).

Some studies have investigated factors associated with breast cancer screening programs participation and have provided significant insights on women’s beliefs and behaviours. Indeed, in accordance to the SDM model, the findings acknowledged an important role in predicting the attendance to screening to both information and individual’s psychosocial factors. However, these studies have mainly focused on attenders’ and non-attenders’ knowledge about the risk of cancer and screening as a strategy to reduce risk (Vahabi and Gastaldo 2003); attitudes toward screening (Berkowitz et al. 2008) (Hersch et al. 2011) and health behaviour (Lagerlund et al. 2000); emotions associated with screening (Ackerson and Preston 2009) (Rosenbaum 2014); socio-demographic factors (Calle et al. 1993) (Selvin and Brett 2003) (Wardle et al. 2015); health care providers endorsement (Spring et al. 2016); and social norms (Smith-McLallen and Fishbein 2008). Interestingly, although being childless and living without a partner appear to be associated with less attendance (Lagerlund et al. 2002), and parental concerns in the oncological setting are rising growing interests (Rauch and Muriel

2004) (Sample and McCance 2010), no specific study on the role of caring relationships and personal moral values in cancer prevention decision-making has yet been performed. Hence, it would be important to investigate a possible common source of values for women aged 40 to 49 in order to provide physicians with some specific knowledge regarding possible values informing preferences and the SDM process.

Two major common characteristics possibly implying some shared values were identified: the population group is indeed composed by 1) healthy women in their 40s; of whom 2) approximately 75% are mothers⁴⁸. Keeping these two characteristics in mind, the PEO (Population, Exposure, Outcome) format was applied to pose a researchable question. The PEO format, together with the PICO (Population, Intervention, Comparison, Outcome), is often used in health research, and especially in nursing research. The PICO format is most widely used in *quantitative* research, and includes the comparison of interventions such as a control group (different treatment or placebo); whereas the PEO format is helpful in determining *qualitative* research questions aiming at exploring experiences in terms of daily living and quality of life (Bettany-Saltikov 2012). To the purpose of this work, the PEO format appears particularly useful, in that it guides posing relevant questions by focusing on the impact of the exposure to a given intervention, treatment or situation on a certain population. The investigated outcome can be physical, psychological, social, cultural, or ethical (Sofaer and Stretch 2012). Therefore, in the present study, the PEO model was applied to formulate the researchable question, which was conceived broadly as follows:

⁴⁸ The data is obtained from the EUROSTAT (EUROSTAT 2015) and US surveys (Taylor et al. 2010), and it's most likely similar to those from other developed countries due to overlapping circumstances influencing postponed parenthood: such as «the rise of effective contraception, increases in women's education and labour market participation, value changes, gender equity, partnership changes, housing conditions, economic uncertainty and the absence of supportive family policies» (Mills et al. 2011).

what is the impact of breast cancer on mothers' experience of parenting? More specifically, the research aims at identifying ethical concepts and themes women concern themselves about and refer to in the context of breast cancer diagnosis, treatment and survivorship.

Therefore, I decided to conduct a review of the literature concerning mothering during breast cancer, in order to investigate both the state of the art in research on the issue, and which ethical concepts and values are commonly related to the experience of parenting during breast cancer. The rationale behind this decision is that the identification of moral themes and concepts common to mothers facing breast cancer may shed some light on common ethical patterns in women's clinical decision-making. In turn, such a conceptualization could be also applied in investigating and better understanding preventive decision-making, thus constituting a helpful source of knowledge for physicians engaging in SDM with women aged 40 to 49 regarding whether to start routine mammography screening.

5.3.1. Methodology

In clinical and health research, systematic literature reviews are very common approaches, and many different guidelines to conduct actual and reliable reviews have been proposed⁴⁹. Given the "evidence-based" aim of such research, protocols usually call for very restrictive search and evaluation methodologies, which are deemed necessary for a transparent and reliable report of systematic reviews. However, while the clinical and health protocolled search strategies certainly assist researchers in correctly posing and reporting findings, the requested strictness may not always serve the purposes of bioethical research - especially

⁴⁹ Among those, the PRISMA Statement (Liberati et al. 2009) consists of 27-item checklist and a 4-phase flow diagram, which guarantees for good reports in the context of biomedical research.

with regard to the evaluation of key articles on moral concepts and ideas. In this respect, it has been argued that although systematic literature search should be maintained in bioethical research, the kind of systematic search and report shall depend both on the research question and the type of available literature on the issue (McDougall 2014) (Sofaer and Stretch 2012). In order to conduct an effective and useful bioethical research, not all the requirements of biomedical research are needed, but some skills shall be added. One of the purposes of bioethical research may be to critically evaluate the current interpretation of specific issues and – hopefully – to produce new knowledge. The need for renewal in evaluation and interpretation calls for a critical analysis of the existing literature, which, in turn, requires the adoption of *critical interpretative reviews* (McDougall 2015). The principle aim of critical interpretative reviews is indeed to identify conceptual contributions to either embody or derive new theories or interpretative models (Grant and Booth 2009). Theorizing therefore comes to the core of the review process, which turns the review's nature into a proper research activity (McDougall 2014). It clearly appears that a crucial limitation of critical interpretative reviews stems from the inevitable individual judgment in deciding which contributions of the existing literature may qualify as key concepts or ideas, and in assessing the quality of such literature⁵⁰. Therefore, this work takes advantage of a combined approach: 1) literature has been identified applying the search strategy common to health and clinical research; while 2) the content analysis of the identified literature has been conducted by adopting the critical interpretative approach in light of the ethics of care.

A comprehensive systematic review approach was used to identify the relevant literature focusing on women's and mothers' experience of parenting

⁵⁰ Consequently to individual judgment comes the risk of biases, which has to be acknowledged both by the researcher and the reader.

during breast cancer (McDougall 2014). The search strategy included the PubMed, PsycINFO, Direct Science and PhilPapers electronic bibliographic databases. The string of search terms used was *parent** OR *mother** AND *breast cancer*. Therefore, the following inclusion criteria were set up: 1) articles exploring women' experience of parenting during breast cancer; including both 2) qualitative and quantitative studies. Dissertations and literature reviews were excluded due to potential subjective interpretations of previous works, which could have biased further content analysis. The last search was performed on June 20th 2016. The search strategy is presented in **Figure 7**, which describes the search findings in a flow chart.

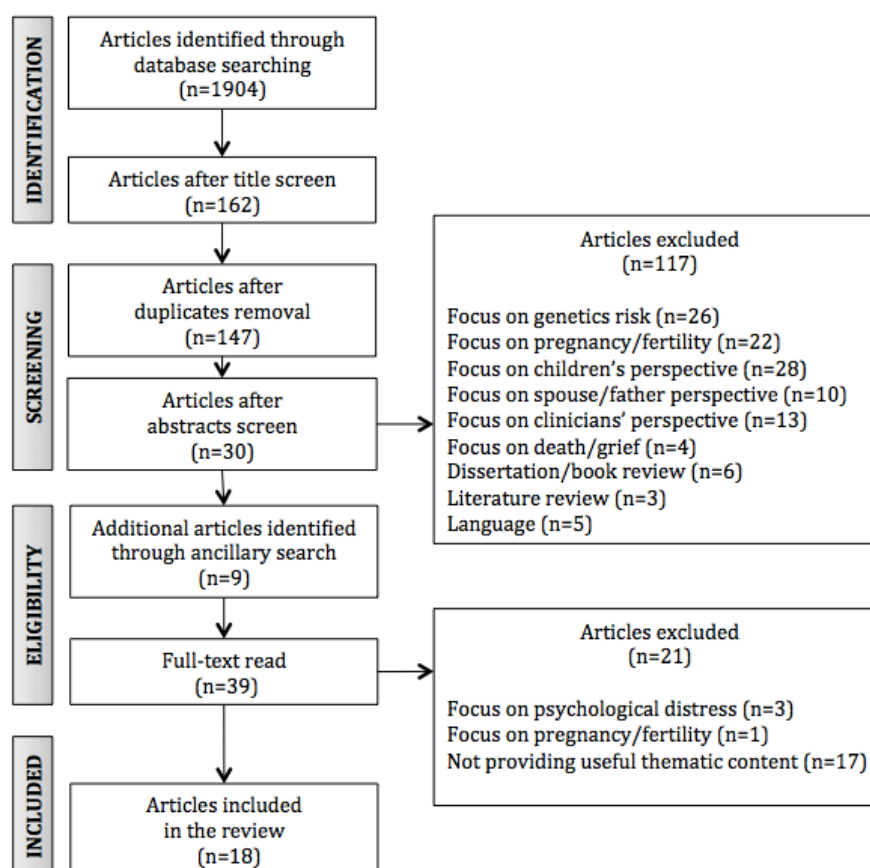


Figure 7 - Flowchart of the literature review

The initial search in the four databases resulted in a total of 1904 articles. Title screen reduced the selection to 162 articles; discarding the duplicates reduced the collection to 147 papers that were selected for abstract read, and 30 papers

meeting the inclusion criteria were selected for full-text reading. The search was supplemented with a manual ancillary search using reference lists and grey literature not indexed on electronic databases but relevant to the subject area, and resulted in a total of 9 additional articles selected for full-text reading. Full-text read revealed that 4 articles didn't meet the inclusion criteria, and 17 did not mention anything that could be considered useful for a thematic content analysis. The 18 studies that met the inclusion criteria are listed in **Table 7**.

