THESE DE DOCTORAT DE

L'UNIVERSITE DE NANTES
Comue Université Bretagne Loire
Ecole Doctorale n° 605
Biologie Santé
Spécialité: *Epidémiologie, Analyse de Risque, Recherche Clinique*

L'UNIVERSITE DE TURIN
Ecole Doctorale en Sciences humaines et sociales

Par
Anna TOSCANO

Clinical and psychological factors associated with Health-related Quality of Life and treatment choice at cancer diagnosis and over the disease course

Thèse présentée et soutenue à Turin, le 21 Novembre 2018

Unités de recherche: UMR INSERM 1246, équipe SPHERE, 22 Boulevard Benoni-Goullin, 44200, Nantes, et Département de Psychologie, 10 rue Verdi, 10124, Turin.

Rapporteurs avant soutenance:

Francis Guillemin   Professeur des universités - Praticien hospitalier, EA4360, Université de Lorraine, Vandoeuvre-les-Nancy, France
Pietro Porcelli   Professeur, Département de sciences psychologiques, santé et sciences du territoire, Université G. D'Annunzio Chieti-Pescara, Pescara, Italie

Composition du Jury:

Examinateurs: Gianluca Castelnuovo   Professeur, Département de Psychologie, Université Cattolica del Sacro Cuore, Milano, Italie

Dir. de thèse: Rosalba Rosato   Professeur, Département de Psychologie, Université de Turin, Turin, Italie
     Veronique Sebille-Rivain   Professeur des universités - Praticien hospitalier, UMR U1246, Université de Nantes, Université de Tours, INSERM, France

Co-enc. de thèse: Myriam Blanchin   Ingénieur de recherche, UMR U1246, Université de Nantes, Université de Tours, INSERM, France

Università degli Studi di Torino

Department of Psychology

Doctorate in
Psychological, anthropological and educational sciences
XXXI cycle

Clinical and psychological factors associated with Health-related Quality of Life and treatment choice at cancer diagnosis and over the disease course

PhD Candidate
Anna Toscano
SSD M-PSI/03

Supervisors
Myriam Blanchin
Rosalba Rosato
Prof. Veronique Sebille-Rivain

PhD coordinator
Prof. Cristina Onesta Mosso

A.Y. 2015-2018

Table of contents

Acronyms

ABC Activating Event, Belief, Consequence

ACT Acceptance and Commitment Therapy

AIC Akaike Information Criterion

AS Active Surveillance

BIC Bayesian Information Criterion

CBT Cognitive-Behavioural Therapy

CIS Carcinoma in situ

DNA Desoxyribonucleic acid

ELCCA Etude Longitudinale des Changements psycho-économiques liés au Cancer

EORTC European Organization for Research and Treatment in Cancer

HADS Hospital Anxiety and Depression Scale

HRQoL Health-related Quality of Life

IIEF-5 International Index of Erectile Function

I-PSS International Prostatic Symptoms Score

LOC Locus of Control

MHLC Multidimensional Health Locus of Control

PC Prostate Cancer

PTGI Post-Traumatic Growth Inventory

QLQ-C30 EORTC Core Quality of Life Questionnaire

QOL Quality of Life

RTs Radical Treatments

SF-36 Short-Form 36

SWLS Subjective Wellbeing Scale

START Epidemiological multicentre study in the oncological network of Piemonte and Valle d'Aosta regions

1. INTRODUCTION

Cancer is a chronic disease throughout the world and widely present in Europe. Even though many people still die from cancer today, advances in treatment, faster diagnosis, and better health conditions before the pathology have helped improve the survival rate for many cancers. Psycho-oncology research has evolved during the last decades and now also incorporates the study of psychosocial issues involved in patients' adaptations to both cancer and treatment. The side effects of the treatments, for example, as well as the anxieties and the concerns regarding the disease progression, can play a part of the physical and mental burden that patients experience during the pathology.

Among the experiences that cancer patients live during their illness, this thesis will specifically focus on the study of perceived Health-related Quality of Life (HRQoL) changes over the pathology, and the study of treatment choice at the time of diagnosis. As cancer experience and needs can differ among individual patients and cancer localisation, due notably to differing social and individual representations of cancer and treatments, three different types of cancer were studied to explore HRQoL changes and patients' experience: i.e., breast and prostate cancer, as well as melanoma.

HRQoL is a multidimensional construct considered today in many clinical research protocols, and is composed of physical, psychological, and social functioning, as well as symptoms due to the pathology and treatments. Several authors have previously tried to define the concept of HRQoL, and the factors associated with its evolution; some of these theoretical models will be presented.

Moreover, in some types of cancer, it has been shown that HRQoL may change over time. Studying the HRQoL changes during cancer, and identifying the factors possibly associated with them can be useful for helping patients to better adjust to stressful cancer situations, and for ameliorating patients' psychological state over time.

Other concepts of psycho-oncology research considered in my thesis are the Locus Of Control (LOC), and the coping. These aspects can give clues on how patients react at the time of diagnosis and over the progression of their illness, and they can be precious tools for psychotherapists who work in cancer settings as they can improve patients' psychological state and HRQoL.

The outline of the thesis is as follows. Firstly, a brief introduction on cancer epidemiology is given followed by the notion of cancer burden related to medical and psychological perspectives. Secondly, the main HRQoL models are presented including those more related to cancer. Thirdly, the two main psychological constructs of LOC and coping are described with the different underlying models and assumptions. Fourthly, the statistical methods that were used are presented with the corresponding statistical models along with their parameters and underlying assumptions. Fifthly, the two main studies named ELCCA and START are fully described with the article of the ELCCA study that was submitted to the journal Psychology & Health, and in the section on the START study. Lastly, a general discussion is provided on the different concepts and results that were covered in this thesis.

1.1. Introduction to cancer disease and its epidemiology

Introduction to cancer disease

Worldwide, cancer is considered a life-threatening disease. It is a multistage process, starting from a transformation of a healthy cell into a tumour cell, through one or, more often, a series of genetic mutations, which escape the cellular DNA (Desoxyribonucleic acid) repair processes. Apart from haematological cancers (e.g., leukaemia, lymphoma, myeloma, etc.) which usually spread out into the whole body at very early stages of development, most of the time the first tumour cell replicates itself into billions of abnormal cells which forms a first abnormal mass called primary tumour[1,2]. Most cancers are carcinomas (developing into an epithelial layer lining the outer surfaces of organs as well as the inner surfaces of cavities in many internal organs).

When a tumour is entirely contained into the epithelial layer, it is called a carcinoma in situ (CIS), which is considered stage 0 of cancer. In the following stages, the tumour cells can spread into nearby tissues and multiply. In early stages (stage I-II), there is still a unique mass. At advanced stages (stage III-IV), the tumour cells have spread out through the lymphatic system or blood vessels and metastases (secondary masses located into lymph nodes or other organs) occur. This staging system (stages I-IV) summarizes info from the primary staging system: the TNM system. The TNM system assesses cancer growth and spread in three ways: extent of the primary tumour (T), absence or presence of regional lymph node involvement (N), and absence or presence of distant metastases (M). When a cancer develops from a type of tissue other than epithelium (e.g., such as sarcoma, which can develop from bone cells), there cannot be a CIS, or initial, phase.

Cancer epidemiology

Apart from a few exceptions where a distinct genetic mutation is very strongly associated with the occurrence of cancer (e.g., familial forms of breast cancer due to BRCA-1 or BRCA-2 mutations), the development of a cancer is usually multi-causal. Even if all the exact possible causes for cancer remain unknown, some combination of risk factors have been identified[3]:

- The first factor is **age**: because the process from the occurrence of one tumour cell to the development of the primary tumour usually takes decades, most cancers are diagnosed after middle-age;

- **Person' genetic predisposition**;

- Exposure to **physical radiations** (such as ultraviolet (UV) radiation[4] or radioactive radiations);

- Exposure to **chemical carcinogens** (e.g., smoking the toxic composites of cigarettes, such as benzene[5], or drinking water and eating food contaminated by harmful substances, such as arsenic[6]);

- Exposure to **biological carcinogens** (e.g., infections from particular viruses, bacteria or parasites that cause chronic inflammation that may lead to cancer, such as Human immunodeficiency virus (HIV)[7], Helicobacter pylori bacterium[8], or the parasite Schistosoma hematobium[9]).

Cancer incidence

The regular occurrence of some of these factors, e.g., cigarette consumption, exposure to the sun's ultraviolet (UV) radiation without any protection, or genetic predisposition, makes cancer a common pathology worldwide, especially in developed countries with long life expectancy. Indeed, more than 3 million new cases of all types of cancer patients (excluding non-melanoma skin cancer) have been estimated in 2018 in Europe (globally in 28 countries of the European Union)[10]. Among these, breast cancer (404 thousand incidence cases) and prostate cancer (375 thousand incidence cases) resulted to be the most common cancer types in 2018[10]. In 2012, in Europe (globally in 40 countries of the four United Nations-defined areas of Europe[11]: Central and Eastern, Northern, Southern, and Western Europe), 3.4 million new cases of cancer were diagnosed (excluding non-melanoma skin cancer from the count)[12]. Among these, breast cancer (464 thousand incidence cases), followed by colorectal (447 thousand incidence cases), prostate (417 thousand incidence cases) and lung cancer (410 thousand incidence cases)[12] were the most common cancer types. Furthermore, the incidence of these types of cancer in Europe represents half of all cancer types incidence[12].

Regarding the differences for all types of cancer among the European countries in 2012 (Fig. 1), Italy (among the Southern countries), Norway (among the Northern countries), Czech Republic (among the central and eastern countries), and Netherlands (among the western

countries), had the highest cancer incidence rates. In Figure 1 there are the age-standardized cancer incidence rates for several European countries. The age-standardised incidence rate is the incidence rate that a population would have if it had a standard age structure of the reference population. It is used for eliminating the effect of differences in population age structures when different groups are compared.

Cancer mortality

Mortality due to cancer is high; each year 1.9 million people die in Europe of this disease[1]: in 2014, cancer was the second leading cause of mortality (mortality rate: 261.5 per 100.000) after circulatory disease (mortality rate: 373.6 per 100.000)[13]. The most life-threatening cancer types in Europe were: lung (353 thousand death cases and 264.0 deaths per 100.000), colorectal (215 thousand death cases and 150.0 per 100.000), breast (131 thousand death cases and 90.6 per 100.000), and stomach cancer (107 thousand death cases and 57.7 per 100.000) in 2012[12].

Figure 1. Cancer incidence per European country
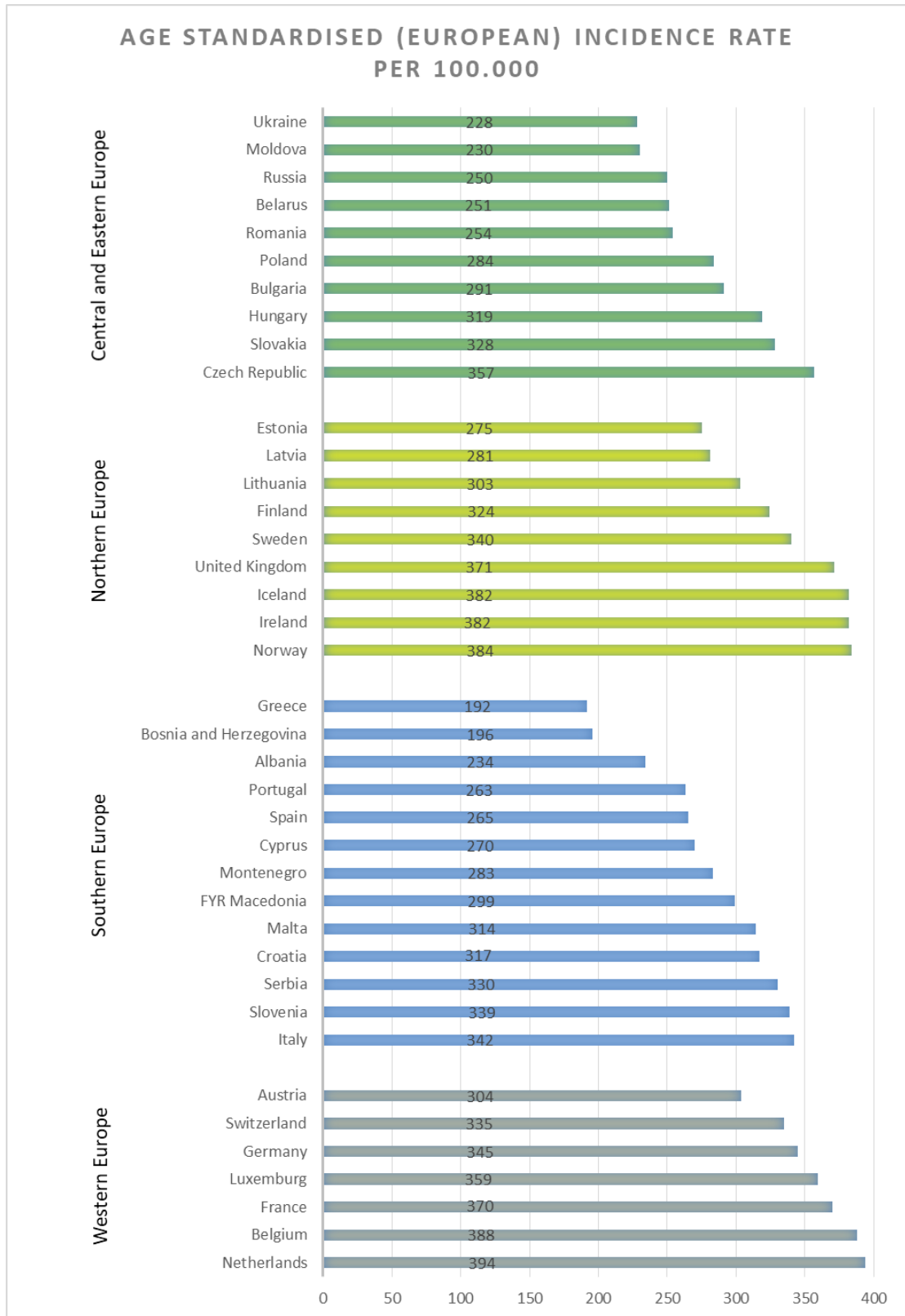
In Steliarova-foucher, E. *et al.* The European Cancer Observatory: A new data resource. *Eur. J. Cancer* **33,** 1–13 (2014).

1.2. Cancer as a chronic disease

Cancer survival

Even though many people die from cancer today, advances in treatment, screening, faster diagnosis, and better health conditions before the pathology have helped improve the survival rate for many cancers. Cancer survival rate can depend on different factors (e.g., cancer stage at diagnosis, country, age at diagnosis, sex, type of cancer-related treatment, etc.)[14], and among these factors, there is the cancer type.

For example, for adult patients diagnosed between 2000-2007 with breast and prostate cancer (the cancer types most diffused in 2018 in Europe, see 1.1), the 5-year relative survival was between 80 and 90%[14]. Among all the cancer types, they are at 4th and 6th places for the best 5-years survival rate. In 5th place there is melanoma, which can have a good prognosis in 5 years (80-90% survival rate), too[14].

However, for adult lung cancer patients (diagnosed in 2000-2007) for example, the 5-years survival rate is lower, between 10 and 20%[14].

Patients' medical and psychological changes during the survival

In order to guarantee a better survival during cancer, clinicians and psychologists must help patients from a medical and psychological point of view, respectively. Researchers, indeed, with this same aim, study both treatments and their side effects, and patients' psychological burden of cancer illness. This is because cancer is a complex condition that requires the multi-disciplinary expertise of several professionals and research from different areas.

From a **medical point of view**, it is important to advise patients of the possible treatment side effects they are going to deal with, and help them to manage these symptoms. Moreover, from a **psychological point of view**, it is important to understand the patients' psychological status due to the illness and the perceived HRQoL, since psychological support might be needed.

These aspects must be considered over the entire course of illness, from the moment of diagnosis to the after treatments period.

At the beginning of cancer, for example, treatment choice must be made by physicians and patients who need to understand the different choice options. Furthermore, the impact of a life-threatening illness diagnosis, associated with fear as well as uncertainty of what it is going to happen, can change the emotional status of the patients. During the treatments, some other

experiences can happen, including the management of the side effects of treatments and changes in physical appearance.

After the treatments, the patients, instead, can return to previous activities: they may return to work and to family, for example, in a physically and emotionally changed state.

Since patients endure several experiences from the onset and during the illness, patients' physical and psychological state and well-being perception can change.

In all these phases, patients may need helped from physicians and psychologists to cope and to manage the illness and its consequences. In the following chapter, in the first part, medical treatments often suggested and their side effects will be described, and in the second part, we will describe the psychological burden due to the cancer illness. This is to better understand the changes cancer patients deal with.