Table 7 - Summary of the studies included in the review

Author(s)	Purpose of the study	Methodology	Sample characteristics	Themes identified
Arés, Lebel and Bielajew (2014)	Explore the impact of motherhood over time on women's with breast cancer wellbeing	Web-based survey (Quantitative)	742 breast cancer survivors 539 mothers 203 non-mothers	Cancer as a major life event Illness intrusiveness Fear of death/recurrence
Asbury, Lalayannis and Walshe (2014)	Investigating the experience of mothers in telling their children of their diagnosis	Semi-structured interviews (Qualitative)	10 mothers with breast cancer	Protecting children from distress Maintaining routine Minimizing own needs Communication management Providing/withholding information
Barnes et al. (2000)	Investigating the experience of mothers in telling their children of their diagnosis and treatment	In-depth interviews (Qualitative)	32 mothers with breast cancer	Protecting children from distress Communication management Providing/withholding information Need for help in communicating with children
Billhult and Segesten (2003)	Investigating the experience of breast cancer in mothers with dependent children, and exploring the strategies mothers use to handle the illness in relation to children	Phenomenological interviews (Qualitative)	10 mothers with non-recurrent breast cancer	Fear of death/recurrence Protecting children from distress Maintaining routine and everyday life Keep positive Communication management Providing/withholding information Balancing roles (patient-mother)
Campbell-Enns and Woodgate (2013)	Exploring the process of treatment decision-making in mothers with cancer	Semi-structured interviews (Qualitative)	8 mothers with cancer 6 mothers with breast cancer 1 mother with leukaemia 1 mother with brain cancer	Protecting children from distress DM about treatments aims at maintaining the mother-child bond Sense of guilt for shifting maternal responsibility Communication management Providing/withholding information

Cho, Yoo and Hwang (2015)	Comparing parent-child communication and parental role satisfaction between women with breast cancer and healthy women	Descriptive survey (Quantitative)	101 mothers 50 mothers with breast cancer 51 healthy mothers	Communication management Providing/withholding information
Connell, Patterson and Newman (2006)	Investigating and identifying concerns of women diagnosed with breast cancer	Semi-structured interviews (Qualitative)	35 women with breast cancer	Fear of death/recurrence Concerns for children psychological wellbeing
Elmberger et al. (2008)	Exploring how women with cancer deal with moral concerns related to their responsibility as parents	Semi-structured interviews (Qualitative)	19 mothers with cancer 9 mothers with breast cancer 10 mothers with lymphoma	Fear of death/recurrence Protecting children from distress Balancing roles (patient-mother) Coming to terms with being a mother
Fisher and O'Connor (2012)	Exploring the impact of breast cancer on the identity of young women as mothers	In-depth interviews (Qualitative)	8 mothers with breast cancer	Balancing roles (patient-mother) Coming to terms with being a mother
Helseth and Ulfsaet (2005)	Understanding how cancer affects childcare, assessing parenting experiences of cancer patients with their children	In-depth interviews (Qualitative)	10 parents with cancer 3 fathers 7 mothers (2 breast cancer)	Protecting children from distress Maintaining routine Minimizing own needs Communication management Providing information Balancing roles (patient-mother) Coming to terms with being a mother
Kim, Ko and Jun (2012)	Exploring the impact of breast cancer on mothers and their children following diagnosis	In-depth interviews (Qualitative)	7 mothers with breast cancer	Balancing roles (patient-mother) Maternal responsibility Treatment side-effects Communication management
Kirkman et al. (2014)	Understanding the mean of managing fertility and motherhood in the years after a breast cancer diagnosis	In-depth interviews (Qualitative)	10 women with breast cancer 3 mothers 7 non-mothers	Cancer as a major life event Protecting children form distress Maximizing chances of being alive
Mackenzie (2014)	Understanding how mothers with breast cancer manage their multiple demands of taking care of themselves, their children and paid work	Semi-structured interviews (Qualitative)	32 mothers with breast cancer	Balancing roles (patient-mother) Protecting children form distress Minimizing own needs Maximizing chances of being alive

Mazzotti et al. (2012)	Exploring the experience of mothers with breast cancer	In-depth interviews (Qualitative)	8 mothers with breast cancer	Protecting children from distress Concerns for children psychological wellbeing
Moore et al. (2015)	Examining relations between parental illness, quality of life, parental functioning, parenting efficacy beliefs and concerns about children distress	Cross-sectional study (Quantitative)	194 parents with cancer 66 mothers with breast cancer	Belief in decline in parenting efficacy due to therapy side effects Protecting children from distress Maintaining routine
Stinsen-Kollberg et al. (2013)	Investigating the association between worrying about own children and low-psychological wellbeing during the year following breast cancer diagnosis	Observational population-based study (Quantitative)	313 mothers with breast cancer	Fear of death/recurrence Concerns for children psychological wellbeing Need for psychological support
Walsh, Manuel and Avis (2005)	Exploring the impact of breast cancer on younger women's relationships with their children	Survey (Mixed: quantitative and qualitative)	204 mothers with breast cancer	Concerns for children psychological wellbeing Balancing roles (patient-mother)
Yoshida et al. (2010)	Exploring decision-making by breast cancer patients about telling their children about their illness	Semi-structured interviews (Qualitative)	30 mothers with breast cancer	Communication management Providing/withholding information Protecting children from distress DM about communication aims at maintaining the mother-child bond

5.3.2. Content analysis: themes and moral concepts

The analysis of the 18 studies on women's parenting experience following a breast cancer diagnosis revealed four predominant themes: 1) protecting children from distress; 2) managing the communication of clinical information to children; 3) balancing the role of being a mother with being a patient; and 4) the need for help from health care providers. The four themes were not consistently reported across the 18 studies, yet some studies reported all, while other studies focused only on some of them. A critical analysis of the four major themes in light of care ethics was hence carried out in order to investigate possible ethical conceptualizations. The ethics of care approach seems to provide not only a suitable framework to inquire gendered moral values, but it also highlights the role of "mothering" in women's lives. Indeed, the ethics of care is a gendered ethical theory that, following the observation of female moral thinking (Gilligan 1982), valorises virtues and values traditionally linked to women.

In general, it has been shown that parenting children while coping with breast cancer can negatively affect women's wellbeing (Connell, Patterson and Newman 2006) (Kirkman et al. 2014). In particular, mothers with breast cancer tend to experience more fear of recurrence, fear of death and illness intrusiveness compared to women without children (Stinsen-Kollberg et al. 2013) (Arés, Lebel and Bielajew 2014). In the first place, at the time of diagnosis the most common concerns reported by parents are how to tell children about the illness, and how to manage parenting responsibility (Billhult and Segesten 2003) (Mazzotti et al. 2012).

Among the ethics of care general features extensively presented in Chapter 3, three are of particular importance to the present analysis: 1) the recognition of

moral significance of fundamental elements of relationships and dependencies; 2) the attention paid to the need for responsiveness in such relationships; and 3) the focus on motivation to care for those who are dependent and vulnerable (Held 2006). Taken together the three features shape the ethical theory central moral duty, which is *to care* by promoting the wellbeing of the self and the other by responding to needs. More interestingly, this approach interprets caring as an activity central to women, a moral disposition gendered from internalized cultural norms and beliefs (Tong 1998). The ideal of *good caring* is well represented by the concept of *mothering*⁵¹, which is considered as a biological and moral activity of caring, of which the moral central dynamic is to take upon oneself the responsibility of child's care for life (Ruddick 1989) (Noddings 2010).

The evidence suggests the image of a *good mother* changes during the course of a serious illness (Elmberger et al. 2008). Indeed, cancer diagnosis and consequent treatments make it impossible for women to keep on acting according to the ideal of *good mothers* (Kim, Ko and Jun 2012). This impossibility implies a conflict between being a *good mother* and being a *good patient*, often resulting in an unsolvable sense of guilt (Campbell-Enns and Woodgate 2013) and can lead to put high demands on oneself (Billhult and Segesten 2003). The conflict between the role of a patient and that of a mother is essentially of moral nature, a conflict between two different moral demands: on the one hand being strong and surviving, and on the other hand sustaining responsibility as a mother (Elmberger et al. 2008). Women diagnosed with breast cancer and undergoing the consequent treatments needed a chance to redefine their mothering by abandoning some ideas

⁵¹ The debate on the concepts and experience of *motherhood* and *mothering* is much more complex than how presented in this work. Feminist scholars have widely inquired the issue and many different (and sometimes opposite) analyses and interpretations have been proposed. For a brief reconstruction of approaches see: Snitow A. (1992), *Feminism and Motherhood: an American Reading*, *Feminist Review*, 40:32-51; Arendell T. (2000), *Conceiving and Investigating Motherhood: the Decade's Scholarship*, *Journal of Marriage and the Family*, 62, 1192-1207.

about ideal mothering and recreating others. Most importantly, managing the new life situation and coming to terms with limits on *good mothering* appeared to be the only way of maintaining acceptable levels of moral self-esteem.

The overarching theme in the analysis is that the aim of maternal activity during breast cancer is protecting children from distress (Helseth and Ulfasaet 2005). Mothers' ways of attending to the protection theme in everyday life included maintaining the normal routine at home and keeping positive while in the presence of children (Billhult and Segesten 2003). Therefore, the first perceived requirement in order to protect children seems to put them first (Asbury, Lalayannis and Walshe 2014) (Mackenzie 2014). This has been reported as particularly important while mastering treatments and side-effects – such as fatigue, chemotherapy and radiation therapy (see Chapter 2.3. *Available treatment for breast cancer*) – that required to minimize mothers' own needs and psychological distress in order not to worry children and to minimize disruptions to them (Elmberger et al. 2008) (Kim, Ko and Jun 2012).

The major theme of managing communication regarding the illness was present in several of the 18 studies. Indeed, mothers reported they struggle with the issue about how and what to tell their children. While some mothers decided to communicate their health condition to children for the sake of sharing the truth (Barnes et al. 2000) (Cho, Yoo and Hwang 2015), others decide to withhold this information. In both cases, mothers did what they thought was the best for their children. Information can be withheld from children for several reasons, for example to avoid questions and especially questions regarding cancer and death, but also because children are not expected to properly understand clinical information – which anyway may significantly change across different ages (Barnes et al. 2000). However, the communication theme partially overlaps with

the protection one in that communicating about the illness needed to be balanced between being truthful and preventing children psychological distress (Helseth and Ulfsaet 2005). While support from family members and social networks about parenting during cancer was somehow valuable, women reported the need for a professional specific help. Specifically, mothers reported the lack of qualified professional knowledge in answering questions regarding how to tell the children about breast cancer, treatments and side effects (Elmberger et al. 2008). Some researchers have proposed the establishment of dedicated family support services and developed a specific distress and parenting concerns measurement questionnaire in order to better address parental issues in cancer management (Muriel et. al. 2012) (Moore et al. 2015).

As seen in Chapter 3, the maternal practice of caring is articulated in three main demands: 1) to preserve the child's life, 2) to foster the child's growth, and 3) to do it according to the community's values. Concerning the latter, indeed, "motherhood" is conceived as a matter of conventions, values and norms that constitute a learned and natural role central to many women's self image according to a community shared ethical ideal of how a *good* mother should act. To maintain the ethical ideal, mothers must care for their children and thereby live in «internal truth and serenity» (Noddings 1984). Clearly, to care for another person assumes continuity in time, for caring is a developmental process, especially in the case of underage dependant children. Hence, a breast cancer diagnosis represents a great hazard to mothers, for it potentially prevents from up taking the maternal role and subsequent responsibilities (Fisher and O'Connor 2012). In the oncological context, potential death is seen as an abandonment of children, causing high distress among parents (Walsh, Manuel and Avis 2005). Indeed, in accordance with the concept of caring outlined above, mothers cannot imagine that a *good*

parent would abandon his or her dependent children and hence decision-making about current treatments is often driven by the need to be alive long-term for their children (Campbell-Enns and Woodgate 2013) and smaller treatments benefits are often considered worthwhile (Kirkman et al. 2014) (Mackenzie 2014).

Interestingly, two studies reported that women explicitly admitted that the process of decision-making regarding communication or treatment options, schedule and organization was strongly influenced by the maternal role (Yoshida et al. 2010) (Campbell-Enns and Woodgate 2013). Specifically, the rationale behind both decisions underlined the aim of maintaining the mother-child bond. As the disease progresses and treatment side effects raise, the persisting of listening activity and parental love maintain the perception of a worth living life (Elmberger et al. 2008) (Fisher and O'Connor 2012). The quality of life is a personal assessment, which is a measure of a patient's self image. The self-assessment reflects the multiple factors that define an individual's identity, including significant relationships such as being a *good parent* to one's children (Mazzotti et al. 2012) (Mackenzie 2014) (Moore et al. 2015).