1.3. The cancer burden: which are the medical and psychological issues?

Medical issues: the treatments' side effects

Cancer is a life-threatening illness and cancer-related treatments are often physically and psychologically very heavy for the patients. Cancer treatments may have physical side effects linked to the specific substances used during the therapeutic procedures, and these side effects may also bring some anxieties and concerns at the time of diagnosis, as well as during and after treatments.

The major treatments for cancer are chemotherapy, radiotherapy, surgery, immunotherapy, and hormonal therapy. Moreover, for some types of cancer, such as prostate cancer, active surveillance (AS) can be also a treatment choice. In metastatic cancer, physicians can often suggest the systemic therapy that is considered as the principal therapeutic modality. This consists of the combination of different therapies such as hormonal therapy, targeted therapy, immune therapy, and chemotherapy.[15] All of them can have an impact on patients' physical and mental well-being.

The **chemotherapy** uses drugs to kill cancer cells, but as chemotherapy kills the cancer cells, it also kills the healthy cells and slows their growth.[16] Possible side effects of chemotherapy include nausea and vomiting[15–17], fatigue[16], hair loss[15–17], mouth sores[15–17], anemia[15,17], diarrhea[17], urinary problems[15,17], infertility[17], low blood cell counts[15,17], fever, and appetite changes[17].

The **radiotherapy** is a therapy using an external machine (external beam radiation therapy) to administer ionizing radiation directed to the part of the body with cancer[18]. During radiotherapy cancer cells are killed, however healthy cells that are near the area being treated are also damaged during treatment. Common radiotherapy side effects are the same as for chemotherapy and include: fatigue[18,19], hair loss[18,19], diarrhea[18,19], nausea and vomiting[18], problems eating and drinking (discomfort when swallowing, sore mouth and taste changes) [18,19], sexual and fertility issues for both genders (loss of sexual interest and infertility)[18,19], and specifically for women (vaginal dryness and, if in menopause, hot flashes and night sweats)[19], and men (difficulty getting an erection and pain when ejaculating)[19]. Furthermore, for both sexes, radiotherapy can lead to urinary problems[18], loss of appetite and weight[19] (with the exception of sore skin[19] effect).

Another possibility for cancer patients at diagnosis or in association with another treatment (e.g., chemotherapy) is **surgery**. The type and the intensity of the side effects depend on several factors, such as the patient's overall health, other treatment received before surgery, type of surgery, and the type and cancer location[20]. Several side effects can affect the patients after a surgical intervention[20]: pain, fatigue, appetite loss, swelling and bruising around the surgery site, drainage from the surgery site, numbness, bleeding, infection (such as at the site of the incision), lymphedema (i.e., condition that results from impaired flow of the lymphatic system and consists in swelling due to excess fluid), organ dysfunction (i.e., dysfunction of the organ, surrounding the body part with cancer cells, that is paralyzed during the surgery)[20]. As secondary side effect, dietary concerns can appear (since patients may have difficulties eating regular food)[20]. Moreover, some types of surgeries, as the radical prostatectomy for example (i.e., the type of surgery used for prostate cancer that consists in the resection of the prostate), or hysterectomy (i.e., the surgical procedure to remove the woman's uterus), can cause problems in sexual and reproductive areas (e.g., erectile dysfunction and loss of ejaculation or vaginal dryness and thinness)[21,22].

Immunotherapy, instead, consists of a different procedure to fight cancer: to boost the body's natural defences. Some patients can have different reactions to this treatment, which also depends on the health status before its initiation[23]. Among the possible negative reactions there are skin reactions (e.g., extensive rash or itching), flu-like symptoms (fatigue and fever), respiratory problems (e.g., shortness of the breath), diarrhoea (that can contain blood), headaches, swelling of the legs (oedema), nausea and vomiting, and numbness[23].

The last main treatment for cancer is **hormonal therapy**. Hormonal treatment has the aim to slow or stop the growth of cancer that uses hormones to grow[24]. Because it blocks the ability of the body to produce hormones or it interferes with the normal behaviours of the hormones in the body, patients can have some side effects[24]. Among them, there can be hot flashes, loss of interest in sex, diarrhoea, nausea, weakened bones, fatigue, and mood changes. Moreover, vaginal dryness for women and problems getting an erection for men are among the possible hormonal therapy side effects[24,25].

At the time of diagnosis, according to their health condition and to the physician, patients can also choose another option for their cancer care, such as **AS**, which is a "waiting strategy". Under AS, patients can experience less complications that are generally related to active

treatments side effects, higher HRQoL, and reduced costs for health care services[26,27]. During AS the patient is regularly monitored for the evolution of the pathology and the Prostate-Specific Antigen (PSA) test is usually performed.

Cancer-related psychological issues

Cancer treatments' side effects can be numerous and can have a strong psychological impact along with the pathology itself.

In a recent work by Jefford et al.[28] on breast, prostate, melanoma and non-Hodgkin lymphoma patients, several psychological dimensions were measured at 1, 3 and 5 years post-diagnosis. It was found that patients reported low level of HRQoL, anxiety and depression, fear of recurrence, concentration difficulties, and difficulties with sleep.

Having a cancer diagnosis can be considered as a traumatic event and a life threat[29].

Patients can feel acute stress because of their fear for the possibility of death, fear of invasive treatments and pain, changes in the body image, and changes in social role and lifestyle[30].

In cancer, anxiety and depression can appear at diagnosis, during and/or after the treatments (e.g., chemotherapy)[29,31–33]. There can be anxieties to facing uncertainty, anxieties for the pre-screening (e.g., in case of family history of cancer), for the efficacy and the side effects of treatments, cancer progression and death, and about treatment effects[29].

The experience and the burden of cancer can be different according to the type of cancer.

Breast cancer patients burden is not only due to the side effects of the treatments (e.g., nausea and vomiting), but also to psychological issues. Breast cancer affects a part of the body, the breast, which is a part that represents the femininity, sexuality, and the motherhood for women. The psychological issues of this type of cancer relate, indeed, not only to anxiety and depression[29,31,32], but also to body image[34], and sexual functioning[34,35]. These are important aspects for them, especially if we think that breast cancer can appear during women's reproductive life[36].

The first psychological issue is about body change. After surgery, indeed, breast cancer patients can often experience psychological concerns focused on body changes such as embarrassment of exposing the body, discomfort regarding scars, lack of sexual interests, and problems with sexual relationships[37,38].

The second psychological issue, linked to the first one, is about the sexual area.

Women's sexual health and sexual functioning is altered by treatments mainly because of the fact that their side effects impair the body (e.g., hair loss)[34]: treatments such as chemotherapy, endocrine therapy, surgeries, radiation or adjuvant treatment are mainly the cause of the sexual issues in breast cancer[34,35]. The effects of the sexual concerns result in significant emotional distress, including sadness/depression, issues related to personal appearance, stigma, and negative impacts on personal relationships[35].

For **melanoma**, the treatments used to cure it, as a minor surgery, don't have the same side effects as other cancer treatments (e.g., chemotherapy for breast cancer or prostatectomy for prostate cancer). From a psychological point of view, melanoma, as breast cancer, can have an impact on the patients' body image. Melanoma surgeries can leave noticeable scars on the body of patients, and some patients can have concerns about it[39]. The most common psychological reactions of melanoma patients to the pathology include: anxiety, depression, decreases in self-esteem and social isolation[40], concerns about appearance, fatigue, and stress[39]. In most serious stages, the patients can start to have fear of the sun and develop agoraphobia (in a study on melanoma patients' sun protection behaviours, it was found that some of them limited sun exposure from 10 a.m to 4 p.m., used protective clothing, avoided tanning salons, wore hats, and 10% avoided the sun completely[41]).

In **prostate cancer**, as in breast cancer, the sexual aspects can cause several anxieties to patients since this type of cancer involves the sexual organs[42,43]. Other anxieties there can be regarding the functioning in specific areas, such as urinary or bowel functioning over time, since these can be the areas damaged by the treatments patients undergo (with the sexual area).
Prostate cancer-specific concerns can also be related to the illness monitoring. There can be different fears of cancer progression: there is the fear regarding the results of PSA screening[44,45], or, for patients who choose AS, the fear of "cancer spreading for not having done any intervention". This type of fear is really common for people who are not aware that under AS there is a strong screening to check for the progression of the illness and that many medical controls are performed[46].

The medical (e.g., treatments and side effects) and psychological (e.g., anxieties and fears) patients' modification can be related to the changed observed in patients' HRQoL. But what is HRQoL? This concept will be explained in detail in the next chapter.

1.4. The notion of Health-Related Quality of Life

Although the notion of HRQoL is relatively recent (this term appeared for the first time in the mid-1980s in an article of Torrance[47,48]), several HRQoL models exist. The choice of the theoretical models presented here fall down amongst the HRQoL models most frequently used in the literature, but also among the HRQoL models that allow to put in relation HRQoL and several other concepts used in psycho-oncology.

1.4.1. *From the Quality of Life to the Health-related Quality of Life*

The notion of quality of life (QoL) is nowadays often used[49–52] in the common language. QoL can encompass many different aspects such as well-being, personal mental and physical state, quality of the environment, socio-economic well-being, etc. But how can QoL be defined?
The term QoL appeared in the 1920 within the work on the economy of welfare[53]. In this book the author, Pigou, cites it when he described the non-economic welfare (defined as state of the mind which reflects human happiness and satisfaction that cannot be measured by money), and the aspects associated with it[53]. Although the author wrote that QoL could influence the non-economic welfare, he didn't give a definition to this concept. It came back in 1948, when the World Health Organization (WHO) gave the concept of QoL its first official definition[54]: The QoL was not defined as an absence of discomfort and infirmity, or as an absence of illness, but it was defined as personal physical, mental and social well-being state of a person. Today there isn't a universal accepted definition of QoL, and several aspects are considered for defining it.

QoL definitions, indeed, can include multidimensional aspects, such as political and life satisfaction aspects[55]. Giving an example, in the comprehensive systemic model of Bagdoniene of QoL[56], subjective as well as objective factors linked to QoL are considered[57]. They include global (macro-environmental, human rights, politics dimensions), external (work, family, standard of living, residence and housing dimensions), interpersonal (family, close relationships, interpersonal relationships dimensions), and personal factors as well (physical, psychological and spiritual dimensions)[56,57].

The concept of QoL is presented in literature alongside another concept, which is the HRQoL. In the 1980's the HRQoL concept was inserted in scientific papers, and one initial article in which the term was mentioned was by Torrance in 1987[47,48].

The concept of HRQoL is related to the disease and treatments effects and their association with health, and, much like QoL, it can change over time[49]. Differently from QoL, HRQoL is linked to the patients' health and it refers to the health context.

1.4.2. *Health-related Quality of Life models*

The influence of the biopsychosocial model

All the models on HRQoL presented in the sub-chapter 1.4.2.2 are successive to the end of the biomedical model and to the emergence of the biopsychosocial model in 1977[58]. The traditional biomedical model followed before the 70's, argued that the cause of the patients' disease could be explained only by objectively measurable factors, such as by etiological, pathological, biological, physiological or clinical factors. Before the 70's, physicians and psychiatrists didn't give space to the measurement of patients' QoL[59], considered as a subjective construct.

The biopsychosocial model of health was introduced by Engel[58], and thanks to his model, not only the cause of disease, but also the explication of health, started to be considered. For Engel, the individual health is the result of a dynamic combination of the person's biological, psychological and social components. So the study of individual health should include not only objective (e.g., medical data), but also subjective factors (e.g., the patients' experience and their health perception).

After the inception of the biopsychosocial model, the interest for subjective factors and their relationship to health started to increase simultaneously with the interest for QoL and HRQoL[60]: many HRQoL models were influenced by the biopsychosocial model framework. The impact of the interaction of several types of factors on the HRQoL started to be widely discussed.

The description of the Health-related Quality of Life models in cancer

The HRQoL models will be presented in order of increasing complexity. All of them have tried to analyse different HRQoL components, which can be relevant to be considered in psycho-oncological research. The following models are the Centre of Health promotion model from the University of Toronto (created by Dennis Raphael, Rebecca Renwick, Ivan Brown, and Ted Myerscough in 2002)[61,62], the contextual model of Ashing-Giwa (2005)[63], and the models of Wilson and Cleary (1995)[59] and Ferrans[64] (2005).

Centre of Health promotion model from the University of Toronto

The centre of Health promotion model from the University of Toronto was born as a model to explain the HRQoL related to disease in general, but it was often considered in cancer studies[62,65]. According to this model, HRQoL depends on 3 areas regarding the person: the being, the belonging, and the becoming.

The **being** represents what the person is. It is composed by physical being (e.g., if the person does exercise or the level of individual physical health), psychological being (e.g., the quality of the cognitions and of psychological health), and the spiritual being (e.g., the individual spiritual beliefs and personal values)[61,62].

This model, considers also environmental aspects grouped in a dimension called belonging. **Belonging** represents the connections with one's environment. It is composed by physical environment (e.g., the connections of the individual with the neighbourhood), the social belonging (e.g., the connections with the friends), and the community belonging (e.g., if the person has an adequate income)[61,62].

The **Becoming** is the third area that is composed by practical becoming (e.g., if the person has the aspiration of starting volunteer activity), leisure becoming (e.g., if the person wants to do activities that promote relaxation), and growth becoming (e.g., if the person adapts to changes)[61,62].

The relations among these three areas are not explained by the authors, and, for how this model is represented graphically[65], it seems that the areas of the model[61,62] independently influence the HRQoL perception.

Ashing-Giwa's model

Ashing-Giwa's model[63] considers all the possible dimensions that can define the HRQoL, included from the wider systemic level to the individual one. Both levels include different components that define the HRQoL: in the macro-systemic level, there are the socio-ecological, cultural, demographic and health care system components, whereas in the micro/individual level, there are general health, cancer specific medical factors, health efficacy and psychological well-being components.

The Ashing-Giwa's model was ideated specifically for the oncological context. Indeed, the variables mentioned in this model are important variables to be considered in research on cancer patients' HRQoL: for example, among the medical factors, age at diagnosis and cancer

characteristics (e.g., the cancer stage, and the treatments patients underwent influencing the HRQoL). Regarding "age at diagnosis" variable considered in this model, indeed, the HRQoL of the younger patients is not the same as the elderly ones[66].

In addition, it is known that undergoing different cancer treatments during cancer can have different effects on HRQoL. For example, in a study conducted in 2018 about the measurement of HRQoL in prostate cancer patients undergoing AS (which doesn't imply active treatments) or prostatectomy with a period of 3.5 years follow-up, some HRQoL differences have been found over time according to the treatment type chosen[67]. Comparing the HRQoL measurements at baseline and after one year, it resulted that the radical prostatectomy patient group had lower levels of global health, emotional, role and social functioning then AS patients[67]. After one year of follow-up, in these dimensions, the two groups showed the same HRQoL levels, with the exception of the social functioning dimension (that for radical prostatectomy group remained lower than for the AS group)[67].

In this model several other context and components impacting HRQoL are considered, and they are summarized in the table 1:

Table 1. Context and components of HRQoL according to Ashing-Gina's model

Context	Components	Sub-components
Macro/systemic level		
Socio-ecological	Socio-economic status	Income, education, employment
	Life burden	Living situation, neighbourhood character & resources, day-to-day strain
	Social support	Emotional, instrumental, social networks
Cultural	Ethnicity	Region of ancestral origin(s)
	Ethnic identity	Level to which ethnicity & cultural heritage defines
	Acculturation	Language, choice of media, social network and practices
	Interconnectedness	Quality & pressure of family life & social relationships
	Worldview	Attitudes and beliefs
	Spirituality	Faith based beliefs and practices
Demographic	Chronological age gender	
Health care system	Access to health care	Cost, insurance, availability of medical centres
	Quality of health care	State of the art, satisfaction with care
	Quality of relationship	Compassion, communication, involvement
Micro/Individual level		
General health	Health status	Disease status, comorbid illness
Medical factors	Cancer characteristics	Stage, surgery, chemotherapy, radiation
	Age at diagnosis	Age at diagnosis
Health efficacy	Motivation & know-how	Health practices, utilization, perceived health efficacy, medical adherence
Psychological well-being	Level of functioning	Depression, anxiety, meaning, resolve

Talking about these last two HRQoL models, you can make several comments.

Differences between the models

The individual and systemic levels are more detailed in the Ashing-Giwa's model, which is a more complex model than the previous one. In the Ashing-Giwa's model, many more dimensions were introduced to define factors influencing the HRQoL, such as the cultural aspects, as well as social support which are not mentioned in the HRQoL model of the University of Toronto[65].

In particular, the social support can be an important factor to consider in the researches on the HRQoL since its positive effect on it in cancer has been demonstrated[68].

Moreover, "growth becoming" factor of the HRQoL model of the University of Toronto didn't appear in the Ashing-Giwa's model. The factor of personal adaption to changes (in this case, the cancer-related changes) was not presented among the dimensions of the second HRQoL model. In a possible chronic pathology, as the cancer is, the way the person adapts to the cancer-related changes can affect the HRQoL and must be considered. In psycho-oncology, to help patients better psychologically adjust during the illness and to have a better HRQoL, psychologists can work on the patients' personal resources used to face the stressful situations (coping strategies).

Points in common between the models

One point of strength of these models (the University of Toronto and the Ashing-Giwa's HRQoL model) is that several levels of factors impacting the HRQoL are considered: the biological, psychological and social levels. This common characteristic can be considered as taken from the biopsychosocial framework, where an individual phenomenon (in this case the HRQoL) can be explicated by the interaction of different types of factors.

The biological and psychological levels are in the "Being" factor of the Toronto University HRQoL model and in the "micro/Individual level" of the Ashing-Giwa's model. While the social level was considered in the "Belonging" factor of the Toronto University model, and in the "macro/systemic" level of the Ashing-Giwa's model.

In psycho-oncology it is important to consider both the individual and the social level, in particular for the organization of psychological interventions that can be focused on HRQoL

improvement. Today several psychological interventions are made on cancer patients' families and couples, since working on the families/couple of the cancer patients (e.g., on their relation between the members during the pathology, or on their management of the diagnosis) can be supportive for the families/couple, but also for the individual (e.g., during and after the psychological intervention the patient can improve social connections with the family/couple and receive more social support from them). Furthermore, in research and in medical communication the systemic point of view can often enrich patient's point of view regarding the evaluation on the pathology (e.g., the description of the patient's state of health and functioning).

These 2 last models (Ashing-Giwa's and University of Toronto's HRQoL models) have also one point of weakness. Since the relations among the several factors included are not explained (e.g., Can factors have a direct and an indirect effects on the HRQoL?), it is not possible to have an idea of how their effect on the HRQoL is (e.g., if a mediation among factors influencing the HRQoL may exist) or how the HRQoL changes over time.

In the following models, reported here as the last ones, the relations among the factors considered explicitly appear, in contrast with the previous models.
As reported in two recent reviews[51,65] on the most widely used HRQoL models, the Wilson and Cleary's model (1995)[51,69,70] has been extensively considered on the cancer patients' HRQoL literature. Ferrans et al. (2005) have supplied a modified version of this former model[64].

Wilson and Cleary's model

The HRQoL's Wilson and Cleary model[59] was conceived to provide clinicians a way to better analyse HRQoL using a causal model that includes 5 levels: biological and physiological factors, symptoms, functioning, general health perception, and overall QoL (Fig.2). These factors are in a continuum of increasing complexity and are all influenced by the individual and the environmental characteristics; with the exception of biological and physiological factors. Although the model was proposed in 1995, some interesting aspects highlighted by the model are still valid today.
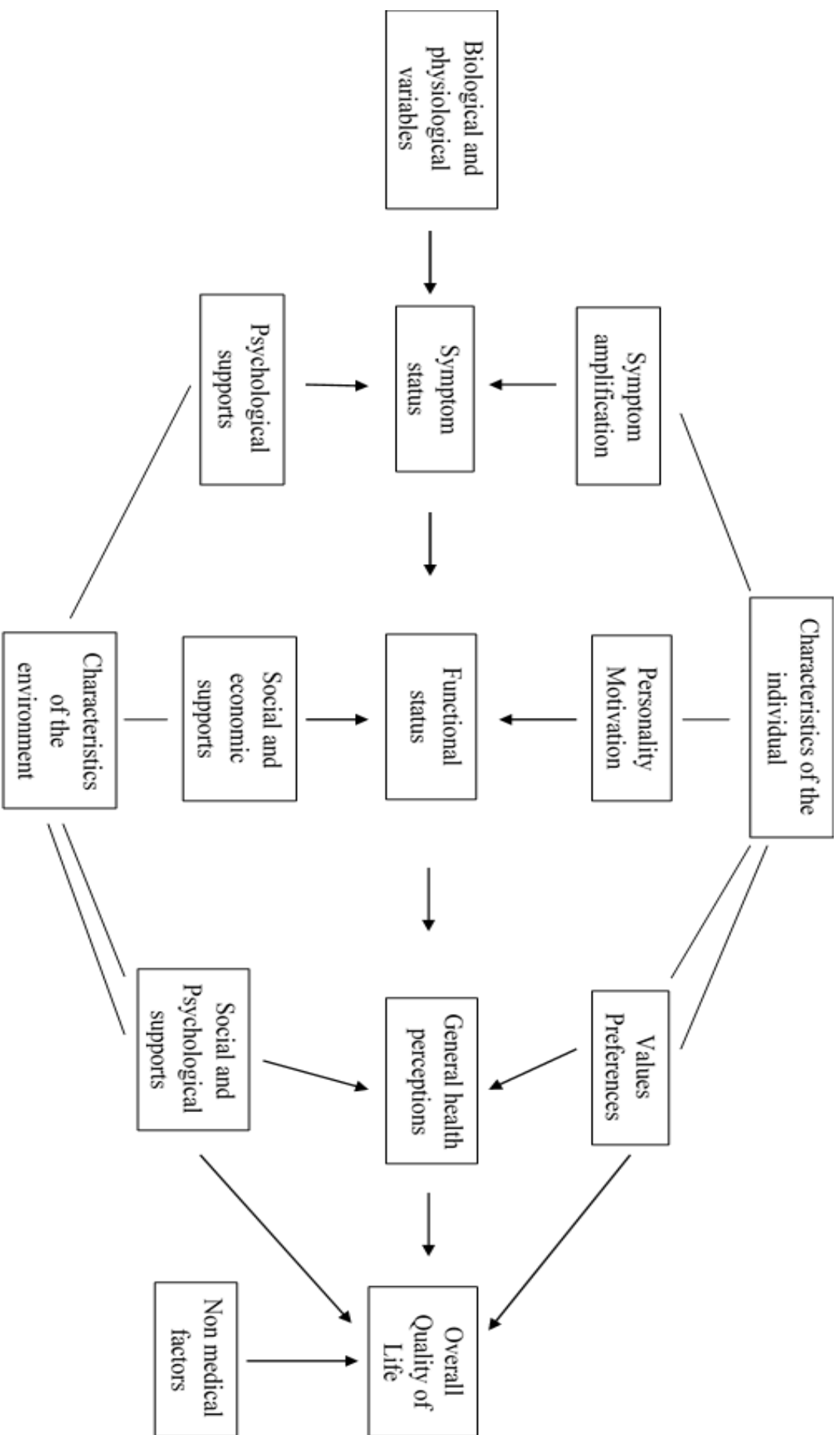
Figure 2. Relationships among measures of patient outcome in a health-related quality of life conceptual model. In Wilson, I. B., & Cleary, P. D. Linking clinical variables with health-related quality of life. *Jama. 273*(1), 59-65 (1995).

The following HRQoL-related factors appear in this model:

- Biological and physiological factors: everything related to the functioning / malfunctioning of the cells and organs system that has an influence on health, and that can be measured by doctors within healthcare systems.

- Symptoms: unlike biological and physiological factors involving organs and cells, when we talk about symptoms we focus on the person perception. A symptom is defined as the patient's perception of an abnormal physical, emotional and cognitive state. It is precisely the perception of the symptom that encourages the individual to self-refer to the institutes of care for assessments and diagnoses, and that determines the cost of interventions and health services.

- Functioning: the personal capability to perform defined tasks. In general, the literature addresses at least four areas: physical, social functioning, role functioning and psychological functioning[59].

- General Health Perception: the perception of health in general concerns perceptions of all the aspects mentioned so far (functioning, symptom, biological and physiological factors).

- Overall Quality of Life: is a holistic measure of HRQoL. Sometimes the authors have used it interchangeably with Quality of Life [59].

- Non-medical factors: changing expectations and aspirations. HRQoL may be influenced by these changes of expectations and aspirations during the life; e.g., if you are not satisfied with your health, changing your expectations can help you feel better.

- Individual characteristics: individual characteristics have an impact on "symptoms", "functioning", "perception of health in general", and "quality of life in general" (e.g., amplification of symptoms, personality, motivation, values and preferences).

- Environmental Characteristics: there are three elements of the environment (the social, economic, and psychological support that the patient has) that impact on "symptoms", "functioning", "perception of health in general", and "Quality of life in general". In this model

psychological support has an impact on symptoms, social support on functioning, while both have an effect on the "perception of health in general", and on the "Quality of life in general".

This model has several **strengths**.

In fact, this model considers the environmental characteristics and the support offered to patients (social, economic, and psychological support) as important factor to be taken into account for HRQoL measurement. In particular, financial support can influence patient-reported functioning (e.g., accessing medical care. For example, having the possibility access medical care to treat one's lymphedema in the arm or legs can alter the person' functioning. Lymphedema is a potential side effect of breast cancer surgery and radiation therapy that can occur in some people during months or even years after the end of treatment[71]), as well as social support of the environment (e.g., friends who drive the patient to the grocery store).

Individual characteristics are also taken into account in the Wilson and Cleary HRQoL model (e.g., hopes, expectancies, values and preferences). For example, according to the authors[59], people may have, among other individual characteristics, values and preferences that may influence their General Health perception and therefore their HRQoL.

For instance, the authors[59] reported that in a study with prostate cancer patients undergoing prostatectomy, with acute post-operative symptoms, some patients were reported not complaining about daily prostate limitations (32%), while others showed concern for their health (19%)[72]. This study shows, according to the authors[59], that although the prostate limitations due to the urinary retention are objective, each patient gives them a different subjective value. Individual characteristic may lead to different perceptions of health and HRQoL in different individuals.

This model has also some **weaknesses**.

The specifications of the environmental and individual characteristics are not always explained in detail[59], and it seems confusing.

The psychological and social supports (environmental characteristics) that influence symptoms perception, General Health perceptions and HRQoL, as well as symptom amplification, and personality/motivation (individual characteristics) that are supposed to have an influence on symptom and functional status, are not explained in the authors' article[59]. Some questions therefore remain unanswered. Among the characteristics of the environment: Does any

difference exist between the psychological support that has an impact on the symptoms and on the General Health perception/HRQoL?

While, among the characteristics of the individual, how does symptomatic amplification of the symptom status work? What are the individual characteristics involved? Perhaps some personality characteristics or age may be involved in the symptom amplification?

Moreover, as a second point of weakness, it is difficult to understand the difference between individual characteristics and non-medical factors. For example, hopes can be considered both a personality trait and a situational status[73]. Where can they be placed in the model? Moreover, the patients' needs, can take place in the model either among nonmedical factors, the motivational aspects (individual characteristics) as they are precious representations that stimulate the individual in their daily activities.

In conclusion, in this model the specifications of individual and environment characteristics and the division of the nonmedical factors / individual characteristics are not very clear. This is a model that considers a type of relations among the dimensions (causal relations), but it is not a simple model.

In order to improve the model of Wilson and Cleary and to overcome its weakness, Ferrans et al.[64] made some changes to the previous model[59].

Ferrans, Zerwic, Wilbur and Larson's HRQoL model

The model of Ferrans, Zerwic, Wilbur and Larson[64], like the previous model, had the objective of explaining the factors influencing the HRQoL, defined as subjective well-being.

In this model, as in the Wilson and Cleary model[59], the expression "Overall Quality of Life" is used in place of HRQoL. The first visible difference from the previous model is that the specifications of the environmental and the individual characteristics were removed. The other revised points are the following:

1. Biological functioning is now influenced by both individual and environmental characteristics (in the previous model these influences on biological functioning did not exist).
2. Since the authors[64] shift the emphasis to the possibility of measuring the HRQoL, questionnaires for measuring each different factor are included in Ferrans et al.' article[64].

3. The functional status here is described more in depth.

4. The influence of non-medical factors on HRQoL was deleted. The "non-medical" factors could also be included among the individual or environmental factors.

In Fig.3 there is the representation of the Ferrans et al.' model[64].
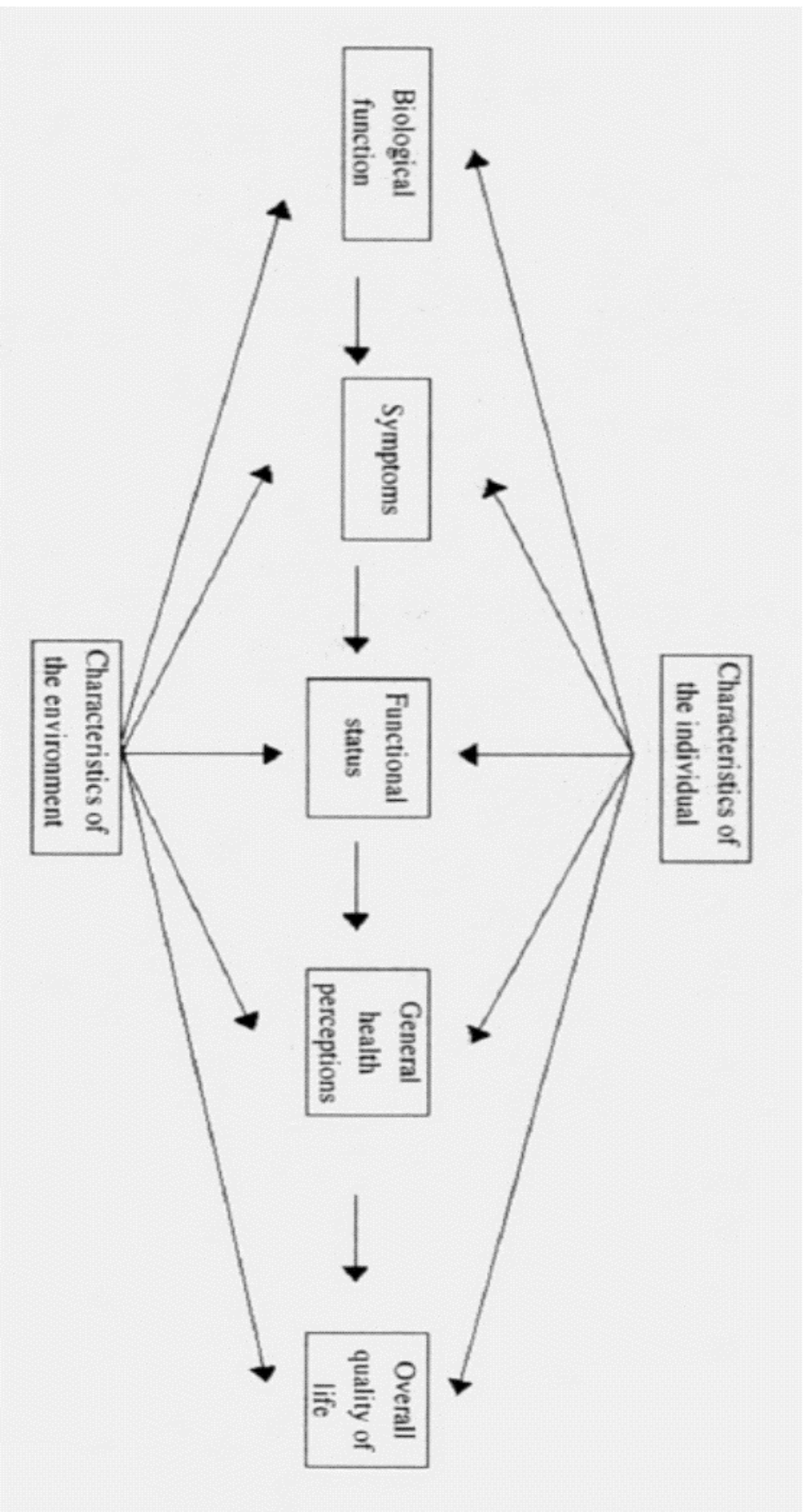
Figure 3. Ferrans et al. model of HRQoL (2005). In Ferrans, C. E., Zerwic, J. J., Wilbur, J. E. & Larson, J. L. Conceptual model of Health-related Quality of Life. *J Nurs Scholarsh.* 37(4), 336-342 (2005).

25

According to the authors there are 4 patient dimensions in this model, as in the previous model[59], that have the same meaning: biological functioning, symptoms, functioning status, and general health perceptions. In the following points, the points of difference with the Wilson and Cleary's HRQoL model will be developed.