5.3.3. Women's values in mammography screening SDM

The themes and concepts identified through the literature review provide two different kinds of knowledge suitable in the mammography screening context. First, the identification of moral patterns and concerns common among women facing breast cancer in their 40s represents a useful tool for physicians to engage in SDM with patients considering whether to uptake mammography. Indeed, while PtDAs help patients understanding scientific information regarding the intervention at stake and beginning a personal evaluation of possible benefits and harms, they cannot properly elicit individual patients' values nor guarantee their incorporation in DM (Fagerlin et al. 2012) (Gorini, Masiero and Pravettoni 2016).

In fact, many PtDAs equip users with a final report that summarizes received information and lists individual preferences in order to enhance patient-physician's encounter by providing a good starting point to discuss individual preferences. However, the generality of sections devoted to values clarification, which usually present rating and ranking scales or discrete choices tasks (Pignone et al. 2012), prevents physicians from a complete understanding of values underlying women's preferences and concerns (O'Connor, Légaré and Stacey 2003) (Parker, Rychetnik and Carter 2015).

In this respect, the four main themes identified through the literature review may serve as the conceptual background for a detailed interpretation of women's preventive preferences. Physicians could therefore take advantage of the proposed conceptualization of mothers' experience of breast cancer to better investigate patients' values underlying different evaluation of mammography screening benefits and harms. Thereby, physicians would be able to actually discuss preferences by addressing women's specific concerns and related values. For example, following the line of reasoning regarding the theme of "protecting children from distress", physicians could enhance women's awareness of the psychosocial outcomes of a *false positive* result and of *overdiagnosis*. Moreover, given the importance of the theme regarding "managing the communication of clinical information to children", women should be provided with some skills possibly useful in the case of need for recall and biopsy. The theme of "balancing the role of being a mother with being a patient" and following concerns could be discussed in relation to both a *true positive* result and *overdiagnosis*. All together, these proactive attentions to women's needs would represent the fulfilment of the fourth theme concerning the "need for help from health care providers" in breast

cancer contexts, from the clinical management of diagnosed conditions to the discussion and evaluation of treatment as well as preventive options.

The acknowledgement of the paramount moral importance not only of involving patients but also of incorporating their personal values and life plans in clinical and preventive DM requires physicians to engage in a kind of relationship that enables women eliciting and evaluating what they consider worthwhile and what means are more suitable to achieve it. Therefore, in mammography screening context, health care providers should seriously take into consideration gendered moral values – to which care ethics provides a structured theorization – and familial social roles endorsed by women, especially motherhood. Indeed, as shown throughout the thesis, the role of mother entails specific moral demands that can be generally identified in meeting the needs of children. Certainly different mothers interpret these moral requirements in different ways and therefore it is not possible to adopt a “one size fits all” approach in mammography SDM. However, the proposed literature review provides a sketch of four general themes commonly experienced by mothers in BC management and therefore provides a conceptual map to establish a fruitful dialogue aiming at eliciting and incorporating women’s values.

However, beyond the identification of moral themes common to young women facing a BC diagnosis and given the absence of pre-existing knowledge on the issue, it would be interesting to carry out an empirical research on the influence of such concerns in preventive DM. Indeed, there are some differences between the experience of mothering during breast cancer and the one of managing one’s health status through preventive medicine. Specifically, the study should address two main questions:

- 1) Which values do women aged 40 to 49 take into account when deciding whether to uptake mammography screening?
- 2) How do *motherhood* and *mothering* inform breast cancer prevention decision-making process?

From a theoretical viewpoint, empirical bioethics frames the research project (Frith 2012): indeed, the integration of moral theory and empirical data helps in contributing to reach a better understanding of specific practices (Hoffmaster and Hooker 2009). In particular, the study category is the one of *lay of the land* (Kon 2009) for it seeks to define current women's and mothers' moral thinking in the context of preventive DM. Such an approach also fits within the classical research approach to the subjects of *mothering* and *motherhood*, which traditionally combines theorizing of the concepts and empirical study of experience (Arendell 2000).

The suggested empirical study should employ a qualitative methodology and the design should be based on the main tenets of grounded theory (Charmaz 2006) for the intention is generating a conceptualization of some features of the DM process by means of understanding people experience, intention and motivation. The study would be guided by the sensitizing concepts (Bowen 2006) of the ethics of care and of *motherhood/mothering*, which derived from the undertaken literature review and in general are proven to be relevant to the study of gender issues (LaRossa 2005). Hence, these sensitizing concepts form the conceptual framework of the study and represent the starting points for building the data analysis (Bowen 2006).

A possible design of the study would be to conduct in-depth semi-structured interviews to a small and homogeneous purposive sample of women aged 40 to 49 years (20 women). In order to avoid biases, the recruitment strategy

should include women who never underwent breast cancer screening divided in those declaring intention and those declaring no intention to uptake a screening program. The study should primarily focus on *values* – and especially *moral values* – informing and supporting cancer preventive intentions. Given the theoretical relevance of the themes identified throughout the literature review, the inquiry will specifically take into account women's close relationships in order to investigate how they are articulated in terms of moral values and moral reasons and which role they play in the DM process. Specifically, the greatest interest shall be put on moral values' role in the explanation, motivation, and justification of preventive choices, as responses to women's and others' needs for care.

The main theoretical work throughout the empirical study would be the development of a proper and useful coding system, which - by nature - has to be carried out during the analysis of the data (Charmaz 2006). The detailed study design (sampling, recruitment strategy, interviews, and development of a coding system) should serve the study purpose within the grounded theory framework. Moreover, such kind of empirical study could also expand toward the enquiry of older women's experience of mammography screening in order to investigate the role of different familial responsibilities in prevention DM.

5.4. Summary

The Chapter presented SDM as an effective way of respecting patients' autonomy by engaging in a partnership that enables women and physicians to share information, values and preferences in order to reach a consensus on the clinical course of action to be implemented. PtDAs hence represent helpful tools in enhancing women's understanding of complex statistical information, as well as in reasoning on their preferences regarding options. However, it has been shown that in order to truly incorporate individual values in the final decision – or to

effectively personalised choices – the encounter between patients and physicians still remains the core of SDM. Therefore, the role of physicians in SDM regarding whether a woman aged 40 to 49 should start routine screening mammography requires different levels and kinds of knowledge. First and foremost, physicians should acknowledge the central role of individual patients in choosing the right option for them, meaning endorsing the ethical perspective of respect for autonomy in its broader sense. Secondly, physicians should be able to build a *partnership* with women as a requisite of SDM.

In this respect, some specific attitudes and relational skills are necessary to be implemented. On the basis of the *partnership*, hence, physicians would have the opportunity to discuss with individual women different breast cancer preventive options, explicitly recognizing the reasonableness of choosing one alternative over another. In this phase of SDM, PtDAs constitute a very helpful tool for providing women with high quality, up-to-date and easily understandable information and statistical data regarding mammography. Moreover, through PtDAs women might explore and elicit their preferences by completing specifically designed tasks, which are often listed in the final PtDA report. The provision of personalised reports, in turn, enables physicians in engaging in a deeper and more detailed discussion by taking into account as the starting point the PtDA information and individual preferences. However, further knowledge might be required in order to effectively elicit and encourage women to share personal values, lifestyles and goals.

In attempting to understand how women make decision regarding breast cancer screening and given the lack of studies on the issues, two major common characteristics possibly implying some shared values were identified: healthy women in their 40s; of whom approximately 75% are mothers. Hence, a systematic

review of the literature concerning the experience of parenting during breast cancer was carried out and a critical analysis of contents was performed in light of the ethics of care. The four major themes were identified as common patterns in experiencing breast cancer and informing clinical decision-making might provide physicians with some specific knowledge regarding possible values and preferences to discuss with women.

The ethics of care, as presented in Chapter 3, therefore represents a suitable ethical framework for mammography screening – especially for women aged 40 to 49. Indeed, care ethics provides a strong normative guidance that justifies and requires the endorsement of SDM, as a means of empowering and respecting patients' autonomy in a broader sense. Secondly, care ethics also provides a fruitful interpretative framework for investigating and exploring women's moral experiences and values. In particular, the fundamental role of relationships in moral life comes to shed light on and hopefully enhance patient-physician relationship itself. Finally, the Chapter closes by briefly presenting a proposal for an empirical study to investigate the role of mothering and in general of significant relationships in light of the ethics of care and guided by the four main themes identified through the proposed literature review.

CONCLUSIONS

This dissertation is a bioethical investigation of breast cancer screening programs and women's decision-making regarding whether to undertake routine mammography screening. In particular, the project focused on the justification of mammography screening programs as means to promote the public good, and on the ethics of patient-physician relationship and the clinical decision-making process. In this respect, the thesis addressed and tried to answer to two different levels of ethical questions. The first kind of questions regards the ethical justification of introducing and implementing population-based mammography screening programs and therefore pertains to the field of public health ethics. The second level of questions, instead, regards which ethical principles and what kind of patient-physician relationship should be endorsed in the context of mammography screening decision-making. The many complexities of breast cancer screening programs range from public health considerations on what good is to be pursued, to individual decision-making under uncertainty, from the establishment of reliable scientific trials, to the acknowledgment of individual women preferences, values and personal goals. The specifically interdisciplinary nature of bioethics, which crosses the boundaries of philosophy, ethics, medicine, biomedical sciences, and public policy, represents a promising approach to the ethical analysis of breast cancer population-based screenings.

Breast cancer is the most common cancer among women and accounts for approximately half a million deaths per year (WHO 2012). However, improvements in treatments at all stages of the disease and *early detection* strategies have changed

the impact of breast cancer significantly for the better. The wide implementation of population-based mammography screening programs has been proven to represent an effective means for *early detection* of breast cancer, which in turn results in better prognosis and allows for a great range of treatment options. However, if on the one hand, mammography screening constitutes a promising and effective way of reducing breast cancer *mortality* and of allowing for less invasive and more effective treatment for early-detected cancers, on the other hand, screening inherently entails possible harmful outcomes for some individuals. Indeed, given the threshold between *sensitivity* and *specificity* of the screening tool, some individuals in the screened population will necessarily receive a *false positive* or a *false negative* result from the test. While the *false positive* results are ruled-out after additional diagnostic tests, *false negative* results could possibly lead to development of the condition between screening intervals. Moreover, another possible harm of screening program is *overdiagnosis*, which has the potential of resulting in *overtreatment* and consequently in a great harm to the individual. Therefore, while prevention and early detection are promising and effective approaches to reduce breast cancer fatalities, still the burden to individual participating screening programs can be significantly high. What are hence the ethical reasons for introducing a screening program? Is there any possibility of solving the intrinsic tension between collective good and individual harm? What has to be considered a reliable source of evidence on which to base screening programs? How should the target population be identified? Is there any room for individual autonomy in public health intervention?