1. **Biological functioning is now influenced by both individual and environmental characteristics.**

   Differently from Wilson and Cleary's model, the influence of environmental and individual characteristics on biological functioning was added in this model [59]. How can we imagine this influence? A good example could be the difference between tobacco smokers who develop lung cancer (biological modification), and those who do not. The smokers, indeed, can have different individual characteristics, such as the genetic predisposition to develop the tumour, and different environmental characteristics, for example, living in a family in which people close to the patient are smokers, or in a city where the pollution is high.

2. **Questionnaires for measuring each type of factor are included.**

   The authors reported several questionnaires with which it is possible to measure the HRQoL dimensions. To measure patients' perceptions, "Symptom-specific measures" questionnaires that investigate the presence of specific symptoms such as depression, exist. An example of the "Symptom-specific measures" questionnaires is the Hospital Anxiety and Depression Scale[74].

   Moreover, the global health perception and the functional status can be measured with the SF-36 Health Survey[75], and the Overall Quality of Life with the Quality of Life index[76].

3. **The functional status here is described more in depth.**

   Regarding the functional status definition, Ferrans et al. focused more than Wilson and Cleary[59] on the optimization of the function that remains during a pathology (Wilson and Cleary[59] gave it a more general definition: it was considered as the ability to perform tasks in multiple domains such as physical, social, role, and psychological function). In order to describe it more in depth, Ferrans et al.[64] refers to the Leidy framework[77] which divides the functional status into 4 dimensions: functional capacity, functional performance, functional capacity utilization and functional reserve. The first is the

potential ability of the individual to carry out a physical, social, psychological or cognitive task using the maximum of his/her abilities. Functional performance is the concrete performance of the individual on a daily basis, and can be determined by motivation, values and personal choices. The functional performance could also be influenced by functional capacity, as in cases when reduced capacity limits performance of day-to-day activities[64]. The capacity utilization is the percentage of functional capacity that is effectively used during the day; while the fourth dimension, the functional reserve, is the difference between the capacity utilization and the functional capacity.

4. **The influence of non-medical factors on HRQoL was deleted.**

The fact that the non-medical factors were deleted and considered as individual or environmental characteristics, simplifies this model.

Is it the best model in psycho-oncology?

The Ferrans's model, in relation to other models presented here, can be considered probably the most fitting in the study of the HRQoL in psycho-oncology setting for the following reasons.

1. The type of dimensions considered in the model and their causal relationship with the HRQoL.

The Ferrans et al.'s model includes important sub-dimensions for cancer patients in the HRQoL definition, such as biological, psychological and social sub-dimensions. This is due to the fact that the biopsychosocial framework influenced the definition of this model.

The sub-dimensions that today are used to study and measure the cancer patients' HRQoL are included in the model (functioning, symptoms, global health, QoL perception): for example, in the EORTC QLQ-C30, a frequently used research tool for measuring HRQoL in cancer patients, the sub-dimensions of social, role, physical, emotional and cognitive functioning, global health, and several symptoms are all considered.

Moreover, the Ferrans et al.'s model offers a map of the aspects to take into consideration for a psycho-oncological intervention for the HRQoL increase (e.g., the study/reinforce of the patients' environment, evaluations of the functioning status, patient' health perceptions, individual characteristics, such as the patients' needs, income, etc.).

The causal relationships among the variables included in the Ferrans et al.'s model in cancer have been tested by Rodriguez et al.[263]. They evaluated if this model can be applied to cancer patients with several types of primary tumour sites (pancreatic, lung, colorectal, breast, prostate, ovarian, etc.) by defining indicators for each dimension of the Ferrans et al.'s model.

In particular, the indicators have been defined for the following dimensions of the Ferrans et al.'s model:

- biological and physiological (e.g., C-reactive protein serum concentration levels, the presence of sarcopenia, body mass index, the skeletal muscle index),
- symptoms (i.e., gastro-intestinal symptoms, energy, pain, psychological wellbeing),
- functioning variables (e.g., physical, psychological function, social and cognitive functions),
- individual characteristics (i.e., age, sex, education, cultural background and number of comorbidities) and
- environmental characteristics (i.e., social support, marital status and number of children).

The result of the Rodriguez et al.[263]'s study showed that social support, general health perception, energy, social function, psychological and physical functions were the most important contributors for the overall HRQoL.

Biological and physiological aspects, not showing significant impact on the overall HRQoL in the Rodriguez et al.[263]'s study, resulted correlated to it in the Innominato et al.'s study performed some years before. This study conducted on colorectal cancer patients showed a correlation between the circadian rhythm parameters (biological indicators) and the HRQoL [264].

In conclusion, significant relationships between the dimensions of the Ferrans et al.'s model and the overall HRQoL have been found, and this suggests that Ferrans et al.'s model can be applied to cancer. An interdisciplinary approach could be necessary in further studies on HRQoL improvement in cancer.

2. The simplicity of the model

The causal relations between the dimensions considered and the deletion of some of them let the HRQoL definition more clear.

3. The conception of HRQoL as changing variable

Differently from the previous models, Ferrans et al.[64] considered and little explained change of HRQoL. They mentioned, in fact, that during significant life events, cognitive, affective and

behavioural processes (e.g., coping, goal reordering, reframing expectations, social support, etc.) used to accommodate the illness[64], together with the individual characteristics preceding the life event (e.g., sociodemographic characteristic), can cause internal changes in standards and values that can lead to changes in HRQoL[78]. In this model, the authors talked about cognitive variables that, together with other characteristics, can influence the HRQoL over time. The arrows of this model let us think that these relations with the HRQoL might be direct.

Among the cognitive resources that can be useful for the resilience of patients, in the cognitive and behavioural oriented psychological support, it is possible to work on several aspects in the psycho-oncological setting. Among these, the locus of control, namely the patients' beliefs about their health, and the coping strategies, strategies used by patients to deal with the stressful situations related to cancer. Due to the importance of the relations of these variables and the HRQoL in psycho-oncology, we tried to better define these concepts in the following chapters.

1.5. Locus of control

1.5.1. *Locus of Control definitions*

The Locus of Control (LOC) is a concept that concerns the beliefs that the events are under the control of external factors and/or internal factors.

The definition of this concept has changed over years as several authors over time have tried to highlight different characteristics. The following LOC models presented generally discussed three points:

1) If the LOC is a personality trait (stable) or if it changes over time;

2) The number and the type of factors composing the LOC;

3) If these LOC factors are mutually exclusive or not (i.e., If it is possible to have one or several control beliefs on the same event).

The first author to start talking about Locus of Control was Rotter[79] in 1954. According to his Social Learning Theory of Rotter[79], the LOC is a **characteristic of personality**, a stable individual characteristic (part of the personality) that can't change over time. For the author[79] there is a relation between the individual (with his/her characteristics and personality) and the environment. The environment can act on individual actions and behaviours by reinforcements, so that the individuals reproduce those actions that have a positive gain for them.

The LOC, according to Rotter[79], was composed of **two factors**: the internal and the external LOC. People having the belief of internal LOC, believe that their own actions determine the positive reinforcement situations, while those having the belief of external LOC believe that the positive reinforcement in life are generally outside of their control.

The two factors, internal and external, were considered **mutually exclusive**, in the sense that one person could have the belief of internal or external LOC, but not both at the same time[80]. It is the initial LOC perspective.

In 1974, Levenson like Rotter[79], considered that the LOC was a personality trait and could not change over time[80].

He hypothesized that the LOC was a **multidimensional construct** composed by more than two factors (instead of Rotter's proposal[79]), i.e., Chance externality (belief that the situations of reinforcement are due to chance), Powerful others externality (belief that the reinforcements

are due to others who have power), and Internality (belief that the reinforcements are due to the individual). Moreover, Levenson[80], unlike Rotter[79], also proposed that the person may use different beliefs to explain the reinforcement situations: these situations could be controlled by himself/herself, and/or by chance, and/or by others as well (i.e., **the LOC beliefs started to be considered as not mutually exclusive**).

Like Levenson[80] and unlike from Rotter[79], the authors reported below, Wallston[81] and Pruyn[82],considered the LOC as a multidimensional construct, and composed of not mutually exclusive factors [81–83].

Moreover, Wallston[81] imagined that the LOC was a personality trait (as the Rotter's Social Learning Theory reported), whereas Pruyn[82] imagined that the LOC was a construct that can change over time (as the Folkman and Lazarus's transactional theory of stress[84] reported).

The fact that the LOC can change over time has to be taken into consideration in the oncological setting. Indeed, cancer is a possible degenerative disease that can lead to changes in health over time, and it is plausible that the perception and the belief of control may change[81].

1.5.2. *The LOC in the field of health and psycho-oncology*

In 1978 Wallston et al.[85] introduced the concept of LOC **in the field of health**. The focus of the authors[85] has shifted from the explication of the reinforment situations (as it was in Rotter[79]), to the health situations. According to the authors[85], the LOC regards the explication of one's health condition. According to them[85], the LOC is composed by 4 factors: internal LOC (i.e., the belief that one's health condition depends on oneself), chance LOC (i.e., the belief that one's health condition depends on chance), powerful others LOC (i.e., the belief that one's health condition depends on other people), and religious LOC (i.e., the belief that one's health condition depend on God)[85]. The chance, powerful others and religion LOC factors are types of external control. External control here means that one's health condition is out of the individual control.

Pruyn in 1988[82,83], used the concept of LOC in the **field of psycho-oncology**. To give more space to the fact that different beliefs there can be at the cancer diagnosis and during the illness, the author highlighted the LOC beliefs timing (at the diagnosis and over the illness). In particular, he suggested that LOC was composed by the following dimensions: Control over the course of the illness (i.e., the patient' belief that himself/herself or other people have control

of his/her own health), internal causal attribution (i.e., the belief that they are responsible for the onset of the disease), and religious control (i.e., the belief that God has control over the onset and the progression of the disease).

Among the items of the "Control over the course of the illness" factor of the Cancer Locus of Control Scale ideated by Pruyn[83], there are some items on internal LOC such as "I can influence the course of my illness by fighting against it", and items on external control, such as "My spouse/partner or family can definitely influence the course of my illness". Also chance LOC (external LOC factor) was included in this factor. Cousson-Gélie[83], the author who validated the French version of this questionnaire, used the phrase "perceived control over the illness" in order to group several items on different types of LOC beliefs that the patients can have during the course of the illness.

In this work, differently from the work of Wallston et al.[85], the attention was to the events related to the oncological pathology and not to health in general. Moreover, here the authors underline the temporal dimension: the construct of control is considered at the time of diagnosis ("internal causal attribution" factor), and during the course of the illness ("control over the course" factor). The only external LOC sub-dimension considered by Cousson-Gélie[83] as a single factor with one type of LOC belief is the religious control dimension, that includes items about the possible influence of God on the onset of the pathology and over the course of the illness.

LOC over time in cancer

There can be different beliefs regarding the onset of the illness in different types of cancer.

At the time of diagnosis, for example, there may be different beliefs on the illness onset that arise from internal causal attribution. In a sample of 471 breast cancer patients, for example, the main causal attributes identified were lifestyle-choices (63%), genetics/heredity (34%), and environmental-exposures (19%)[86].

For melanoma patients, exposure to ultraviolet radiation, heredity/genetics, phenotype, and personal history of melanoma can be perceived as the causes of illness[87].

Since the illness causal attribution is a representation, it may change over time. It can be modified in different ways, including social influences (e.g., media campaigns) and educational, psychosocial, and self-management interventions[88].

Over the course of the illness, patients' perception of control may change and, in particular, can decrease over time[89,90]. For example, it has been shown that low level of control was the most common issue reported by breast cancer patients before and after surgery[89,91], but also in cancer patients who were assessed at various points after diagnosis[89] compared to non-patients.

In addition, in a heterogeneous sample of cancer patients, it was evidenced that the perceived control decreased during 1 year following diagnosis[89]. During the course of the pathology, cancer patients can use potentially adaptive cognitive mechanisms to achieve a higher level of perceived control, including positive illusions and re-evaluating other aspects of life[89].

Psychological intervention techniques

Since cancer patients can have dysfunctional beliefs, psychological support focused on the change of LOC beliefs may be necessary.

It is possible to work using the "situational reconstruction" technique (i.e. an imaginative task designed to suggest alternative ways of thinking about the stressor that may provoke a broadened perspective and a deepened understanding)[92,93]. For example, it may invite the patient to think about himself reaching a goal he never actually reached. In this imaginative situation, the patient feels that the goal is reachable, and he/she can analyse the strategies used. Once these strategies are analysed, the patient can use/re-use them in other situations. If the efforts of situational reconstruction are unsuccessful, it is possible to use the technique of "focusing"[94], with the objective of recognizing the emotional reactions that interfere with the imagination (i.e., reflection on body sensation of emotional upset)[92,93]. Moreover, in order to increase the perceived control, mindfulness (method based on techniques focused on the awareness) can be beneficial[95].

Psychological support of control beliefs can increase HRQoL and patients' resilience as well. Resilience, indeed, is the capacity of dealing with the stressful and traumatic period. For doing so, it can be useful also to work on the coping strategies. For example, if the patient's hope is "to be free from cancer" after a diagnosis of low-risk cancer, the psychologist, if the aim is considered appropriate, can help the patient to reach this goal. The psychologist can help the patient by using positive and useful coping strategies (for example, developing an action plan to reach the objective), but also by increasing the belief that the patient has the power of reaching this goal by his/her own actions. In this way, the patient can increase compliance with the therapy, attend all radiation appointments, read articles on cancer prevention and treatment, participate in a cancer support group or clearly communicate any new symptoms to their oncologist. In the next chapter coping strategies are explained in depth.

1.6. Coping

1.6.1. *Coping and the defence mechanism*

Today coping is defined as "the cognitive or behavioural efforts used to deal with a source of stress"[96]. Coping is also an emotional, cognitive and behavioural response of a patient, a complex mental process by which a person deals with stress, solves problems and makes decisions[97].

It was originally defined as a type of defence mechanism (i.e., mental mechanism that alters the perception of reality[98]. e.g., the removal of a traumatic memory), but then it started to be considered by some authors as a different concept[99].

Regarding defence, in the 1890's Freud wrote about the existence of unconscious mechanisms of defence that were activated in pathologies such as hallucinatory psychosis, hysteria and obsession in response to a situation that is difficult to bear by the patient (e.g., repression of threatening or disturbing sexual thoughts in hysteria)[100,101].

The coping, instead, was firstly defined by Lazarus and Folkman[84] one century later, as a process in which individuals appraise potential stressors and develop maladaptive and/or adaptive coping strategies to manage the situation. So coping was not considered by these authors[84] as a defence mechanism.

The different positions of the literature regarding the characteristics of coping and defence mechanisms have generated a debate related to the question of whether they should be considered as the same concept. In the past, defence seemed to be more linked to psychopathology and psychoanalysis, while coping was more connected to adaptation[102], and to cognitive-behavioural theories[103].

Cramer[98,104] highlighted the differences between defence mechanism and coping in the psychological processes involved: the awareness and the intentionality. Although they are two adaptation processes, coping strategies differ from the defence mechanisms because, for the author, they consist in intentional and conscious processes[98] whereas the defence mechanisms are unconscious and unintentional[98].

1.6.2. *Coping definitions in psycho-oncology*

Although there are possible links between coping and defence mechanisms, in oncological research settings, they are separate concepts. Coping is presented more as a pool of strategies with an adaptive function, as it is reported in the theory of Lazarus and Folkman[84].

Lazarus and Folkman[96] introduced two categories of coping: emotion and problem-focused coping.

Emotion-focused coping strategies have the aim of managing the emotional distress that is associated with a situation[84]. The strategies included in this category are denial, distracting yourself, emotional disclosure (venting of emotions), praying, using drugs, positive reinterpretation of events, and seeking out social support (e.g., for emotional reasons).

Problem-focused coping strategies have the aim to manage the stress in practical ways trying to reduce it. The coping strategies of this category are problem-solving, and instrumental social support (e.g., for practical reasons, such as bringing the patient by car to the hospital).

Carver[105] divided the problem-focused coping into several coping strategies, such as active coping, planning, suppression of competing activities, restraint coping, seeking of instrumental social support; and the emotion-focused coping as well, in seeking emotional social support, positive reinterpretation, acceptance, denial, and turning to religion. Moreover, the author[105] added 3 other scales which are focusing, behavioural disengagement and mental disengagement.

These are the most used coping strategies categorization.

Why is there interest for coping in psycho-oncology?

The psycho-oncological research literature tries to find a way to help patients reach a better health state, making way for the possible psychological evolution and growth of the patient over the pathology (e.g., as in positive psychology literature)[106]. In fact, coping strategies are studied and proposed to patients for their adaptive function in several psychological interventions that aim to help cancer patients for stress management and to enhance HRQoL.

Nowadays there are several types of psychological interventions that offer a way to work on patients' coping strategies, such as stress coping skills training[107,108], Cognitive Behavioural Therapy[109], Acceptance and Commitment Therapy[110] (a type of Cognitive Behavioural Therapy), and so on.

1.6.3. *Coping can change over time*

The coping can change over time. A coping model, highlighting this, is the cognitive-transactional model of Lazarus and Folkman [84]. According to this model (Fig. 4), coping strategies can be resources activated by the person after having evaluated the stressful situation. Does the person, according to this theory, make a first evaluation of the situation (**primary appraisal**) in which the stressful situation is analysed, and in particular, whether the situation may lead to a possible benefit or harm (e.g., Does the situation represent a damage or a benefit for me? For my self-esteem? For a one loved person?)[111]? It consists of the analysis of the stressful situation (e.g., factors that caused the situation, if there is the motivation for fighting the situation, etc.)

In the second evaluation (**secondary appraisal**) the person starts to consider what she/he can do to cope with the threat and what possible resources can be used to face the situation. What is my control of the situation? Do I have the abilities to deal with the situation and control it?

After this secondary appraisal, the possible coping strategies to use in order to not proceed in an impulsive or unproductive way are evaluated, such as acceptance of the situation, its alteration, information seeking, etc[111].

The theory of Lazarus and Folkman can be considered as process and context oriented. Process-oriented means that the coping is activated in a process that starts with the cognitive appraisal of the stressful situation[111].

Context-oriented means that the coping strategies are activated in specific situations with specific stressful circumstances. Since the situations can change each time, coping is considered as a construct that **can change over time**[84].

Coping is a dynamic process that evolves according to endogenous and exogenous factors (the available internal resources and the type of external situation, respectively), and to the evaluation of the menacing situation[112,113]. As Folkman and Lazarus wrote in the 1984[84]: "we define coping as constantly changing cognitive and behavioural efforts to manage specific external or internal demands that are appraised as taxing or exceeding the resources of a person" (p.141). This process focuses on the adaptation, the health status and well-being improving, and it seems particularly useful since it expresses the relation between coping and HRQoL.
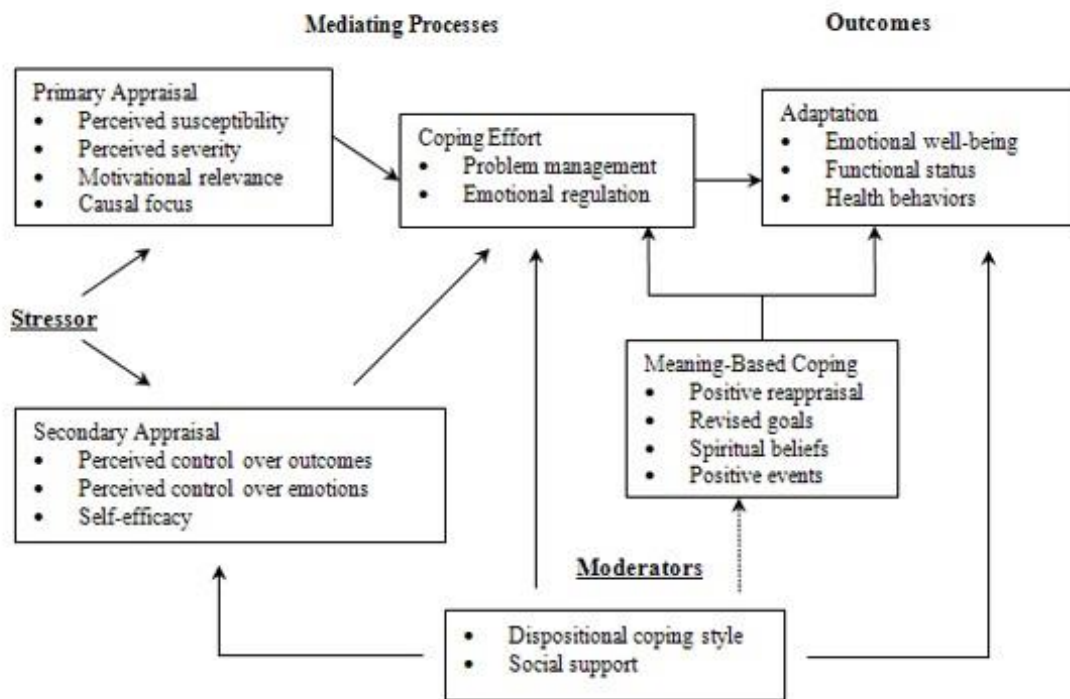
Figure 4. The representation of the model of Lazarus and Folkman. In Lazarus, R. S. (1966). Psychological stress and coping process. New York: McGraw-Hill

As it appears in this model, the way the people adapt to the stress depends not only on the coping efforts, the different coping strategies that can change according to the stressful situation (situational coping), but also the dispositional coping style (dispositional coping). The latter is a habitual way of dealing with stress (e.g., the attitude of using active coping strategies).

Situations, such as cancer diagnosis, can cause several changes in patients that activate different coping strategies to face them.

Moos and Schaefer in 1986 proposed another model (Fig. 5) called the life crises and transitions model[114]. It is considered an integrated model because it comes from several theories such as evolutionary theory, psychoanalytic concepts and life-cycle development approaches to crisis theory. The crisis, according to the authors, is something temporary as the events that can occur in life (such as a disease diagnosis) and can cause several changes to patients, such as[115,116]:

Changes in identity: from healthy person to patient;

Changes in location: from home to hospital, if the patient must be hospitalized;

Changes in role: from independent to dependent as a patient;

Changes in social support: illness can affect the level of socialization, and can bring the individual to isolation;

Changes in the future: the future, as though before the event, can become uncertain.

There are several types of coping strategies that help the person to adapt to a crisis event. They can be structured in three groups such as

Appraisal-focused coping, composed by strategies that allow to manage the situations by the thought, cognition and so by modifying the cognitive meaning of the event. For example, in this category there are cognitive redefinition, and cognitive avoidance or denial strategies, that consist in positively redefine the situation (the situation is not totally a personal loss, but can have some positive consequences for the person), and in avoiding it, respectively.

Another group of strategies is the **problem-focused** coping group, which is composed by strategies that are focused on solving problems in a practical way. Some examples of strategies of this group are seeking information, taking problem-solving action and identifying alternative rewards.

- Seeking information and support, and logical analysis, used to restore a sense of control and to prepare themselves mentally to go over the problem using the thought.
- Taking problem-solving action strategy to face the crisis or its consequences. The latter is a strategy that allows to solve problems and have a sense of self-esteem and competence.
- The strategy of identifying alternative rewards can consist in changing activities that can reward the person after that she/he has had a loss due to the crisis. For example, a way to have an alternative reward in an unalterable situation (a situation in which you don't have the power to change it, as the illness of a parent), is to see other people managing negotiating in similar crisis or transitions[117].

The last strategies group is the **emotion-focused** group, which is composed by strategies, such as affective regulations, emotional discharge and resigned acceptance strategies, that allow managing feelings related to the event.

- Affective regulations strategy regards the efforts to maintain hope and control of the emotions during a stressful situation. For example, in a dangerous situation this strategy allows you to react in a calm manner without reacting impulsively.

- Emotional discharge is a strategy according to which the person vents negative feelings such as anger and desperation (for example, after the news of a diagnosis). This strategy is tension-reductive, such as smoking.

- Resigned acceptance is a strategy that allows accepting a situation that can't be changed. For example, when a parent is going to die, this strategy help the person to mitigate the stress, since accepting the situation, the person can detach him/herself emotively from the situation[117].

General determinants of outcome

Resolution Phase

Ultimate outcome

Background and Personal factors

Event-related factors

Physical and Social Environmental factors

Cognitive Appraisal (Perceived Meaning of Event)

Adaptive Tasks
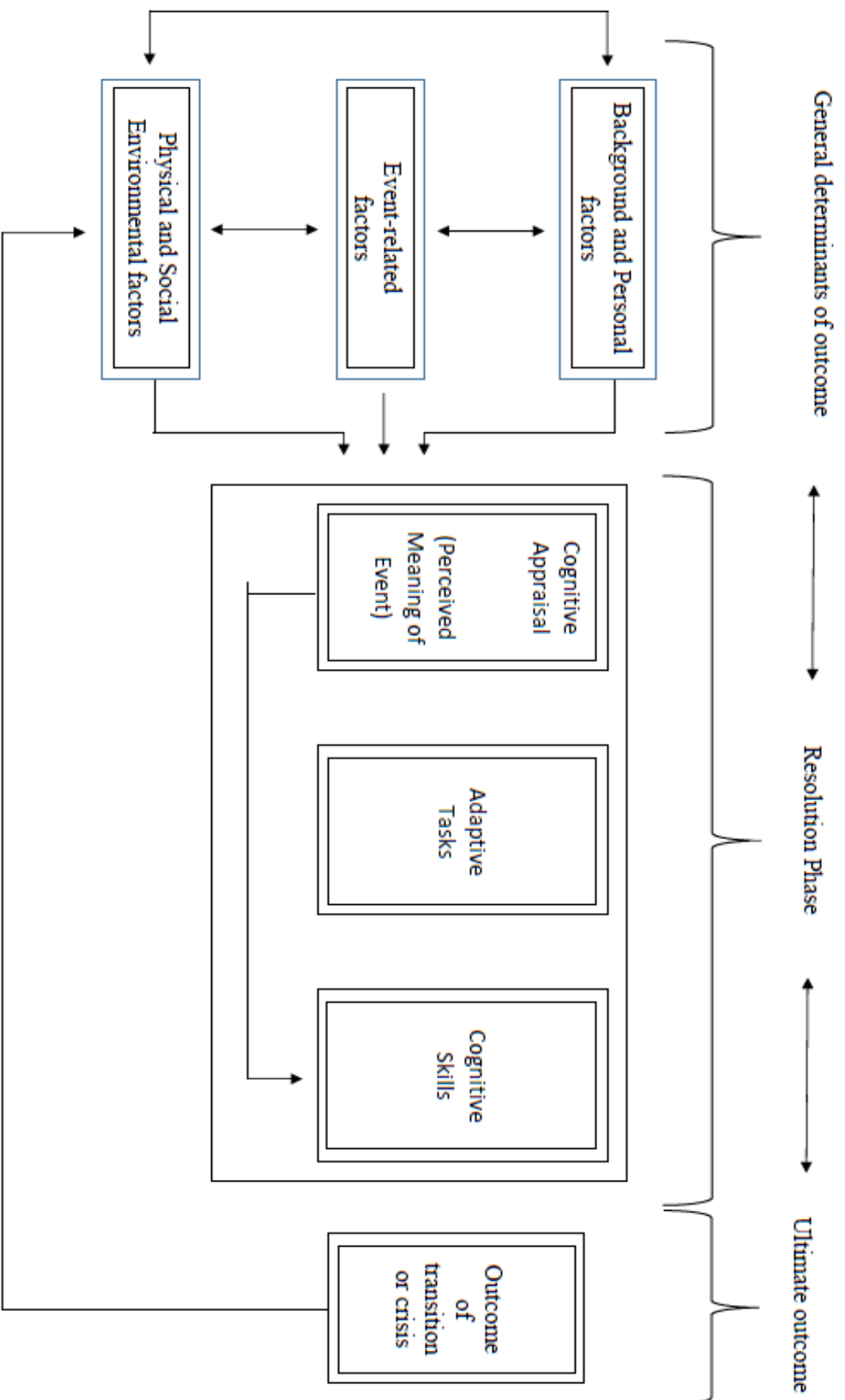
Cognitive Skills

Outcome of transition or crisis

Figure 5. A conceptual model for understanding life crises and transitions. The integrated model of Moos and Schaefer. In Moos, R H & Schaefer, J A. *Coping with life crises. An integrated approach*. p.20 (Plenum Press, 1986).

40

As we have seen in the model of Lazarus and Folkman[84], and Moos and Schaefer[114]the coping was considered, because of its adaptive role, as a precious resource in case of stressful events and situations that helps the person to overcome their problems, or to face them, doing practical, cognitive or emotional efforts.

So, because of their adaptive role, coping strategies are important tool to use in psychological intervention in oncology where there are many stressful situations. After cancer diagnosis, for example, patients try to manage the impact of the disease and make the reality more acceptable via the domains of cognitions, affects and behaviours[118,119]. So it results necessary to work with the patients on coping strategies in order to help them maintain/improve their psychological health.

For example, a possible way of psychologically working on coping strategies is to propose some adaptive coping strategies, such as positive reappraisal, using the ABC (Activating Event, Belief, Consequence) Technique of Irrational Beliefs of cognitive therapy[93,120]. It consists in showing the irrational nature of some maladaptive/dysfunctional thoughts and replacing them with more positive and adaptive ones[121].

If it is possible to use religious coping, instead, it can propose meditation or yoga, also to cancer patients[93,122,123].

In psychological works, it is possible to work together on control beliefs using coping strategies to promote the adoption of adaptive behaviours/thoughts and by extension improve HRQoL. In the next chapter the relation between control, coping and HRQoL will be discussed.

1.7. The cognitive-behavioural processing from the diagnosis and over the illness adaptation: the HRQoL, coping and locus of control

As Lazarus and Folkman have shown in their cognitive-transactional model (Figure 5), patient adaptation and well-being can be influenced by a process including the evaluations of the situations, and coping strategies used to face the situations. The relation described in the model is a mediation between the cognitive appraisal that influence the adaptation by an effect mediated by the coping.

In cancer literature about LOC, coping and HRQoL, the relation among these variables is often studied, since coping strategies and the patients' beliefs can be precious tools to use for the HRQoL improvement by psychologists.

Several researches (that will be presented below) have shown that the association between coping, LOC and HRQoL exists both in cross-sectional and in longitudinal studies over time in cancer.

Relation between the LOC and HRQoL

In a cross-sectional study on breast cancer patients at different stages of the pathology, for example, internal and external LOC were associated with functional HRQoL, in a positive and negative way respectively[124], whereas in a longitudinal study with breast cancer patients during 4 years after diagnosis, perceived control was associated with patients' mental and physical functioning[125].

Relation between LOC and coping

The LOC has been found to have a relation with the coping. For example, the belief of responsibility for the onset of cancer ("internal causal attribution") has been found to be related with the self-blame in breast cancer[126], whereas perceived control seems positively correlated with active coping strategies, such as fighting spirit[127]. Moreover, Cousson-gélie found a positive correlation between perceived control over the illness, internal causal attribution and emotion and problem focused coping in breast cancer. In the same study, religious control was negatively associated with perceived stress[83].

Relation between coping and HRQoL

In a recent randomized study on breast cancer patients[128], a coping training of 8 weeks changed patients' HRQoL level (measured by the EORTC QLQ C30 questionnaire). In particular, it has been found that the functional (role functioning and emotional functioning), symptomatic

(fatigue), and general health scales changed positively for patients who underwent the coping training intervention. The coping strategies changed after the training coping program were acceptance, planning, positive reframing, active coping, and using emotional support.

Relation between LOC, coping and HRQoL

In a cross-sectional study[129] on a sample of breast and colorectal cancer patients with cancer duration from one to three years, patients' internal LOC was positively correlated to positive thinking (optimistic coping), and facing up the problem (confrontive coping); whereas the external LOC was positively associated with pessimistic thinking (fatalistic coping). In the same work, the external LOC (Chance) resulted negatively related to mental health as measured by the SF-36, and the Internal LOC was positively associated with the global overall score of HRQoL of SF-36[129].

Relation between LOC, coping and HRQoL over time

Although perceived control has a positive effect **over time** and is related to positive coping strategies, some have argued that there are situations where perceptions of internal control are actually detrimental to HRQoL[130] such as at the time of cancer **diagnosis**. In this period, the beliefs of internal control regarding the diagnosis, the internal causal attributions, can be associated with the self-blame, and together can be deleterious for the HRQoL[126,131,132].

In addition, the relation between the self-blame and the HRQoL over time was found as well: in the study of Paek in 2016, the self-blame, measured at the time of diagnosis, was negatively correlated with the HRQoL measured between 0 and 8 months post-diagnosis[133].

Like the internal LOC that can be deleterious or not according to the timing (perceive control at diagnosis can be deleterious unlike the perceived control over the course of the illness), the avoidance coping strategies can have different effect according to the timing in which they are used. Denial, for instance, can be adaptive in the short term (e.g., after a stressful situations can be positive to go out and not think about it), but maladaptive in the long term (i.e., it can impede you from finding information and solutions for the problem being avoided it).