Mammography screening has been extensively studied through RCTs and has often been highly debated especially with regard to the balance between benefits and possible harms. As a matter of fact, recent studies have shown that benefits might be

lower than originally estimated, while the magnitude of harms might be higher, especially for women aged 40 to 49. Indeed, the latest evidence-based recommendations have acknowledged that the assessment of mammography screening net benefit for this age group cannot be objectively determined. On the contrary, such assessment depends on individual values and preferences that each woman places in determining what constitutes a worthwhile benefit and what constitutes a great harm. Most of the Western countries establishing population-based screening programs have accepted this line of reasoning and therefore identify women younger than 50 years as *eligible* for routine mammography screening. In this respect, the second kind of ethical issues and questions arise, mainly related to the patient-physician relationship. What are physicians' duties – if any? How should physicians strive to communicate complex probabilistic information to women? Do they have any moral obligation in empowering women? What are the values women refer to when deciding whether to undergo mammography screening? How can physicians incorporate women's value in the decision-making process? Is there any duty to help women to explore their preferences and values in order to reach a consistent decision?

In order to effectively analyse how different methodologies face and conceptualize the moral questions arising from population-based mammography screenings, the thesis provides an historical and analytic description of the most commonly methodologies adopted in bioethics, which can be grouped into principle-based and non-principle-based methods. Among principle-based methods, the dissertation provides *consequentialism*, *deontology* and *principlism*. The three methodologies adopt general moral principles from which to derive moral rules as concrete guides for action, and propose rational, abstract and general accounts of

morality systematized in principle-based theories. Differently, *virtue ethics* and the *ethics of care* draw attention to moral agent's character, disposition, capacity of moral judgment, and emotions. Beside this fundamental feature, the major distinction between the two approaches stands in the focus on disposition and character traits of the *virtue ethics*, while the *ethics of care* emphasises the importance of relations, dependency and needs. In this respect, *care ethics* involves a further shift in moral perspective by focusing on how to respond to the needs of others.

Taking advantage of the ethical concepts of the methodologies, the thesis hence analyses public health ethics arguments to justify the introduction and implementation of population-based mammography screening programs. Specifically, while *consequentialism* is often invoked to provide moral justification and foundation of mammographic screenings, it is usually constrained by *deontological* and *principlistic* considerations often unveiling the intrinsic tension between improving and promoting the public good and protecting individual rights, goals and preferences.

Therefore, the ethical analysis includes consideration of traditional ethical principles – such as *autonomy*, *beneficence*, *non-maleficence* and *justice* – that contribute to the constraining and defining of the greatest good in mammography screening programs. Rules derived from the *principle of beneficence* require that screening should benefit the participants by means of allowing earlier and more effective treatment for the screened-for disease, and thereby improving physiological wellbeing; rules derived from the *principle of non-maleficence* require the avoidance of any kind of harm – from inconveniences of getting tested to *overdiagnosis*. In this respect, further specifications of the *principle of autonomy* are presented, specifically regarding the right to autonomously choose whether to undertake the screening.

Finally, the *principle of justice* provides concrete rules regarding the equal opportunity of access to mammography for all women for whom scientific evidence shows a benefit for undergoing routine tests.

From the individual perspective, the dissertation focuses especially on women aged 40 to 49, who are considered *eligible* to participate mammography routine screening. The decision-making process takes place within the concrete relationship between women and their physicians, especially general practitioners and gynaecologists. The ethical analysis of mammography from an individual perspective specifically takes into account the peculiarity of the kind of relationship women and physicians might engage in and the subsequent different decision-making processes, from the *paternalistic model* to the *informed model*, and the *shared decision-making model*. First, the question regarding the moral legitimacy of advising for or advising against mammography screening is evaluated from a *paternalistic* viewpoint. In this respect, the *principle of beneficence* and the *principle of non-maleficence* play the central role in moral reasoning. The two main arguments against the adoption of a paternalistic approach revolve around the failure in acknowledging patients' agency and in providing an objective guide to action.

Therefore, the thesis introduces the *principle of autonomy* as the core ethical element to the patient-physician relationship implying to general levels of duties for physicians: 1) the negative duty of non-interference with patients' decisions and choices; and 2) the positive duty to provide all the information needed to enable patients making autonomous and informed decisions. In the context of mammography, hence the *informed decision-making* model acknowledges that the assessment between benefits and harms of screening depends on individual preferences and values regarding what goal to achieve. However, while adopting the

informed decision-making model implies the recognition of the fundamental autonomy of women, nevertheless the complexity of information to be provided, as well as some psychological and emotional characteristic features of the oncological field might prevent women reaching a truly *informed decision* regarding whether to participate mammography screening.

The dissertation hence proposes the *shared decision-making* model of patient-physician relationship as an effective way of respecting patients' autonomy by engaging in a *partnership* that enables women and physicians to share information, values and preferences. Therefore, first and foremost physicians should endorse the ethical perspective of respect for autonomy in its broader sense; secondly, physicians should encourage women to share information and values. In doing so, patient decision aids (PtDAs) represent a useful tool for women to explore and elicit their preferences. The provision of personalised PtDAs reports, in turn, enables physicians in engaging in a deeper and more detailed discussion. However, further knowledge might be required in order to effectively elicit and encourage women to understand and share personal values, lifestyles and goals. In this sense, the ethics of care constitutes a suitable normative ethical framework for it requires a wider conception of autonomy, which takes into account not only the rational moral capacity of agents, but also the fundamental importance of relationships, emotions and needs in human moral experience. Although the thesis mainly deals with women's aged 40 to 49 DM regarding whether to uptake routine mammography screening, the adoption of the ethics of care normative framework appears to be a promising ethical guidance also for older women. Indeed, while the responsibility of younger women is commonly towards their children, care ethics, by emphasizing the central moral role of significant relationships, sheds some light on the importance of taking into account

psychosocial factors of any patient during SDM. Therefore, the proposed model could be successfully expanded to other age groups of women considering mammography screening, and especially those older than 70/75 who, according to the most up-to-date guidelines are *eligible* to screening and therefore face a situation similar to that of women younger than 50. However, given the different familial situation and consequent peculiar responsibilities towards family members, the findings of the present study cannot be *tout court* translated in the analysis of older women's mammography screening DM. A targeted study in light of care ethics is therefore suggested in order to investigate the specific circumstances and needs of this age group.

In attempting to understand how women make decision regarding breast cancer screening and given the lack of studies on the issues, the dissertation presents a systematic and critical interpretative review of the literature concerning the experience of mothering during breast cancer. From the critical analysis of contents in light of the ethics of care the review identifies four major themes as common patterns in experiencing breast cancer and informing clinical decision-making, which might provide useful insights and pieces of knowledge to physicians in addressing and discussing breast cancer preventive options. Therefore, care ethics also provides a fruitful interpretative framework for investigating and exploring women's moral experiences and values. In particular, the fundamental role of relationships in moral life comes to shed light on and hopefully enhance patient-physician relationship itself, as well as SDM. On the basis of the findings of the literature review, the thesis closes by presenting a proposal for a qualitative empirical research on the experience of breast cancer prevention DM in women aged 40 to 49. Further research is needed in the field of preventive medicine, which, as demonstrated throughout the thesis,

challenges the endorsement of traditional clinical ethics' approaches. The thesis suggests the adoption of care ethics both as a normative moral theory and a fruitful interpretative framework of individual patients' needs.

BIBLIOGRAPHY

- Ackerson K. and Preston S.D. (2009), *A Decision Theory Perspective on Why Women Do Or Do Not Decide to Have Cancer Screening: Systematic Review*, Journal of Advanced Nursing, 65 (6):1130-1140.
- Alexander F.E. et al. (1999), *14 years of Follow-Up From Edinburgh Randomized Trial of Breast Cancer Screening*, Lancet, 353:1903-1908.
- American Cancer Society (2015), *Global Cancer Facts & Figures - 3rd Edition*, American Cancer Society, Atlanta.
- Anscombe G.E.M. (1958), *Modern Moral Philosophy*, Philosophy, 33 (124):1-19.
- Anderman A. et al. (2008), *Revisiting Wilson and Jungner in the Genomic Age: A Review of Screening Criteria Over the Past 40 Years*, Bulletin of the World Health Organization, 84 (4): 317-319.
- Arendell T. (2000), *Conceiving and Investigating Motherhood: the Decade's Scholarship*, Journal of Marriage and the Family, 62:1192-1207.
- Arés I., Lebel S. and Bielajew C. (2014), *The Impact of Motherhood on Perceived Stress, Illness Intrusiveness and Fear of Cancer Recurrence in Young Breast Cancer Survivors Over Time*, Psychology & Health, doi:10.1080/08870446.2014.881998.
- Armstrong K. et al. (2007), *Screening Mammography in Women 40 to 49 Years of Age: A Systematic Review for the American College of Physicians*, Annals of Internal Medicine, 146:516-526.

- Asbury N., Lalayiannis L. and Walshe A. (2014), *How Do I Tell the Children? Women's Experiences of Sharing Information About Breast Cancer Diagnosis and Treatment*, *European Journal of Oncology Nursing*, 18:564-570.
- Autier P. et al. (2010), *Disparities in Breast Cancer Mortality Trends Between 30 European Countries: Retrospective Trend Analysis of WHO Mortality Database*, *British Medical Journal*, 341:c3620.
- Avis N.E., Crawford S. and Manuel J. (2004), *Psychosocial Problems Among Younger Women with Breast Cancer*, *Psychooncology*, 13 (5):295-308.
- Baker L.H. (1982), *Breast Cancer Detection Demonstration Project: Five-Year Summary Report*, *Cancer*, 32:194-225.
- Barilan Y.M. and Brusa M. (2013), *Deliberation at the Hub of Medical Education: Beyond Virtue Ethics and Codes of Practice*, *Medicine, Health Care, and Philosophy*, 16 (1):3-12.
- Barnato A.E. et al. (2007), *Communication and Decision Making in Cancer Care: Setting Research Priorities for decision support/patients' decision aids*, *Medical Decision Making*, 27 (5):626-634.
- Barnes J. et al. (2000), *Qualitative Interview Study of Communication Between Parents and Children About Maternal Breast Cancer*, *British Medical Journal*, 321:479-482.
- Barratt A. et al. (2004), *Use of Decision Aids to Support Informed Choices About Screening*, *British Medical Journal*, 329 (7464):507-10.