Longitudinal studies, differently from cross-sectional studies, can help us to find how this relation between these variables (LOC, coping and HRQoL) evolves over time. A part from the studies done, there are some elements that let us think that the relation between LOC, HRQoL and coping could evolve in different ways over time. First of all, HRQoL in cancer can

positively and negatively change over the pathology: e.g., it is possible to observe a recurring reduction of HRQoL in cancer after initial improvement over time, called rebound effect. This particular HRQoL trend can be observed in cancer for different HRQoL dimensions, such as emotional, role, social and sexual functioning[134]. So it is possible to imagine that since the association between LOC, coping and HRQoL exists, the changes in coping strategies usage or in patients' beliefs can be associated with HRQoL changes over time.

Moreover, we can imagine that this association can be different according to patients with different types of cancer that can adapt in different ways over the illness. In breast cancer and melanoma patients, for example, different HRQoL trends have been observed[66,135]. So it is possible that, in these cancer types, HRQoL, LOC and coping can be differently associated over time.

Anyway, today the lack of the literature on the association among HRQoL, LOC and coping variables over time on a long follow-up, and on the HRQoL trends comparison between cancer types over time impedes us from having the information regarding how psychologists can work in a different manner according to the timing during the cancer illness, and according to cancer type.

1.8. Main objectives

In different types of cancer with similar prognosis at early stage, such as breast cancer and melanoma, there can be different HRQoL trends[66,135], maybe because of the different treatments and side effects these patients undergo, and/or related to the different psychological burden due to the illness (see chapters 1.2 and 1.3).

Because of these different HRQoL trends, psychologists need to know what can be the tools to use to help patients to stay better. The LOC and coping strategies are psychological variables that can be associated with the HRQoL, and psychological aspects to work on during the daily work of psychologists in order to increase patients' HRQoL.

Although it has been shown that there is a relation between the psychological constructs of LOC, coping and HRQoL (see chapter 1.7), longitudinal studies remain rather scarce and sometimes the short follow-up period does not allow assessing how variables and their association change over time.

The patients' beliefs can also have a role in important shared decisions in clinical practice[136].

In the era of shared decision medicine, understanding how the treatment choice is made between AS and more radical treatments (RTs) and its repercussions on HRQoL can give more insight into which aspects of the physician and of the clinical and psychological characteristics of the patients intervene in that decision and their association with HRQoL change.

The first objective of this thesis was to explore, within the longitudinal ELCCA study, if an association between coping and LOC changes, and HRQoL changes exists over time in breast cancer and melanoma patients on a follow-up of two years.

The second objective of this thesis was to explore, within the START study, whether different patients' and physicians' characteristics are associated to prostate cancer treatment choice at the time of diagnosis (RTs versus AS) and the repercussions of this choice on medical and psychological outcomes over time on a follow-up of two years.

2. MATERIAL AND METHODS

2.1. Patient-Reported Outcomes (PRO)

The aim of Patient-Reported Outcomes (PRO) instrument is to gather patients' perceptions directly from the patient themselves without using interpretations by clinicians or others; although sometimes a proxy person is asked to fill in the PRO when the patient cannot answer (e.g. in paediatrics or for cognitively impaired patients)[137]. As such, most PRO instruments are self-administered questionnaires (although some of them are semi-structured or structured interviews). They usually take the form of single- or more often multi-item measurement scales where one (or more) item(s) can be grouped into one (or more) dimension(s). Ordinal response items is the most common type of items encountered in health science. When the ordered response levels are numbered 1 in 1, the response format is called Likert[138]. The items' responses can also be presented as a Visual Analogue Scale[139].

In health-related research, the range of concepts and outcomes that are covered by PRO is broad and lastly, since the early 1980's[140], a lot of PRO are now designed to assess concepts related to impairment through the measurement of the level of symptoms or to assess concepts such as QoL, or HRQoL[141]. Some PRO instruments are intended for general use, irrespective of the illness or condition of patients and they may also be used with healthy people. They are generic questionnaires to measure HRQoL[142]. As they intend to cover a wide range of conditions, they can be used to compare QoL levels between medical conditions or against the general population[140,141,143,144]. Nevertheless, they can fail to cover very specific aspects of the impact of a particular disease on one's HRQoL and can be less responsive to change than more disease-specific questionnaires[139]. Thus, a lot of disease-specific questionnaires have been developed. An example of one of the most used disease-specific questionnaire is the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30[145]) which focuses on cancer specific aspects.

2.2. Measurement and Analysis of Patient-Reported Outcomes

Several approaches have been proposed for the analysis of PRO among which the Classical Test Theory (CTT)[146], the Rasch Measurement Theory Models[147], Item Response Theory Models[148], Structural Equation Models[149], etc. All these measurement theories describe the relationships between the items and the concept one is trying to measure (e.g., HRQoL). The theories are distinguished in particular by the analysis of the responses observed to the questionnaire. Classical Test Theory (CTT) is the most commonly used measurement theory that was also used in this work to perform the analyses and interpretation of the results.

Under the CTT, the measure we usually use is a manifest (observed) variable called the score. The observed score is taken to be an appropriate representation of the level of a concept we want to measure (e.g., HRQoL). The score is a combination of the responses to all items (global items) or items within a given dimension. Usually, this combination is simply the sum or mean of the responses to the items (sometimes with different weights applied to each item). CTT makes it possible to apprehend a latent observed variable through the analysis of observed variables considered as representative of the latent variable of interest (e.g. HRQoL). CTT provides ordinal measures of the latent trait.

In CTT, according to the study design (cross-sectional, longitudinal), t-tests or non-parametric tests, regressions models, mixed or hierarchical models can be used for a CTT analysis based on the observed scores.

CTT analysis was used in the two projects included in this thesis because the instrument used to measure cancer patients' HRQoL, the EORTC QLQ C-30, was validated in Italian and French languages using this type of analysis[145]. IRT models couldn't be used in this specific case because of the sample size of two patients' subgroups (<80). Larger samples could be required in multidimensional IRT analysis with polytomous items response options in order to have a good estimation of the items parameters. For example, in case of responses options on Likert scales and in case of multidimensional questionnaires (e.g., EORTC QLQ-C30), where the fitting model could be the Multidimensional Graded Response Model, 500 cases are required to provide accurate parameter estimations[150,151]. Moreover, for longitudinal IRT models, the sample size needed for a good parameters estimates can increase as the model complexity increases[152].

2.3. Mixed models

Longitudinal designs are often used in clinical and epidemiological research to assess the change of a patient's HRQoL between, for instance, the diagnosis of a pathology and the end of treatment. For this purpose, the same PRO instrument is repeatedly completed by the patient over time. This repetition of the same measurement on the same individuals generates correlations that have to be accounted for.

Linear mixed models allow considering fixed (mean trajectory of the individual over time) and random (deviation of each individual from the mean trajectory) effects as well as taking into consideration the repeated measurement (correlation among measurements of the same patient). These are characteristics that make mixed model appropriate to use with longitudinal data.

Linear Mixed models are often used in physical, biological, and social sciences. In particular, this method is mostly used when there are repeated measurements in longitudinal studies or when there are measurements on clusters of statistical units.

The distinctive characteristic of linear mixed models is that the mean response of the individual is the combination of populations' characteristics that are assumed to be shared by all individuals, and subject-specific effects. The effect due to the characteristic population shared by all the individuals is called fixed effect, whereas the subject-specific effect is called random effect and it has a specific probability distribution (often normal). This type of models are called mixed as both the fixed and the random effects are considered in the model[153].

2.3.1. *The model*

Linear mixed model can be written as follow.

Let

n_i be the number of observations of patient i, $i=1...N$ and $M = \sum_{i=1}^{N} n_i$ be the total number of observations

p and k be the number of fixed and random effects, respectively

Y_i be the $(n_i \ x \ 1)$ vector containing the scores of the patient i

X_i and Z_i be the $(n_i \ x \ p)$ design matrix characterizing the fixed part of the model and $(n_i \ x \ k)$ design matrix characterizing the random part of the model, respectively

β be the $(p \ x \ 1)$ vector of fixed effects parameters

b_i be the $(k \ x \ 1)$ vector of random effects parameters, $b_i \sim N_k(0, D)$

e_i be the (n_i x 1) vector of error terms, characterizing variation due to within-unit and measurement error sources, $e_i \sim N_{ni}(0, \mathbf{R}_i)$

Σ_i be the (n_i x n_i) covariance matrix

$b_1, \ldots, b_N$, $e_1, \ldots, e_N$ are assumed to be independent

$$Y_i = \left(Y_i^{(t)}\right)' = X_i\beta + Z_ib_i + e_i$$
$$var(Y_i) = Z_iDZ_i + R_i = V_i$$
$$Y_i \sim N_{ni}(X_i\beta V_i)$$

It means that the response for the ith subject at the tth occasion $Y_{ij}^{(t)}$ is assumed to differ from the population mean (given by $X_i\beta$) because of the subject effect, b_i, and the measurement error, e_{ij}[153].

2.3.2. *Estimation of the parameters*

The parameters to be estimated in the model are the mean parameters $\boldsymbol{\beta}$ that characterize the mean and the covariance parameters $\boldsymbol{\omega}$, the parameters that makes up V_i. The parameters can be estimated using the REstricted Maximum Likelihood (REML) method in order to reduce the bias on covariance parameters in comparison to the use of Maximum Likelihood (ML) estimation.

2.3.3. *Structures of the variance and covariance matrix*

The correlation between measurements of the same patient measured across different occasions in linear mixed models is taken into account by specifying the structure of the variance-covariance matrix.

The variance and covariance matrix (V_i) can have different structures[154]:

Compound symmetry

In this matrix all the observations Y_{ij} at each time have the same variance that is equal to σ^2, and all the measurement times are assumed to be all equally correlated (ρ).

$$
\begin{bmatrix}
1 & \rho & \cdots & \rho \\
\rho & 1 & \cdots & \rho \\
\vdots & \vdots & \ddots & \vdots \\
\rho & \cdots & \rho & 1
\end{bmatrix} \sigma^2
$$

Number of parameters to estimate: 2

Heterogeneous Compound symmetry

The structure is similar to Compound symmetry structure, but it considers different variance at each time.

$$
\begin{bmatrix}
\sigma_1^2 & \sigma_1\sigma_2\rho & \cdots & \sigma_1\sigma_j\rho \\
\sigma_2\sigma_1\rho & \sigma_2^2 & \cdots & \sigma_2\sigma_j\rho \\
\vdots & \vdots & \ddots & \vdots \\
\sigma_j\sigma_1\rho & \sigma_j\sigma_2\rho & \cdots & \sigma_j^2
\end{bmatrix} \sigma^2
$$

where j represents the jth occasion

Number of parameters to estimate: J+1 where J is the total number of measurement occasion

First-order autoregressive

This structure has homogeneous variances and correlations among the times that decrease when the observations get farther apart from each other in time.

$$
\begin{bmatrix}
1 & \rho & \rho^2 & \cdots & \rho^{j-1} \\
\rho & 1 & \rho & \cdots & \rho^{j-2} \\
\rho^2 & \rho & 1 & \cdots & \rho^{j-3} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
\rho^{j-1} & \rho^{j-2} & \cdots & \rho & 1
\end{bmatrix} \sigma^2
$$

where j represents the jth occasion

Number of parameters to estimate: 2

Heterogeneous first-order autoregressive

The structure is similar to first-order autoregressive structure, but it considers different variance at each time.

$$\begin{bmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho & \sigma_1\sigma_3\rho^2 & \cdots & \sigma_1\sigma_j\rho^{j-1} \\ \sigma_2\sigma_1\rho & \sigma_2^2 & \sigma_2\sigma_3\rho & \cdots & \sigma_2\sigma_j\rho^{j-2} \\ \sigma_2\sigma_1\rho^2 & \sigma_3\sigma_2\rho & \sigma_3^2 & \cdots & \sigma_3\sigma_j\rho^{j-3} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \sigma_j\sigma_1\rho^{j-1} & \sigma_j\sigma_2\rho^{j-2} & \sigma_j\sigma_3\rho^{j-3} & \cdots & \sigma_j^2 \end{bmatrix}$$

where j represents the jth occasion

Number of parameters to estimate: J+1

Unstructured matrix

This structure is characterized by unconstrained parameters.

$$\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \cdots & \sigma_{1j} \\ \sigma_{21} & \sigma_2^2 & \cdots & \sigma_{2j} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{j1} & \sigma_{j2} & \sigma_{j3} & \sigma_j^2 \end{bmatrix}$$

where j represents the jth occasion

Number of parameters to estimate: J (J+1) / 2

2.3.4. *Goodness-of-fit indices*

For identifying the best model using linear mixed models, several indices can be used.

One of these is the AIC (Akaike Information Criterion)[155,156] that says how much the model fits the data (goodness-of-fit). Another goodness-of-fit criterion is the BIC (Bayesian Information Criterion) which is similar to AIC: the model with the lowest AIC or BIC will be preferred among the models with different random effects, and with different variance and covariance matrices as well.

The AIC formula is the following:

AIC= -2(maximized log-likelihood) + 2(number of parameters)

The BIC is equal to:

BIC= -2(maximized log-likelihood) + log N (number of parameters)
where N is the number of subjects

2.3.5. Goodness-of-fit criteria for the variables selection in the final models

Variables selection in the final model can be based on AIC but also on R^2 statistic[157]. It quantifies the percentage of variability of the independent variable explained by the model[157]. The method to calculate this R^2 is based on a Wald test F statistic that will be explained as follows.

Nullity of some parameters of the fixed effects can be tested with a F-test.

For a matrix L, the F-test can be written as:

$$H_0: L\beta = 0 \; versus \; H_1: L\beta \neq 0$$

$$W = (\hat{\beta} - \beta)'L'\left[L\left(\sum_{i=1}^{N} X_i'V_i^{-1}(\widehat{\omega})X_i \right)^{-1} L' \right] L(\hat{\beta} - \beta)$$

Under H_0, W/rank(L) has an approximate F distribution with rank(L) being the numerator degrees of freedom and v denominator degrees of freedom. The number of denominator degrees of freedom for the tests of fixed effects can be approximated by Satterthwaite[158] or Kenward-Roger[157] methods amongst others with SAS Proc MIXED.

The method for the evaluation of goodness-of-fit of fixed-effect covariates in linear mixed models using R² statistic is relatively new. Amongst different R² statistics in linear mixed models[159], the R² statistic proposed by Edwards et al. [160] is simple to implement as it can be computed with results from the model of interest. This R² measures multivariate association between the repeated measures and the fixed effects for a given covariance structure and helps comparing mean models (i.e. different fixed effects) with the same covariance structure. In fact, the proposed R² is simply defined using an approximate F statistic for a Wald test of fixed effects.

$$R^2 = \frac{(q-1)v^{-1}F}{1 + (q-1)v^{-1}F}$$

The model of interest (full model) with q-1 predictors in the fixed effects is compared to a null model with only the intercept in the fixed effects and the same covariance structure so that R^2 relies on a F-test of the null hypothesis $H_0: \beta_1 = \beta_2 = \cdots = \beta_q - 1 = 0$. F is the statistic of the Kenward-Roger F-test computed during the fitting of the model of interest and ν are the associated denominator degrees of freedom.

The AIC, the R^2 and the p-value of the F-test can be used together for the variable selections. Anyway, R^2 differs from the p-value of the F-test, which instead, takes into consideration the effect of the single independent variable on the dependent variable. The R^2 [157], instead, has the advantage of taking in consideration the effect of all the covariates together.

2.4. The Logistic Regression

Since the logistic regression model can be used in case of dichotomous variables, it is used for estimating the probability of having success or not, or that an event will happen or not (e.g., active cancer treatment choice or not).

The estimation of the probability of this binary response is based on one or more predictor (or independent) variables[161].

2.4.1. *The model*

The Logistic regression is characterized by having a binary or dichotomous variable as outcome, and it estimates the logit of the probability of having values 1 and 0 (the probability of success/failure, or that an event there can be or not), depending on the values of the explanatory variables X=$(X_1, ..., X_k)$. The specificity of the logistic regression, differently from the linear regression, is the fact that the regression part of the model, i.e., a linear combination of the values of the explanatory variables and the regression coefficients, is a logistic transformation of the probabilities of the response categories.

The logistic transformation is given by the function:

$$y = \ln\left(\frac{x}{1-x}\right)$$

The values of y are always between 0 and 1 independently from the real values of x. In other words, this logistic function, called logit (the logarithm of the odd between the probability of success and probability of failure), assures that the response on the Y will be always included in the interval 0-1.

The logistic regression model is the following:

$$\text{Log}\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x$$

In this way, large positive values of the term $\beta_1 x$ will predict probabilities near 1, and large negative values of $\beta_1 x$ will predict probabilities near 0, without going outside the range of p (0, 1).