- Barratt A. et al. (2005), *Model of Outcomes of Screening Mammography: Information to Support Informed Choices*, British Medical Journal, 330 (7497):936; doi: 10.1136/bmj.38398.469479.8F.
- Barry M.J. and Edgman-Levitan S. (2012), *Shared Decision Making—Pinnacle of Patient-Centered Care*, 366 (9):780-781.
- Beauchamp T.L. and Childress J.F. (2013), *Principles of Biomedical Ethics*, 7th Edition, Oxford University Press, New York.
- Beckmann K.R. et al. (2015), *A Novel Case-Control Design to Estimate the Extent of Overdiagnosis of Breast Cancer Due to Organised Population-Based Mammography Screening*, Int. J. Cancer, 136:1411-1421.
- Begg C.B. (2002), *The Mammography Controversy*, The Oncologist, 7:174-176.
- Berkowitz Z. et al. (2008), *Beliefs, Risk Perception, and Gaps in Knowledge as Barriers to Colorectal Cancer Screening in Older Adults*, Journal of the American Geriatrics Society, 56 (2):307-314.
- Bettany-Saltikov J. (2012), *How to Do a Systematic Literature Review in Nursing: A Step-By-Step Guide*, Maidenhead: McGraw-Hill/Open University Press.
- Billhult A. and Segesten K. (2003), *Strength of Motherhood: Nonrecurrent Breast Cancer As Experienced By Mothers With Dependent Children*, Scand J Caring Sci, 17:122-128.
- Biesecker B.B, Schwartz M.D. and Marteau T.M. (2013), *Enhancing Informed Choice to Undergo Health Screening: a Systematic Review*, American Journal of Health Behaviour, 37 (3):351-359.

- Bjurstam N. et al. (1997), *The Gothenburg Breast Screening Trial: First Results on Mortality, Incidence, and Mode of Detection for Women Ages 39-49 Years at Randomization*, *Cancer*, 80:2091-2099.
- Bjurstam N. et al. (2003), *The Gothenburg Breast Screening Trial*, *Cancer*, 97:2387-2396.
- Bowen G.A. (2006), *Grounded Theory and Sensitizing Concepts*, *International Journal of Qualitative Methods*, 5 (3):12-23.
- Bower J.E. et al. (2006), *Fatigue in Long-Term Breast Carcinoma Survivors: a Longitudinal Investigation*, *Cancer*, 106 (4):751-758.
- Bradley P. and Burls A. eds. (2000), *Ethics in Public and Community Health*, Routledge, London.
- Bradley P. (2000), *Application of Ethical Theory to Rationing in Health Care in the UK: A Move to More Explicit Principles?*. Chap. 1 in *Ethics in Public and Community Health*, edited by Bradley P. and Burls A., Routledge, London.
- Breitsameter C. (2010), *Medical Decision-Making and Communication of Risks: An Ethical Perspective*, *J Med Ethics*, 36:349-352.
- Bretthauer M. and Kalager M. (2013), *Principles, Effectiveness and Caveats in Screening for Cancer*, *The British Journal of Surgery*, 100 (1):55-65.
- Briss P. et al. (2004), *Promoting Informed Decisions about Cancer Screening in Communities and Healthcare Systems*, *American Journal of Preventive Medicine*, 26 (1):67-80.

- Brodersen J., Schwartz L.M. and Woloshin S. (2014), *Overdiagnosis: How Cancer Screening Can Turn Indolent Pathology into Illness*, APMIS – Acta Pathologica, Microbiologica, et Immunologica Scandinavica, 122 (8):683-689.
- Bubeck D. (1995), *Care, Gender, and Justice*, Oxford University Press, Oxford.
- Buchholz T.A. (2009), *Radiation Therapy for Early-Stage Breast Cancer After Breast-Conserving Surgery*, New England Journal of Medicine, 360 (1):63-70.
- Bulliard J-C. and Chiolero A. (2015), *Screening and Overdiagnosis: Public Health Implications*, Public Health Reviews, 36:8.
- Calle E.E. et al. (1993), *Demographic Predictors of Mammography and Pap Smear Screening in US Women*, American Journal of Public Health, 83 (1):53-60.
- Campbell-Enns H.J. and Woodgate R.L. (2013), *Decision-making for Mothers with Cancer: Maintaining the Mother-child Bond*, European Journal of Oncology Nursing, 17:261-268.
- Canadian Task Force on Preventive Health Care (2011), *Recommendations on Screening for Breast Cancer in Average-Risk Women Aged 40-74 Years*, Canadian Medical Association Journal, 183 (17):1991-2001.
- Carter J.J., Coletti R.J. and Harris R.P. (2015), *Quantifying and Monitoring Overdiagnosis in Cancer Screening: A Systematic Review of Methods*, BMJ Open, 350:g7773.
- Carter S.M., et al. (2016), *A Definition and Ethical Evaluation of Overdiagnosis*, Journal of Medical Ethics Published Online First on July 8 2016, 0:1-10.

- Chapman S., Barratt A., and Stockler M. (2010), *Let Sleeping Dogs Lie? What Men Should Know Before Getting Tested for Prostate Cancer*, Sydney University Press, Sydney.
- Charles C., Gafni A. and Whelan T. (1997), *Shared Decision-Making in the Medical Encounter: What Does It Means? (Or It Takes at Least Two To Tango)*, Soc Sci Med, 5:681-692.
- Charmaz K. (2006), *Constructing Grounded Theory. A Practical Guide Through Qualitative Analysis*, SAGE Publication, London.
- Childress J.F. et al. (2002), *Public Health Ethics. Mapping the Terrain*, Journal of Law, Medicine and Ethics, 30 (2):170-178.
- Childress J.F. (2009), *A Principle-Based Approach*, Chapter 7 (pp. 67-76) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.
- Chiolero A. et al. (2015), *How to Prevent Overdiagnosis*, Swiss Medical Weekly, 145:w14060.
- Cho O., Yoo Y. and Hwang K . (2015), *Comparison of Parent-Child Communication Patterns and Parental Role Satisfaction Among Mothers With and Without Breast Cancer*, Applied Nursing Research, 28:263-168.
- Clouser K.D. and Gert B. (1990), *A Critique of Principlism*, Journal of Medicine and Philosophy, 15:219-236.
- Connell S., Patterson C. and Newman B. (2006), *Issues and Concerns of Young Women With Breast Cancer*, Support Care Cancer, 14:419-426.
- Copp D. (2007), *The Oxford Handbook of Ethical Theory*, Oxford University Press.

- Coughlin S.S. (2008), *How Many Principles for Public Health Ethics?*, Open Public Health Journal, 1: 8–16. doi:10.2174/1874944500801010008.
- Croswell J.M., Ransohoff D.F., and Kramer B.S. (2010), *Principles of Cancer Screening: Lessons from History and Study Design Issues*, Seminars in Oncology 37:202–215.
- Dancy J. (2013), *Moral Particularism*, The Stanford Encyclopedia of Philosophy, Fall 2013 Edition: <https://plato.stanford.edu/archives/fall2013/entries/moral-particularism/> (last accessed 10.13.2017).
- Dawson A. (2011), *Resetting the Parameters: Public Health as the Foundation for public Health Ethics (Section 1 – Chapter 1, 1-19)*, in Dawson A. (ed) *Public Health Ethics*, Cambridge University Press, New York.
- Delatycki M.B. (2012), *The Ethics of Screening for Disease*, Pathology, 44 (2):63-68.
- Diprose R (2000), *What is (Feminist) Philosophy?*, Hypatia, 15 (2):115-132.
- Djulbegovic M. et al. (2010), *Screening for Prostate Cancer: Systematic Review and Meta-Analysis of Randomised Controlled Trials*, British Medical Journal, 341:c4543. doi: <https://doi.org/10.1136/bmj.c4543>
- Domenighetti G. et al. (2003), *Women's Perception of The Benefits of Mammography Screening: Population-Based Survey in Four Countries*, International Journal of Epidemiology, 32:816-821.
- Dolan J.G. and Iadarola S. (2008), *Risk Communication Formats for Low Probability Events: an Exploratory Study of Patients Preferences*, BMC Medical Information and Decision Making, 8:14, doi:10.1186/1472-6947-8-14.

- Donchin A. (2001), *Understanding Autonomy Relationally: Toward a Reconfiguration of Bioethical Principle*, Journal of Medicine and Philosophy, 26 (4):365-386.
- Duric V. and Stockler M. (2001), *Patients' Preferences for Adjuvant Chemotherapy in Early Breast Cancer: a Review of What Makes it Worthwhile*, The Lancet Oncology, 2:691-697.
- Eden K.B. et al. (2015), *Mammography Decision Aid Reduces Decisional Conflict For Women in Their Forties Considering Screening*, J Women's Health, 24 (12):1013-1020.
- Egan R.L. (1960), *Experience with Mammography in a Tumor Institution: Evaluation of 1,000 Studies*, Radiology, 75:895.
- Elkin E.B. et al. (2017), *Facilitating Informed Decisions About Breast Cancer Screening: Development and Evaluation of a Web-Based Decision Aid for Women in Their 40s*, BMC Medical Informatics and Decision Making, <https://doi.org/10.1186/s12911-017-0423-7>
- Elmberger E., Bolund C. and Lutzén K. (2005), *Experience of Dealing with Moral Responsibility as a Mother with Cancer*, Nursing Ethics, 12 (3):253-262.
- Elmberger E. et al. (2008), *Being a Mother with Cancer. Achieving a Sense of Balance in the Transition Process*, Cancer Nursing, 31 (1):58-66.
- Elmore J.G. and Etzioni R. (2015), *Effect of Screening Mammography on Cancer Incidence and Mortality*, JAMA Internal Medicine, Published Online July 6.
- Elwyn G. et al. (2012), *Shared Decision Making: A Model fro Clinical Practice*, J Gen Intern Med, 27 (10):1361-1367.

- Emanuel E.J. and Emanuel L.L. (1992), *Four Models of the Physician-Patient Relationship*, JAMA Journal of the American Medical Association, 267 (16):2221-2230.
- Engelhardt H.T. (1996), *The Foundations of Bioethics*, 2nd edition Oxford University Press, New York.
- Fagerlin A., Zikmund-Fisher B.J. and Ubel P.A. (2011), *Helping Patients Decide: Ten Steps to Better Risk Communication*, J Natl Cancer Inst, 103:1436-1443.
- Feary V. (2003), *Virtue-Based Feminist Philosophical Counselling*, Practical Philosophy, 6 (1):7-26.
- Feig S.A. (2014), *Screening Mammography Benefit Controversies. Sorting the Evidence*, Radiologic Clinic of North America, 52:455-480.
- Ferretti G. (2016), *Overdiagnosis*, in “Ethical Counselling and Medical Decision-Making in the Era of Personalised Medicine” (Boniolo G. and Sanchini V. editors), Springer, 105-113.
- Ferretti G., Linkeviciute A. and Boniolo G. (2017), *Comprehending and Communicating Statistics in Breast Cancer Screening. Ethical Implications and Potential Solutions*, in Gadebush Bondio M., Spöring F. and Gordon John-Stewart (eds.), *Medical Ethics, Prediction, and Prognosis. Interdisciplinary Perspectives*, Routledge, London.
- Fielding H. et al. (eds) (2007), *The Other. Feminist Reflections in Ethics*, Palgrave MacMillan, New York.
- Fisher C. and O'Connor M. (2012), *“Motherhood” in the Context of Living with Breast Cancer*, Cancer Nursing, 35 (2):157-163.

Foot P. (1977), *Euthanasia*, *Philosophy and Public Affairs*, 6:85-122.

Forbes L.J. and Ramirez A.J. (2014), *Expert Group on Information about Breast Screening. Offering Informed Choice about Breast Screening*, *J Med Screen*, 21 (4):194-200.

Frisell J. et al. (1997), *Randomized Study of Mammography Screening: Preliminary Report on Mortality in the Stockholm Trial*, *Breast Cancer Res Treat*, 18:49-56.

Frith L. (2012), *Symbiotic Empirical Ethics: a Practical Methodology*, *Bioethics*, 26 (4):198-206.

Ganz P.A. et al. (2004), *Quality of Life at the End of Primary Treatment for Breast Cancer: First Results From the Moving Beyond Cancer Randomized Trials*, *J Natl Cancer Inst*, 96 (5):376-387.

Gardner K.E. (2006), *Early Detection: Women, Cancer, and Awareness Campaigns in the Twentieth-Century United States*, *Library of Congress Cataloging-in-Publication Data*.

Gardiner P. (2003), *A Virtue Ethics Approach to Moral Dilemmas in Medicine*, *Journal of Medical Ethics*, 29:297-302.

Gershon-Cohen et al. (1961), *Detection of Breast Cancer by Periodic X-Ray Examinations*, *JAMA Journal of the American Medical Association*, 176:1114-1116.

Gigerenzer G. et al. (2008), *Helping Doctors and Patients Make Sense of Health Statistics*, *Psychological Science in the Public Interest*, 8 (2):53-69.

Gigerenzer G. (2014), *Breast Cancer Screening Pamphlets Mislead Women*, *British Medical Journal*, 348:g2636.

- Gilligan C. (1982), *In a Different Voice. Psychological Theory and Women's Development*, Harvard University Press, Cambridge.
- Ginsburg O. et al. (2017), *The Global Burden of Women's Cancers: a Grand Challenge in Global Health*, *The Lancet*, 389:847-860.
- Glaziou P. and Houssami N. (2011), *The Evidence Base for Breast Cancer Screening*, *Preventive Medicine*, 53:100-102.
- Goel V. (2001), *Appraising Organised Screening Programmes for Testing for Genetic Susceptibility to Cancer*, *British Medical Journal*, 322 (7295):1174-1178.
- Gold R.H. (1992), *The Evolution of Mammography*, *Radiol Clin North Am*, 30:1-19.
- Goldacre B. (2012), *Bad Pharma. How Drug Companies Mislead Doctors and Harm Patients*, Fourth Estate, London.
- Gorini A. and Pravettoni G. (2011), *An Overview on Cognitive Aspects Implicated in Medical Decisions*, *European Journal of Internal Medicine*, 22:547-553.
- Gorini A., Masiero M. and Pravettoni G. (2016), *Patients Decision Aids for Prevention and Treatment of Cancer Disease: Are They Really Personalised Tools?*, *European Journal of Cancer Care*, 25:936-960.
- Gøtzsche P.C. and Jørgensen K.J. (2013), *Screening for Breast Cancer with Mammography (Review)*, *The Cochrane Library*, 6.
- Grant M.J. and Booth A. (2009), *A Typology of Reviews: An Analysis of 14 Review Types and Associated Methodologies*, *Health Info Libr J*, 26 (2):91-108.
- Gummersbach E. et al. (2010), *Are Women Getting Relevant Information About Mammography Screening for an Informed Consent: A Critical Appraisal of*

Information Brochures Used for Screening Invitation in Germany, Italy, Spain and France, Eur J Public Health, 20 (4):409-414.

Gunsoy N.B., Garcia-Closas M. and Moss S.M. (2012), *Modelling the Overdiagnosis of Breast Cancer Due to Mammography Screening in Women Aged 40 to 49 in the United Kingdom*, Breast Cancer Research, 14:R152.

Hanahan D. and Weinberg R.A. (2000), *The Hallmarks of Cancer*, Cell, 100 (1):57-70.

Hanahan D. and Weinberg R.A. (2011), *Hallmarks of Cancer: The Next Generation*, Cell, 144 (5):646-674.

Hare R.M. (2009), *A Utilitarian Approach*, Chapter 9 (pp. 85-90) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.

Hartl K. et al. (2003), *Impact of Medical and Demographic Factors on Long-Term Quality of Life and Body Image of Breast Cancer Patients*, Ann Oncol, 14 (7):1064-1071.

Held V. (2002), *Moral Subjects: The Natural and the Normative*, Proceedings and Addresses of the American Philosophical Association, 76 (2):7-24.

Held V. (2006), *The Ethics of Care: Personal, Political, and Global*, Oxford University Press, Oxford.

Helseth S. and Ulfset N. (2005), *Parenting Experience During Cancer*, Journal of Advanced Nursing, 52 (1):38-46.

Hersch J. et al. (2011), *How Do We Achieve Informed Choice for Women Considering Breast Cancer Screening?*, Preventive Medicine, 53:144-146.

- Hersch, J. et al. (2013), *Women's views on overdiagnosis in breast cancer screening: a qualitative study*, BMJ (Clinical Research Ed.), 346(jan23_1), f158. doi:10.1136/bmj.f158.
- Hersch J. et al. (2015), *Use of a Decision Aid Including Information on Overdetection to Support Informed Choice about Breast Cancer Screening: A Randomized Controlled Trial*, The Lancet, 385 (9978):1642-1652.
- Hoffman R.M. et al. (2010), *Decision-Making Processes for Breast, Colorectal, and Prostate Cancer Screening: The DECISIONS Survey*, Medical Decision Making, 30:53-64.
- Hoffman R.M. et al. (2014), *Lack of Shared Decision Making in Cancer Screening Discussion: Results from a National Survey*, Am J Prev Med, 47 (3):251-259.
- Hoffmaster B. and Hooker K. (2009), *How Experience Confronts Ethics*, Bioethics, 23 (4):214-225.
- Hofman B. (2014), *Diagnosing Overdiagnosis: Conceptual Challenges and Suggested Solutions*, Eur J Epidemiol Online First June 1.
- Holland S. (2007), *Screening (Chapter 8, 160-187)*, in Holland S., *Public Health Ethics*, Polity Press, Cambridge.
- Holland S. (2011), *The Virtue Ethics Approach to Bioethics*, Bioethics, 24 (4):192-201.
- Hooker B. (2002), *Ideal Code, Real World: A Rule-Consequentialist Theory of Morality*, Oxford University Press, Oxford.
- Hunink M.G.M. et al. (2001), *Decision Making in Health and Medicine: Integrating Evidence and Values*, Cambridge University Press, Cambridge.

Hursthouse R. (1991), *Virtue Theory and Abortion*, Philosophy and Public Affairs, 20 (3):223-246.

IARC International Agency for Research on Cancer (2016), *IARC Handbooks of Cancer Prevention Vol. 15: Breast Cancer*, IARC, Lyon.

IARC International Agency for Research on Cancer (2017), *Cancer Screening in the European Union. Report on the Implementation of the Council Recommendation on Cancer Screening*, European Commission, Lyon.

Ilic D. et al. (2013), *Screening for Prostate Cancer*, The Cochrane Library (Review).

Ingleby H. and Gershon-Cohen J. (1960), *Comparative Anatomy, Pathology, and Roentgenology of the Breast*, University of Pennsylvania Press, Philadelphia.

IPDAS (2005), *International Patient Decision Aids Standards (IPDAS) Collaboration. Criteria for Judging the Quality of Patient Decision Aids*. Available at: www.ipdas.ohri.ca (last accessed on 10.13.2017).

Ivlev I. et al. (2017), *Use of Patient Decision Aids Increased Younger Women's Reluctance to Begin Screening Mammography: A Systematic Review and Meta-Analysis*, Journal of General Internal Medicine, 32 (7):803-812.

Janz N.K. et al. (2007), *Symptoms Experience and Quality of Life of Women Following Breast Cancer Treatment*, J Womens Health, 16 (9):1348-1361.

Jatoi I. (2011), *The Impact of Advances in Treatments on the Efficacy of Mammography Screening*, Preventive Medicine, 53:103-104.

Johns L.E. and Moss S.M. (2010), *Randomized Controlled Trial of Mammographic Screening from Age 40 ('Age' Trial): Patterns of Screening Attendance*, Journal of Medical Screening, 17 (1):37-43.

- Joosten E.A.G. et al. (2008), *Systematic Review of the Effects of Shared Decision-Making on Patients Satisfaction, Treatment Adherence and Health Status*, *Psychother Psychosom*, 77:219-226.
- Jørgensen K.J. and Gøtzsche P.C. (2009), *Overdiagnosis in Publicly Organised Mammography Screening Programmes: Systematic Review of Incidence Trends*, *British Medical Journal*, 339:b2587.
- Jørgensen K.J. (2013), *Mammography Screening. Benefits, Harms, and Informed Choice*, *Danish Medical Journal*, 60 (4):B4614.
- Jørgensen K.J. et al. (2017), *Overview of Guidelines on Breast Screening: Why Recommendations Differ and What To Do About It*, *The Breast*, 31:261-269.
- Juth N. and Munthe C. (2012), *The Ethics of Screening in Health Care and Medicine. Serving Society or Serving the Patient?*, *International Library of Ethics, Law and the new Medicine*, Volume 51, Springer.
- Kaldjian L.C. (2010), *Teaching Practical Wisdom in Medicine Through Clinical Judgment, Goals of Care, and Ethical Reasoning*, *Journal of Medical Ethics*, 36:558-562.
- Kaldjian L.C., Weir R.F., and Duffy T.P. (2005), *A Clinician's Approach to Clinical Ethical Reasoning*, *Journal of General Internal Medicine*, 20:306-311.
- King J.S. and Moulton B.W. (2006), *Rethinking Informed Consent The Case Of Shared Medical decision-Making*, *American Journal of Law and Medicine*, 32:429-501.
- Kim S., Ko Y.H. and Jun E.Y. (2012), *The Impact of Breast Cancer on Mother-Child Relationship in Korea*, *Psycho-Oncology*, 21:640-646.