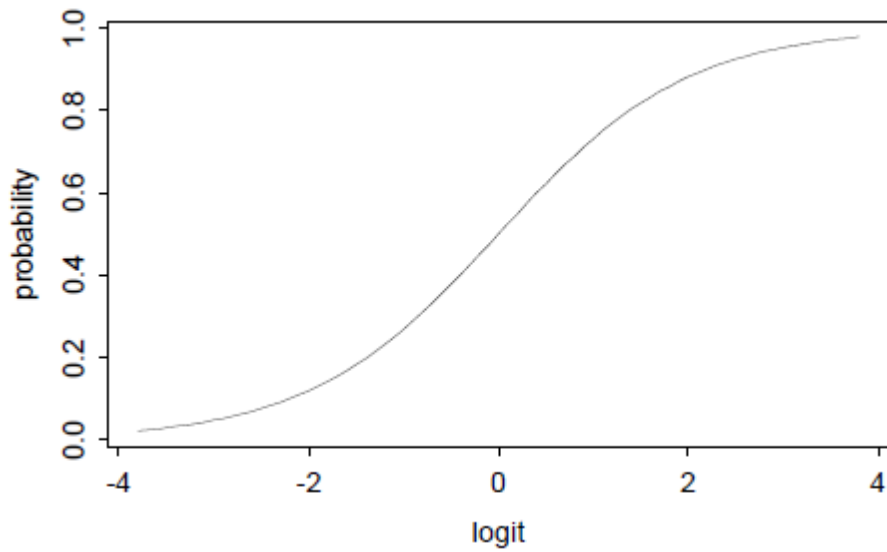The curve derived by the distribution function is said to be S-sharped as in figure 6.

Figure 6. Example of Logistic regression graph

2.4.2. *Estimation of the parameters*

In the logistic regression the independent variables can have an effect on the dependent variable quantified by **β** (see the last formula). It is the parameter to estimate for each of the K +1 covariates that are in the model. This is done with maximum likelihood estimation.

2.4.3. *Specificities*

Aside of the assumption of the dichotomous dependent variable, and the relation between this variable and the independent variables is a logistic function, in the logistic regression there are other assumptions. The error term (residuals) has a binomial distribution, and the homoscedasticity is not required.

Moreover, the logistic regression requires that the observations are independent of each other.

3. ELCCA STUDY

Abstract

Objective

Longitudinal studies assessing the association between coping, LOC, and HRQoL in breast cancer and melanoma patients are needed to identify the best supportive strategies and the best timing for initiating them, according to the type of cancer and the patterns of change. The objective of this study was to assess the association of coping and LOC changes, with change in HRQoL over time in breast cancer and melanoma patients.

Methods

The Brief Cope, Cancer Locus of Control Scale, EORTC QLQ-C30 were administered to newly-diagnosed breast cancer (N=215) and melanoma (N=78) patients at 1, 6, 12 and 24-months post-diagnosis.

Results

At baseline, HRQoL levels were almost always higher for breast cancer as compared to melanoma patients. In breast cancer, some HRQoL scores decreased steeply during the first 6 months, then slightly increased and remained mainly stable during the last year of follow-up, without reaching their baseline levels. By contrast, for melanoma patients, some HRQoL scores linearly increased or decreased over time. For both cancer types, the perceived control over the course of illness had a positive association with the HRQoL changes, and negative coping had a negative association. A negative association with the change of HRQoL was evidenced for internal causal attribution and emotional coping (breast cancer patients), and religious LOC (melanoma patients).

Conclusion

It seems that psychological therapies or support, that consider the patients' coping strategies and beliefs, should be specific according to the type of cancer and to the time post-diagnosis.

Keywords

Cancer; coping; health locus of control; Health-related quality of life; longitudinal data.

3.1 Background

Breast cancer is the most common cancer in women. Worldwide nearly 1.7 million of new breast cancer cases were diagnosed in 2012[162], and in France, almost 60000 new cases were observed in 2017[163]. In comparison, melanoma is not as frequent (132.000 melanoma skin cancers occur globally each year[164]), although its incidence is increasing each year. A better understanding of the experience of cancer patients using Patient-reported outcomes (PRO) to investigate perceived Health-related Quality of Life (HRQoL) is now deemed essential to assess treatment and health care effectiveness. Previous research, including one on the same sample of patients, suggests that breast cancer and melanoma patients do not experience the same level of HRQoL[66,135]. Melanoma patients seem to have higher levels regarding functioning dimensions (global health, physical, role, emotional, cognitive, social functioning) as compared to breast cancer patients 2 years after treatments initiation[135]. Moreover, the patterns of HRQoL change differ between these two cancer types with a delayed increase in global health, physical and role functioning dimensions for melanoma as compared to breast cancer patients[66]. Some hypotheses might be put forward. From a medical viewpoint, breast cancer patients undergo treatments that may cause potential physical disabilities, while melanoma patients often have less invasive treatments and side-effects. From a psychological viewpoint, breast cancer involves a part of the body that usually represents the femininity and sexuality of women[165], which might not be the case for melanoma patients (e.g. spots on the hand's surface). Hence the supportive care needs might differ during the course of illness for breast cancer and melanoma patients.

A diagnosis of cancer is a traumatic life event that can lead patients to question beliefs about themselves and about the future[166]. Patients will try to decrease, control or accept the impact of the disease on their physical and psychological well-being and make the reality more acceptable via the domains of cognitions, affects and behaviors[118,119]. Cancer patients' HRQoL is often related to psychological variables[167], like coping strategies and LOC beliefs[68,83,133,168–171] which are relevant variables to consider in psychological therapies for cancer support. Targeting perceived control and coping strategies may help patients to interpret their personal and interpersonal context, promote the adoption of adaptive behaviors and by extension improve their HRQoL.

Positive (e.g. acceptance) and negative coping (e.g. cognitive escape-avoidance) strategies were found to be positively and negatively associated with HRQoL respectively, in breast cancer patients[68,168,169]. The same associations with negative coping (e.g. behavioral disengagement)

were evidenced for melanoma patients; active coping and religious coping strategies were also negatively associated with negative cognitive functioning 2 years after diagnosis[171]. A high belief of internal causal attribution (i.e. self-attribution for illness beginning) at diagnosis was related to higher social functioning 2 years later for breast cancer patients[83]; perceived control over the course of the illness at time of diagnosis was positively associated to HRQoL 2 years later for melanoma patients[171].

These studies, however, did not consider coping, LOC and HRQoL longitudinally[68,83,168,169,171] although coping and control variables are situational process that might not be stable over time[84].

Longitudinal studies remain rather scarce and sometimes the short follow-up period does not allow assessing how variables change over time, how they are related to change in HRQoL, and so how to support cancer patients' psychological needs that can take time to appear. In the study of Paek et al.[133] in breast cancer, the measures were taken from the diagnosis to almost until 2 years later, but, as in Danhauer et al.[172], the authors considered the associations between coping and HRQoL at two distinct time points. It means that the analyses did not allow understanding changes in coping strategies and HRQoL and identifying how they are related. The results of the work of Peak et al.[133] suggested that the more the patients used negative coping strategies (denial, behavioral disengagement, and self-blame) in the first 0-8 months from the diagnosis the less their HRQoL at 12–20 months' post-diagnosis was. To our knowledge, no similar longitudinal studies focusing on coping or locus of control, and HRQoL have been conducted in early stage melanoma patients.

Assessing the association between coping, LOC, and HRQoL changes over time could help identifying the coping strategies and the cognitions that might be targeted in supportive therapies and their best timing for improvement of HRQOL in breast cancer and melanoma patients. It is also likely that breast cancer and melanoma patients should not be managed in the same way but in a more personalized manner for effective support.
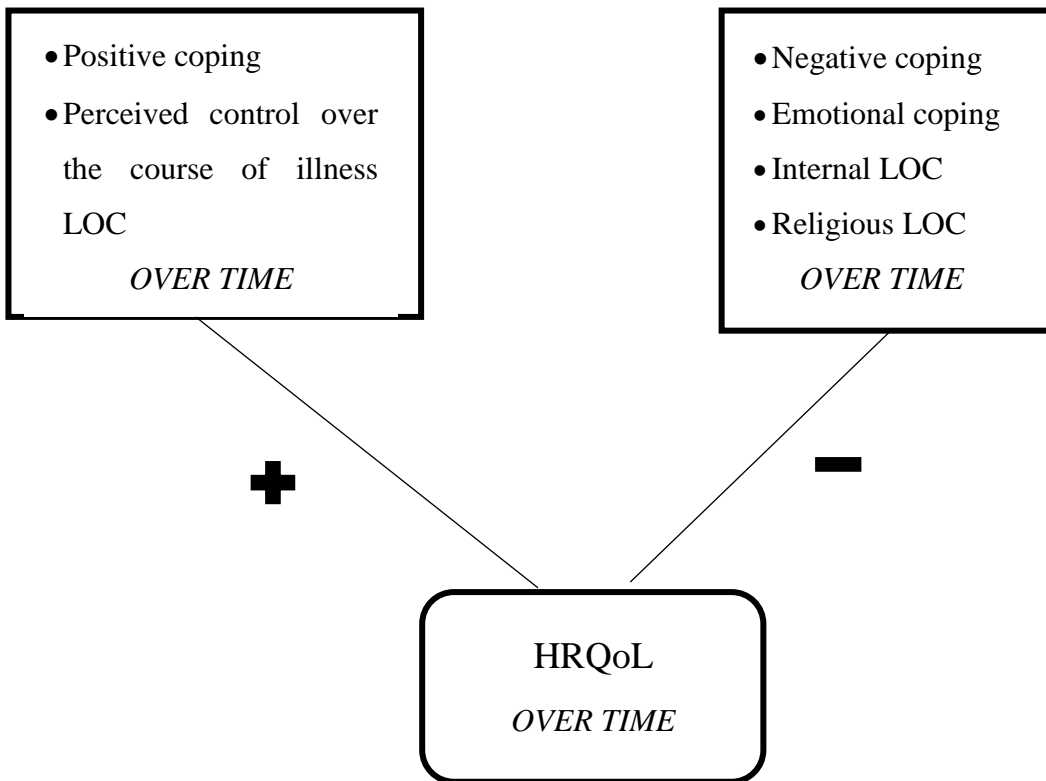
The aim of this study is to assess the associations between changes in coping and LOC, and changes in HRQoL and to compare these associations between breast cancer and melanoma patients.

This study started with some hypotheses regarding the types of associations between LOC, coping variables and the HRQoL over time, based more on breast cancer patients literature than melanoma patients one. No hypothesis have been done about the possible difference of these associations between breast cancer and melanoma patients and the comparison has been carried out in an explorative way. This is due to the fact that the comparison studies between the two

cancer groups are very few in this field, as well as the studies on the associations between LOC or coping variables and HRQoL in melanoma patients.

The assumed association types between LOC, coping and HRQoL over time are presented in the following schema. Positive coping and perceived control over the course of the illness could have a positive association with HRQoL dimensions over time, whereas emotional (i.e., using instrumental support, using emotional support, venting and religion), negative coping, religious LOC (i.e., the belief that God controls the illness, that resulted to be negatively associated with psychological adjustment in cancer[173]) and internal LOC could not.

Figure 7. Schema of the hypotheses:

3.2. Methods

Participants

The longitudinal ELCCA study aims at assessing the changes experienced by patients since diagnosis of breast cancer or melanoma in the Department of Onco-Dermatology (for melanoma patients) and a Cancerology Institute (for breast cancer patients) in Nantes, France. Patients diagnosed with a stage I or II (early stage, non-metastatic) cancer were eligible for the study. Among them, 220 breast cancer patients and 82 melanoma patients agreed to participate. Patients completed self-administered questionnaires within 1-month post-diagnosis (mpd), and 6, 12, and 24 months later. At each time point, HRQoL, coping, LOC, and sociodemographic variables (age, gender, living with a partner, education level and perceived standard of living) were assessed as well as medical information.

Measures

The EORTC quality of life questionnaire (QLQ-C30)[145] was used to assess HRQoL. This scale has 30 items and we focused on the 6 functioning dimensions measuring physical (5 items), role (2 items), emotional (4 items), cognitive (2 items), social functioning (2 items), and global health (2 items). These dimensions are composed of four or seven point Likert items and all the dimension scores range from 0 to 100. A higher score represents a higher level of HRQoL.

The Cancer Locus of Control scale[82,83] assesses the perceived control over the illness. This 14-item scale has 3 dimensions composed of four-point Likert items: perceived control over the course of the illness (6 items), internal causal attribution (5 items), and religious control (3 items). A higher score indicates a higher agreement (e.g. If I follow the advice of my doctor).

Coping strategies were assessed with the 28-item Brief Cope questionnaire[174,175] which measures 14 coping dimensions: active coping, planning, using instrumental support, using emotional support, venting, behavioral disengagement, self-distraction, self-blame, positive reframing, humor, denial, acceptance, religion, and substance use. Each dimension is composed of two four-point Likert items with a higher score indicating a higher use of a given strategy to deal with stressful life events.

Statistical Methods

The coping dimensions which were strongly related to each other were first grouped together using the clustering around latent variables method[176] to assemble the 14 dimensions into homogeneous clusters representing different latent variables. The coping dimensions which

were strongly related to each other were grouped together. The possible number of clusters was therefore between 1 and 14. The number of clusters for our analysis was determined by inspecting the dendrogram and identifying clinically meaningful clusters of coping dimensions. All coping dimensions' clusters and LOC scores were subsequently standardized between 0 and 100 to be on the same metric as HRQoL scores.

Changes of each LOC and clusters of coping dimensions were investigated with linear mixed models[155] by cancer type (see Appendix 1 for details). These models include fixed effects that characterize the mean behavior of the sample over time (intercept as mean value at 1 mpd and time variable to assess change) as well as random effects to model individual variation around the mean trajectory (possibly intercept and/or time in our study to model a different value at 1 mpd and/or change for each patient from the mean of the sample). The correlation between measurements of the same patient measured across different occasions is taken into account by specifying the structure of the variance-covariance matrix (see Appendix 1). For each variable (LOC dimension and coping dimensions' clusters) and each type of cancer, the addition of random effects and/or the choice of the structure for the variance-covariance matrix were based on the Akaike Information Criteria (AIC)[156] to choose the best fitting model. A significant time effect resulted in considering the corresponding LOC or coping variable as a time-dependent covariate in the following multivariate analyses, otherwise, their values at 1 mpd were used.

Before using LOC and coping variables as independent variables in the same model, Spearman correlations among these variables have been tested in order to avoid the multicollinearity and see whether they are independent each other. Spearman correlations were tested for each time of measurement among all the LOC and coping variables.

To assess the effect of coping strategies, LOC and sociodemographic variables on HRQoL changes, a linear mixed model was fitted on each dimension score for melanoma and breast cancer separately.

In addition to coping and LOC dimensions, age, level of education, perceived standard of living, living with a partner or not at 1 mpd were included into the fixed-effect part of the mixed model. As recommended, the fixed-effect part also included time and all potential interactions between LOC or coping covariates and time[177]. The inclusion of the main effects as well as interactions allow distinguishing between the mean effect of the covariate on HRQOL over time (main effect) and a change from the mean effect at a given time (interaction with time). The strategy for statistical analysis was as follows. First, the addition of a random intercept and/or time and

the choice of the structure of the covariance matrix were based on the AIC. Second, the fixed-effect part of the best fitting model was reduced by deleting first non-significant interactions and last non-significant main effects using the AIC, p-value of the Wald test and a specific R^2 statistic developed for mixed models[159] (see Appendix 1 for more details). SAS 9.2 Proc MIXED was used for the analyses.

3.3. Results

Participants' characteristics at 1 mpd are presented in Table 2. Overall, 78 melanoma patients and 215 breast cancer patients completed the questionnaires at 1 mpd. Patients were on average 51 and 53 years old, mostly lived with a partner (82.8% and 79.5%) for breast cancer and melanoma patients, respectively. Most patients had an education level higher than elementary school (83.6%) and declared to have an intermediate standard of living (80.5%).

Clusters of coping dimensions

According to the clustering around latent variables method, the 14 dimensions of coping were grouped into 4 clusters. Both the data from melanoma and breast cancer patients were considered together in this analysis. The first cluster, Negative COPing (NCOP), included behavioral disengagement, self-blame and denial. The second cluster Emotional COPing (ECOP) included using instrumental support, using emotional support, venting and religion. The third cluster Positive COPing (PCOP) included active coping, planning, self-distraction, positive reframing, humor and acceptance. Substance use alone constituted the fourth cluster.

Usage of coping and LOC dimensions

At 1 mpd, among the coping and LOC dimensions (Table 2), the perceived CONtrol over the course of illness LOC (CONLOC) seemed the strongest belief (on average 67.2 for breast cancer and 69.1 for melanoma) and the PCOP the most used coping strategy (on average 50.7 for breast cancer and 50.6 for melanoma). As substance use was very rarely used (on average 6.0 for breast cancer and 7.7 for melanoma), this strategy was not considered for the subsequent analyses.