- Kirkman M. et al. (2014), *Women's Reflections on Fertility and Motherhood After Breast Cancer and Its Treatment*, European Journal of Cancer Care, 23:502-513.
- Klawiter M. (2008), *The Biopolitics of Breast Cancer: Changing Cultures of Disease and Activism*, University of Minnesota Press, Minneapolis.
- Klein, W.M.P. and Stefanek, M.E. (2007), *Cancer Risk Elicitation and Communication : Lessons from the Psychology of Risk Perception*, CA: A Cancer Journal for Clinicians, 57(3), 147–167.
- Kon A.A. (2009), *The Role of Empirical Research in Bioethics*, American Journal of Bioethics, 9 (6-7):59-65.
- Koning H.J. (2003), *Mammographic Screening: Evidence from Randomised Controlled Trials*, Annals of Oncology, 14:1185-1189.
- Kornblith A.B. and Ligibel J (2003), *Psychosocial and Sexual Functioning of Survivors of Breast Cancer*, Semin Oncol, 30 (6):799-813.
- Korsgaard K. (1986), *The Right to Lie: Kant on Dealing with Evil*, Philosophy & Public Affairs, 15 (4):325-349.
- Kotzee B., Ignatowicz A., and Thomas H. (2017), *Virtue in Medical Practice: An Exploratory Study*, HEC Forum, 29:1-19.
- Kriegel U. (2007), *Moral Phenomenology: Foundational Issues*, Phenom Cogn Sci, DOI 10.1007/s11097-007-9057-z.
- Kuhse H. and Singer P. (2009), *What is Bioethics? A Historical Introduction*, Chapter 1 (pp. 3-11) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.

- Lagerlund M. et al. (2000), *Attitudes, Beliefs and Knowledge as Predictors of Nonattendance in a Swedish Population-Based Mammography Screening Program*, Preventive Medicine, 31:417-428.
- Lagerlund M. et al. (2002), *Sociodemographic Predictors of Non-Attendance at Invitational Mammographic Screening – A Population-Based Register Study (Sweden)*, Cancer Causes and Controls, 13:73-82.
- LaRossa R. (2005), *Grounded Theory Methods and Qualitative Family Research*, Journal of Marriage and Family, 67:837-857.
- Lauby-Secretan et al. (2015), *Breast Cancer Screening – Viewpoint of the IARC Working Group*, The New England Journal of Medicine, 372 (24):2353-2358.
- Lee W. and Peters G. (2013), *Mammographic Screening for Breast Cancer: A Review*, Journal of Medical Radiation Sciences, 60:35-39.
- Lerner B.H. (2001), *The Breast Cancer Wars: Hope, Fear and the Pursuit of a Cure in Twentieth-century America*, Oxford University Press, New York.
- Liberati A. et al. (2009), *The PRISMA Statement for Reporting Systematic Reviews and Meta-Analysis of Studies that Evaluate Health Care Interventions: Explanation and Elaboration*, PLoS Med, 6 (7): e1000100.
doi:10.1371/journal.pmed.1000100
- Mackenzie C.R. (2014), *“It Is Hard for Mums to Put Themselves First”: How Mothers Diagnosed with Breast Cancer Manage the Sociological Boundaries Between Paid Work, Family and Caring For the Self*, Social Science & Medicine, 117:96-106.

- Mandelblatt J.S. et al. (2009), *Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms*, Clinical Guidelines - Annals of Internal Medicine, 151:738-747.
- Manning R.C. (2009), *A Care Approach*, Chapter 11 (pp. 105-116) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.
- Marmot et al. (2013), *Benefits and Harms of Breast Cancer Screening: an Independent Review*, British Journal of Cancer, 108:2205-2240.
- Mathieu E. et al. (2007), *Informed Choice in Mammography Screening: A Randomized Trial of a Decision Aid for 70-Year-Old Women*, Arch Intern Med, 167 (19):2039-2046.
- Mathieu et al. (2010), *Helping Women Make Choices About Mammography Screening: An Online Randomized Trial of a Decision Aid For 40-Year-Old Women*, Patient Educ Couns, 81 (1):63-72.
- Mazzotti E. et al. (2012), *Mother-Child Relationship as Perceived by Breast Cancer Women*, Psychology, 3 (12):1027-1034.
- McCaffery K.J. et al. (2016), *Walking the Tightrope: Communicating Overdiagnosis in Modern Health Care*, British Medical Journal, 352:i348; doi:10.1136/bmj.i348.
- McDougall R. (2014), *Systematic Reviews in Bioethics: Types, Challenges and Values*, The Journal of Medicine and Philosophy, 39 (1):89-97.
- McDougall R. (2015), *Reviewing Literature in Bioethics Research: Increasing Rigour in Non-Systematic Reviews*, Bioethics, 29 (7):523-528.
- Metsch L.R. et al. (1998), *The role of physician as an information source on mammography*, Cancer Pract, 6:229-236.

- Miller A.B. et al. (1992), *Canadian National Breast Cancer Screening Study: 2. Breast Cancer Detection and Death Rates Among Women aged 50-59 years*, Can Med Assoc J, 147 (10):1477-1488.
- Miller A.B. et al. (2014), *Twenty Five Years Follow-Up for Breast Cancer Incidence and Mortality of the Canadian National Breast Screening Study: Randomised Screening Trial*, British Medical Journal, 348:g366.
- Mills M. et al. (2011), *Why do People Postpone Parenthood? Reasons and Social Policies Incentives*, Human Reproduction Update, 17 (6):848-860.
- Moore C.W. et al. (2015), *Parenting Changes in Adults with Cancer*, Cancer, 121 (19):3551-3557.
- Montessori M. (2007), *The Absorbent Mind*, Wilder Publication, Radford.
- Morrow M., Schnitt S.J. and Norton L. (2015), *Current Management of Lesions Associated with an Increased Risk of Breast Cancer*, Nat Rev Clin Oncol, 12 (4):227-238.
- Moynihan R., Doust J. and Henry D. (2012), *Preventing Overdiagnosis: How to Stop Harming the Healthy*, British Medical Journal, 344:e3502.
- Morrow M., Schnitt S.J. and Norton L. (2015), *Current Management of Lesions Associated With an Increased Risk of Breast Cancer*, Nature Reviews Clinical Oncology, 12:227-238.
- Moss S.M. et al. (2005), *Randomized Controlled trial of Mammographic Screening in Women fro Age 40: Predicted Mortality Based on Surrogate Outcome Measures*, British Journal of Cancer, 92:955-960.

- Moss S.M. et al. (2006), *Effect of Mammographic Screening from Age 40 Years on Breast Cancer Mortality at 10 Years' Follow-Up: a Randomised Controlled Trial*, Lancet, 368:2053-2060.
- Muriel et al. (2012), *Measuring Psychosocial Distress and Parenting Concerns among Adults with Cancer: The Parenting Concerns Questionnaire*, Cancer, 118 (22):5671-5678.
- Nelson E.P. (2011), *Screening Mammography: A Decision Aid for Women Ages 38-48: Technical Implementation*, Scholar Archive, 662.
- Newson A.J. (2011), *Population Screening (Section 2, Chapter 7, 118-142)*, in *Public Health Ethics*, ed. Dawson A., Cambridge University Press, New York.
- Noddings, N. (1984), *Caring: A Feminine Approach to Ethics and Moral Education*, University of California Press, London.
- Noddings N. (2010), *The Maternal Factor: Two Paths to Morality*, University of California Press, London.
- Nystrom L. et al. (2002), *Long-Term Effects of Mammography Screening: Updated Overview of the Swedish Randomised Trials*, Lancet, 359:909-919.
- Oakley J. (2009), *A Virtue Ethics Approach*, Chapter 10 (pp. 91-104) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.
- O'Connor A.M., Légaré F. and Stacey D. (2003), *Risk Communication in Practice: the Contribution of Decision Aids*, British Medical Journal, 327 (7417):736-740.
- O'Donnell S. et al. (2006), *Understanding and Overcoming the Barriers of Implementing Patient Decision Aids in Clinical Practice*, Journal of Evaluation in Clinical Practice, 12 (2):174-181.

- O'Neill O. (2004), *Autonomy and Trust in Bioethics*, Cambridge University Press, Cambridge.
- Oeffinger K.C. et al. (2015), *Breast Cancer Screening for Women at Average Risk. 2015 Guideline Update From the American Cancer Society*, JAMA, 314 (15):1599-1614.
- Ormiston-Smith N., Scowcroft H. and Thomson C.S. (2013), *Mortality Benefits and Overdiagnosis Estimates for Women Attending Breast Screening*, British Journal of Cancer, 108:2413-2414.
- Pace L.E. and Keating N.L. (2014), *A Systematic Assessment of Benefits and Risks to Guide Breast Cancer Screening Decisions*, JAMA, 311 (13):1327-1335.
- Paul C. et al. (2008), *Making Policy Decisions About Population Screening for Breast Cancer: The Role of Citizens' Deliberation*, 85:314-320.
- Parker P.A. et al. (2007), *Short-Term and Long-Term Psychosocial Adjustment and Quality of Life in Women Undergoing Different Surgical Procedures for Breast Cancer*, Ann Surg Oncol, 14 (11):3078-3089.
- Parker L., Rychetnik L. and Carter S. (2015), *Values in Breast Cancer Screening: an Empirical Study with Australian Experts*, BMJ Open, 5:e006333.
- Patterson J.T. (1987), *The Dread Disease: Cancer and Modern American Culture*, Harvard University Press, Cambridge MA.
- Pellegrino E. D. (1995), *Toward a Virtue-Based Normative Ethics for the Health Professions*, Kennedy Institute of Ethics Journal, 5 (3):253-277.

- Petrova D. et al. (2015), *Understanding the Harms and Benefits of Cancer Screening: A Model of Factors That Shape Informed Decision Making*, Medical Decision Making, 35:847-858.
- Pignone M. et al. (2012), *Clarifying and Expressing Values*, in Volk R. and Llewellyn-Thomas H. (editors), *2012 Update of the International Patient Decision Aids Standards (IPDAS). Collaboration's Background Document. Chapter D.* available at: <http://ipdas.ohri.ca/resources.html> (last accessed on 13.10.2017).
- Plutynski A. (2012), *Ethical issues in cancer screening and prevention*, Journal of Medicine and Philosophy, 7:310-323.
- Pravettoni G and Gorini A. (2011), *A P5 Cancer Medicine Approach: Why Personalized Medicine Cannot Ignore Psychology*, Journal of Evaluation in Clinical Practice, 17:594-596.
- Pravettoni G. et al. (2016), *Eliminating "ductal carcinoma in situ" and "lobular carcinoma in situ" (DCIS and LCIS) terminology in clinical breast practice: The cognitive psychology point of view*, Breast, 25:82-85.
- Puliti D., Miccinesi G. and Paci E. (2011), *Overdiagnosis in Breast Cancer: Design and Methods of Estimation in Observational Studies*, Preventive Medicine, 53:131-133.
- Puliti D. et al., (2012), *Overdiagnosis in Mammographic Screening for Breast Cancer in Europe: a Literature Review*, Journal of Medical Screening, 19 (Suppl 1):42-56.
- Rachels J. (2007), *The Elements of Moral Philosophy*, 5th edition McGraw-Hill International, London.

- Rachels J. (2009), *Ethical Theory and Bioethics*, Chapter 2 (pp. 15-23) in Kuhse H. and Singer P. (eds.), *A Companion to Bioethics*, 2nd edition, Blackwell, Oxford.
- Raffle E.A. (2001), *Information About Screening - Is It to Achieve High Uptake or to Ensure Informed Choice?*, *Health Expect*, 4 (2):92-98.
- Raffle A.E. and Grey J.A.M. (2007), *Screening: Evidence and Practice*, Oxford University Press, New York.
- Rauch P.K. and Muriel A.C. (2004), *The Importance of Parenting Concerns Among Patients with Cancer*, *Critical Reviews in Oncology/Haematology*, 49:37-42.
- Reynolds H. (2012), *The Big Squeeze. A Social and Political History of the Controversial Mammogram*, Cornell University Press, Ithaca.
- Richardson H. (1990), *Specifying Norms as a Way to Resolve Concrete Ethical Problems*, *Philosophy & Public Affairs*, 19:279-310.
- Rimer B.K. et al. (2004), *Informed Decision Making: What is its Role in Cancer Screening?*, *Cancer Supplement*, 101 (5):1214-1228.
- Roberts M.M. et al. (1990), *Edinburgh Trial of Screening for Breast Cancer: Mortality at Seven Years*, *Lancet*, 335:241-246.
- Roberts M.J. and Reich M.R. (2002), *Ethical Analysis in Public Health*, *Lancet*, 359:1055-1059.
- Rosenbaum L. (2014), *Invisible Risks, Emotional Choices – Mammography and Medical Decision Making*, *New England Journal of Medicine*, 371 (16):1549-1552.
- Ruddick S. (1980), *Maternal Thinking: Toward a Politics of Peace*, New York: Ballantine Books.

- Rychetnik L. et al. (2013), *Enhancing Citizen Engagement in Cancer Screening through Deliberative Democracy*, Journal of National Cancer Institute, 105:380-386.
- Sample C.J. and McCance T. (2010), *Parents' Experience Of Cancer Who Have Young Children. A Literature Review*, Cancer Nursing, 33 (2):110-118.
- Scariati P. et al. (2015), *Impact of a Decision Aid in Reducing Uncertainty: Pilot Study of Women in Their 40s and Screening Mammography*, BMC Medical Informatics and Decision Making, 15:89, DOI 10.1186/s12911-015-0210-2.
- Schwartz L.M. et al. (1997), *The Role of Numeracy in Understanding the Benefit of Screening Mammography*, Annals of Internal Medicine, 127 (11):966-972.
- Schwartz P.H. and Meslin E.M. (2008), *The Ethics of Information: Absolute Risk Reduction and Patient Understanding of Screening*, Journal of General Internal Medicine, 23 (6):867-870.
- Selvin E. and Brett K.M. (2003), *Breast and Cervical Cancer Screening: Sociodemographic Predictors Among White, Black, and Hispanic Women*, American Journal of Public Health, 93 (4):618-623.
- Shapiro S., Strax P. and Venet L. (1971), *Periodic Breast Cancer Screening in Reducing Mortality from Breast Cancer*, Journal of the American Medical Association, 215:1777-1785.
- Shapiro S. (1977), *Evidence on Screening for Breast Cancer from a Randomized Trial*, Cancer, 39 (6 Suppl):2772-2782.
- Shapiro S. (1997), *Periodic Screening for Breast Cancer: The HIP Randomized Controlled Trial*, J Nat Cancer Inst Monogr, (22):27-30.

- Shickle D. and Chadwick R. (1994), *The Ethics of Screening: Is "Screeningitis" an Incurable Disease?*, Journal of Medical Ethics, 20:12-18.
- Schnipper H.H. (2001), *Life After Breast Cancer*, J Clin Oncol, 19 (15):3581-3584.
- Schonberg M.A. et al. (2014), *Development and Evaluation of A Decision Aid on Mammography Screening for Women Aged 75 and Older*, JAMA Intern med, 174 (3):417-424.
- Singer P. (2011), *Practical Ethics*, 3rd edition, Cambridge University Press, New York.
- Siu A.L., Preventive Service Task Force (2016), *Screening for Breast Cancer: U.S. Preventive Service Task Force Recommendation Statement*, Annals of Internal Medicine, 164:279-296.
- Smith-McLallen A. and Fishbein M. (2008), *Predictors of Intentions to Perform Six Cancer-Related Behaviours: Roles for Injunctive and Descriptive Norms*, Psychology, Health & Medicine, 13 (4):389-401.
- Snitow A. (1992), *Feminism and Motherhood: an American Reading*, Feminist Review, 40:32-51.
- Sofaer N. and Stretch D. (2012), *The Need for Systematic Reviews of Reasons*, Bioethics, 26 (6):315-328.
- Spring L.M. et al. (2016), *Mammography Decision Making: Trend and Predictors of Provider Communication in the Health Information National Trends Survey, 2011 to 2014*, Cancer, DOI: 10.1002/cncr.30378.
- Stafford W. (1930), *A Roentgenologic Study of the Breast*, American Journal of Roentgenology and Radium Therapy, 24:113-124.

- Stacey D. et al. (2017), *Decision Aids for People Facing Health Treatment or Screening Decisions*, Cochrane Database Syst Rev, (4):CD001431.
- Steinbock B. (2007), *The Oxford Handbook of Bioethics*, Oxford University Press, Oxford.
- Stinesen-Kollberg K. et al. (2013), *Worry About One's Own Children, Psychological Well-Being and Interest in Psychosocial Intervention*, Psycho-Oncology, 22:2117-2123.
- Svendsen A.L. et al. (2006), *Breast Cancer Incidence After the Introduction of Mammography Screening. What Should Be Expected?*, Cancer, 106 (9):1883-1890.
- Tabàr L., Fagerberg G., Duffy S. and Day N.E. (1989), *The Swedish Two County Trial of Mammographic Screening for Breast Cancer: Recent Results and Calculation of Benefit*, Journal of Epidemiology and Community Health, (43):107-114.
- Tabàr et al. (1995), *Efficacy of Breast Cancer Screening by Age. New Results from the Swedish Two-County Trial*, Cancer, 75 (10):2507-2517.
- Tabàr L. et al. (2015), *Insights from the Breast Cancer Screening Trials: How Screening Affects the Natural History of Breast Cancer and Implications for Evaluating Service Screening Programs*, The Breast Journal, 21 (1):13-20.
- Taylor P. et al. (2010), *The New Demography of American Motherhood*, Pw Research Center, Washington DC.
- Thorne S., Oliffe J.L. and Stajduhar K.I. (2013), *Communicating Shared Decision-Making: Cancer Patient Perspective*, Patient Education & Counseling, 90 (3):291-296.

- Toledo-Chàvarri A. et al. (2017), *A Qualitative Study on a Decision Aid for Breast Cancer Screening: Views from Women and Health Professionals*, Eur J Cancer Care, e12660, doi:10.1111/ecc.12660.
- Tong R. (1998), *The Ethics of Care: a Feminist Virtue Ethics of Care for Healthcare Practitioners*, Journal of Medicine and Philosophy, 23 (2):131-152.
- Torre L.A. et al. (2015), *Global Cancer Statistics, 2012*, Ca Cancer J Clin, 65:87-108.
- Towle A. and Godolphin W. (1999), *Framework for Teaching and Learning Informed Shared Decision Making*, British Medical Journal, 319 (7212):766-771.
- Tronto J. (1994), *Moral Boundaries: A Political Argument for an Ethic of Care*, Routledge, New York.
- Tronto J.C. and Fischer B. (1990), *Toward a Feminist Theory of Caring*, Chapter 2 in Abel E.K. and Nelson M.K.(Eds.), *Circles of Care* . Suny Press, Albany.
- Troop P. (2000), *Screening: General Principles*, Chap. 6 in *Ethics in Public and Community Health*, edited by Bradley P. and Burls A., Routledge, London.
- Twomey M. (2012), *Autonomy and Reason: Treatment Choice in Breast Cancer*, Journal of Evaluation in Clinical Practice, 18:1045-1050.
- Vahabi M. and Gastaldo D. (2003), *Rational Choice(s)? Rethinking Decision-Making on Breast Cancer Risk and Screening Mammography*, Nursing Inquiry, 10 (4):245-256.
- Veatch R.M. (1995), *Resolving Conflicts Among Principles: Ranking, Balancing, and Specifying*, Kennedy Institute of Ethics Journal, 5 (3):199-218.

- Visshers V.H.M. et al. (2009), *Probability Information in Risk Communication: a Review of the Research Literature*, Risk Analysis, 2:267-287.
- Walsh S.R., Manuel J.C. and Avis N.E. (2005), *The Impact of Breast Cancer on Younger Women's Relationships With Their Partner and Children*, Families, Systems, & Health, 23 (1):80-93.
- Wang A.T. et al. (2014), *Impact of the 2009 US Preventive Service Task Force Guidelines on Screening Mammography Rates on Women in Their 40s*, PLoS ONE, 9 (3):e91399.
- Wardle J., Robb K., Vernon S. and Waller J. (2015), *Screening for Prevention and Early Detection of Cancer*, American Psychologist, 70 (2):119-133.
- Welch H.G. and Black W.C. (2010), *Overdiagnosis in Cancer*, J Natl Cancer Inst, 102:605-613.
- Welch H.G., Schwartz L., Woloshin S. (2011), *Overdiagnosis. Making People Sick in the Pursuit of Health*, Bacon Press, Boston.
- Welch H.G. and Passow H.J. (2014), *Quantifying the Benefits and Harms of Screening Mammography*, JAMA Internal Medicine, 174:448-454.
- Welch H.G., Prorok P.C., O'Malley A.J. and Kramer B.S. (2016), *Breast-Cancer Tumor Size, Overdiagnosis and Mammography Screening Effectiveness*, The New England Journal of Medicine, 375 (15):1438-1447.
- WHO (2012), *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012*, International Agency for Research on Cancer, World Health Organization.

- Wilson J.M.G. and Jungner G. – WHO (1968), *Principles and Practice of Screening for Disease*, Public Health Papers 34, WHO, Geneva.
- Woloshin S. et al. (2012), *Cancer Screening Campaigns – Getting Past Uninformative Persuasion*, N Engl J Med, 367 (18):1677-1679.
- Yoshida S. et al. (2010), *A Qualitative Study of Decision-Making By Breast Cancer Patients About Telling Their Children About Their Illness*, Support Care Cancer, 18:439-447.
- Youlden D.R. et al. (2012), *The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality*, Cancer Epidemiol, 36:237-248.
- Zahl P.H., Jørgensen K.J. and Gøtzsche P.C. (2013), *Overestimated Lead Times in Cancer Screening Has Led to Substantial Underestimation of Overdiagnosis*, British Journal of Cancer, 109:2014-2019.
- Zarvadas D., Fouad T.M. and Piccart M. (2015), *Optimal Adjuvant Treatment for Patients with HER2-positive Breast Cancer in 2015*, Breast, Suppl. 2, 143-8. doi: 10.1016/j.breast.2015.07.034.