Table 2. Characteristics of breast cancer and melanoma patients within 1 month post-diagnosis

	All the patients (N=293)	Breast cancer patients (N=215)	Melanoma patients (N=78)
	n(%)	**n(%)**	**n(%)**
Gender			
Female	246 (83.9%)	213 (99.1%)	33 (42.3%)
Male	45 (15.3%)	0 (0.0%)	45 (57.7%)
Missing data	2 (0.7%)	2 (0.9%)	0 (0.0%)
Living with a partner			
Yes	240 (81.9%)	178 (82.8%)	62 (79.5%)
No	51 (17.4%)	35 (16.3%)	16 (20.5%)
Missing data	2 (0.7%)	2 (0.9%)	0 (0.0%)
Education			
≤ Elementary school	44 (15.0%)	30 (13.9%)	14 (17.9%)
> Elementary school	245 (83.6%)	181 (84.2%)	64 (82.0%)
Missing data	4 (1.4%)	4 (1.9%)	0 (0.0%)
Standard of living			
High	36 (12.3%)	24 (11.2%)	12 (15.4%)
Intermediate	236 (80.5%)	175 (81.4%)	61 (78.2%)
Low	16 (5.5%)	12 (5.6%)	4 (5.1%)
Missing data	5 (1.7%)	4 (1.9%)	1 (1.3%)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age (years)	52.2 (9.9)	53.0 (8.6)	51.3 (12.7)
Coping dimensions			
NCOP	16.0 (15.6)	16.6 (16.6)	14.4 (12.1)
ECOP	36.0 (17.8)	38.2 (18.2)	30.4 (15.4)
PCOP	50.6 (16.6)	50.7 (17.4)	50.6 (14.4)
SUBUSE	6.5 (15.6)	6.0 (14.9)	7.7 (17.3)
LOC dimensions			
INTLOC	31.6 (21.2)	32.4 (21.9)	29.4 (19.5)
CONLOC	67.8 (19.6)	67.2 (20.5)	69.1 (16.8)
RELLOC	13.3 (21.2)	13.7 (21.4)	12.1 (21.0)

NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; SUBUSE: substance use; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control. Range of the coping and locus of control scores: 0-100

Longitudinal change in coping and LOC dimensions

The first analyses, stratified by cancer type, assessed whether coping and LOC changed over time (Table 3). For breast cancer patients, ECOP and CONLOC scores both significantly decreased over time (-2.2 and -1.0 on average from one time to another, respectively), whereas INTernal LOC (INTLOC) significantly increased (1.4 on average over time). For melanoma patients, NCOP significantly increased over time, whereas ECOP, PCOP and CONLOC significantly decreased.

All these covariates were considered as time-dependent for all further analyses. The variables not changing over time were considered as time-independent variables; their values at 1 mpd were used for all further analyses.

Table 3. Changing over time of the dimensions of coping and locus of control

Dimensions	Breast		Melanoma	
	Estimate	SE	Estimate	SE
NCOP	-0.1	0.3	0.2*	0.1
ECOP	-2.2**	0.4	-0.2*	0.1
PCOP	0.1	0.4	-1.4*	0.6
INTLOC	1.4*	0.4	0.0	0.7
CONLOC	-1.0*	0.4	-1.7*	0.7
RELLOC	-0.1	0.0	-0.6	0.6

* p-value for the test of nullity of the coefficient <0.05; ** p value for the test of nullity of the coefficient <0.0001. SE: Standard Error. NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control.

Spearman correlations among coping and LOC dimensions by each time and type of cancer

Since all variables were not normally distributed, non-parametric correlations (Spearman correlations) were used to test the independence among LOC and coping variables. Globally, significant correlations were not higher than .5. Lower significant correlations emerged between ECOP and RELLOC, and PCOP and CONLOC in both the two cancer groups at all the measurement times. The highest correlations emerged between PCOP and CONLOC for melanoma patients at 6 mpd (R=.498, p<.0001), and 24 mpd (R=.489;p<.0001).

Longitudinal change in Health-Related Quality of Life

The results of the multivariate analyses on emotional functioning (EF), physical functioning (PF), global health (GH), cognitive functioning (CF), role functioning (RF), social functioning (SF), dimensions of the QLQ-C30, are presented in Table 4. The levels of all HRQoL dimensions at 1 mpd were always higher for breast cancer than melanoma patients indicating an overall better HRQoL for breast cancer patients at 1 mpd (except for CF, estimated intercepts: 66.6 and 91.0 for breast cancer and melanoma, respectively).

Time effect

Regarding change over time, rebound effects were observed for some dimensions of HRQoL for breast cancer patients: the PF, GH, RF and SF scores decreased steeply from 1 to 6 mpd, then increased slightly from 6 to 12 mpd, and remained stable from 12 to 24 mpd. Globally, during the 2-year follow-up (24 vs 1 mpd in Table 4), breast cancer patients' PF, RF, SF scores had an average decrease of -5.3, -7.5, and -4.9 points, respectively whereas GH and EF remained globally stable.

In contrast, melanoma patients' EF linearly increased (+3.3 points on average between each visit) and melanoma patients' PF linearly decreased (-2.6 points on average between each visit) over time.

*Covariates' effects: common to breast cancer and melanoma*

For both cancer types, NCOP and living with a partner were negatively associated with changes in EF, SF, and RF, SF, respectively. For example, an increase of 10 points in the NCOP score was associated with an average decrease of 3 points in EF score for breast cancer patients and of 5 points for melanoma patients. Moreover, CONLOC and age were positively associated with changes in GH, RF, and SF, EF, respectively. In particular, an increase of 10 points of CONLOC was associated with an average increase of 2 points in GH for melanoma patients, and of 1 point for breast cancer patients.

Covariates' effects: breast cancer

For breast cancer patients only, PCOP was positively associated with EF changes (+ 1 points of EF for each 10 points of PCOP increase). ECOP and INTLOC were negatively associated with changes in PF, GH, SF, and EF, GH, CF, RF, respectively. In addition, ECOP was negatively associated with breast cancer patients' EF but only at 1 mpd. Change in the EF mean scores depending on the level of ECOP are shown in Figure 8. The patients with higher scores

of ECOP (observed third quartile of ECOP scores) had a lower mean level of EF at 1 mpd compared to the patients with lower ECOP scores (first quartile). From 6 mpd, the EF mean scores were higher than 1 mpd scores and similar whatever the level of ECOP.

Figure 8. Mean scores of emotional functioning over time according to the level of emotional coping in breast cancer patients
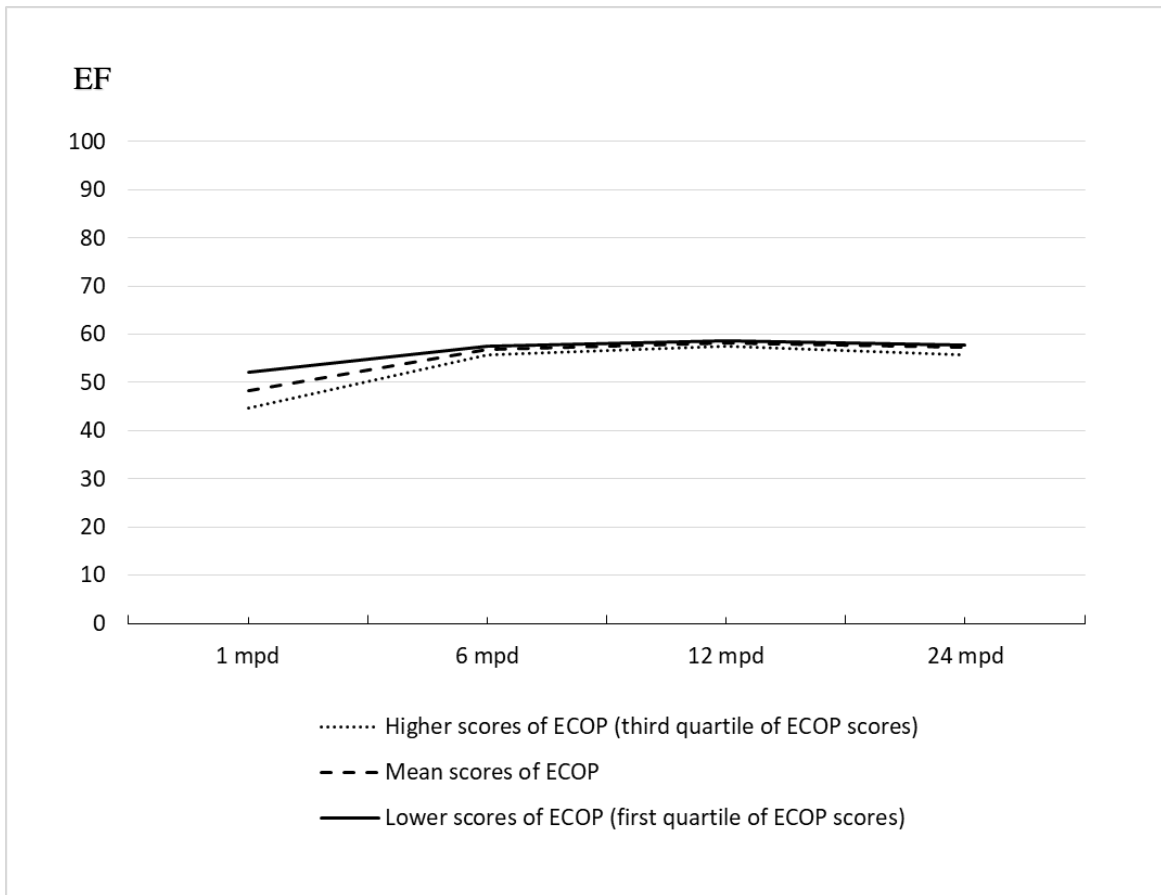
EF: emotional functioning; ECOP: emotional coping; mpd: months post-diagnosis.

Observed levels of emotional coping in the sample:

- mean: 39.9
- 1st quartile: 25
- 3rd quartile: 50

Covariates' effects: melanoma

For melanoma patients only, PCOP was positively associated with PF changes (+ 2 points increase in PF for each 10 points of PCOP increase). RELLOC was negatively associated with changes in EF and SF (both -2 points for each 10 points of RELLOC increase).

Explained variance

For breast cancer patients, the ECOP scores at 1 mpd and the time variable explained 30% of the variance in PF over time (R^2=30%). For melanoma patients, NCOP, CONLOC, RELLOC, age, living with a partner and the time variable all contribute to 33% of the explanation of the variance of EF over time (R^2=33%). For both cancer types, the lowest R^2 was observed for CF (R^2, <10%).

Table 4. Results of the multivariate analyses of the coping, locus of control and sociodemographic variables on the dimensions of Health-Related Quality of Life

	Emotional Functioning (EF)				Physical Functioning (PF)				Global Health (GH)			
	Breast cancer		Melanoma		Breast cancer		Melanoma		Breast cancer		Melanoma	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
Intercept	59.58**	8.18	33.74*	9.75	95.57**	2.05	88.04**	3.80	67.71**	2.94	33.16**	7.76
NCOP	-0.27*	0.07	-0.50**†	0.10	--	--	-0.57**†	0.13	--	--	-0.23*†	0.08
ECOP	-0.30**†	0.05	--	--	-0.06*†	0.03	--	--	-0.11*†	0.04	--	--
PCOP	0.15*	0.07	--	--	--	--	0.19*†	0.05	--	--	--	--
INTLOC	-0.12*†	0.04	--	--	--	--	--	--	-0.13*†	0.03	--	--
CONLOC	--	--	0.28*†	0.08	--	--	--	--	0.15*†	0.04	0.21*†	0.07
RELLOC	--	--	-0.24*	0.08	--	--	--	--	--	--	--	--
Age	0.34*	0.13	0.42*	0.14	--	--	--	--	--	--	0.41*	0.12
Living with a partner	--	--	-13.50*	4.28	--	--	--	--	--	--	-10.16*	3.66
Standard of living	--	--	--	--	--	--	--	--	7.34*	2.76	--	--
Time	--	--									--	--
6 vs 1 mpd			3.30*	1.20	-12.37**	1.15	-2.62*	0.97	-6.87*	1.74		
12 vs 6 mpd			3.30*	1.20	5.28**	0.94	-2.62*	0.97	6.88**	1.32		
24 vs 12 mpd			3.30*	1.20	1.76*	0.66	-2.62*	0.97	0.45	1.24		
24 vs 1 mpd			9.89*	3.59	-5.33**	0.92	-7.85*	2.91	0.46	1.63		
Interactions between ECOP and time	0.22**(6 mpd) 0.26**(12 mpd) 0.22**(24 mpd)	0.04 0.04 0.05	--	--	--	--	--	--	--	--	--	--
Interactions between NCOP and time	--	--	--	--	--	--	0.13*	0.05	--	--	--	--
R²	18%		33%		30%		19%		15%		18%	

Table 4 (Continued)

	Cognitive Functioning (CF)				Role Functioning (RF)				Social Functioning (SF)			
	Breast cancer		Melanoma		Breast cancer		Melanoma		Breast cancer		Melanoma	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
Intercept	66.59**	7.18	91.01**	2.10	92.72**	4.47	23.91	12.35	87.55**	7.26	38.13*	10.72
NCOP	--	--	-0.36**✝	0.08	--	--	--	--	-0.20*	0.06	-0.31*✝	0.12
ECOP	--	--	--	--	--	--	--	--	-0.13*✝	0.04	--	--
INTLOC	-0.14*✝	0.04	--	--	-0.12*✝	0.05	--	--	--	--	--	--
CONLOC	--	--	--	--	0.10*✝	0.05	0.25*✝	0.10	--	--	0.25*✝	0.09
RELLOC	--	--	--	--	--	--	--	--	--	--	-0.19*	0.09
Age	0.37*	0.13	--	--	--	--	0.61*	0.19	0.31*	0.12	0.52*	0.16
Living with a partner	--	--	--	--	-8.79*	3.05	-13.38*	5.78	-6.73*	2.80	-17.53*	4.95
Time	--	--	--	--			--	--			--	--
6 vs 1 mpd					-17.79**	2.21			-14.39**	1.76		
12 vs 6 mpd					10.17**	2.00			7.58**	1.90		
24 vs 12 mpd					0.10	1.63			1.94	1.71		
24 vs 1 mpd					-7.52*	2.02			-4.87*	1.57		
R²	6%		9%		17%		15%		18%		14%	

* p value for the test of nullity of the coefficient <0.05

** p value for the test of nullity of the coefficient <0.0001

✝=Time-dependent variable.

Reference levels: household living standard: low intermediate, education: ≤ certificate of elementary school, living with a partner: no, time: time 1. mpd: months post-diagnosis; NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control.

3.4. Discussion

This study assessed the association of change in coping and LOC dimensions with change in HRQoL over time for breast cancer and melanoma patients.

Breast cancer

For breast cancer patients, ECOP had a negative association with HRQoL over time (EF, PF, GH, and SF dimensions). ECOP was mainly composed of coping strategies that consist in the sharing of thoughts and feelings with others (i.e. instrumental support, venting, using emotional support). Emotionally expressive strategies, aiming at managing negative emotions, can be relatively ineffective in improving HRQoL[178,179]. The use of emotionally expressive coping can indeed be associated with the perception that quality of life is poor, i.e. the coping efforts may then contribute to decrease rather than increase HRQoL. The social sharing of thoughts and feelings may indeed not facilitate psychological adjustment in case of a perceived unsupportive social context[166,180]. In fact, the patients' social environment (friends, relatives, partner, etc.) may find it difficult to face the illness of their friend or partner over time[181,182] and have negative supportive attitudes, that can influence the way people will cope with the situation[166].

Also, reverse causality cannot be ruled out and it is also possible that poorer scores in HRQoL contribute to a greater use of emotionally expressive strategies. When HRQoL of patients is threatened, expressing and sharing their emotions may help them to get a better understanding of the disease and its treatments, reinterpret the situation, decrease anxiety and motivate problem-focused coping strategies to gain reassurance of disease control.[125,178].

The negative association between INTLOC (self-attribution for illness onset) and HRQoL changes (EF, GH, CF, RF) in breast cancer patients, suggest that the more patients think of having the responsibility for the illness, the more negative their change of HRQoL is. It seems in line with the results of previous studies that found a negative association between internal causal attributions and psychological adjustment or HRQoL[126,183,184]. Nevertheless, most of these studies were cross-sectional and did not take into consideration the psychological change over time[126,183], apart from the longitudinal work of Kulik et al.[184] that considered 2 time points to test this negative association. The negative association between INTLOC and HRQoL change over time can be due to negative feelings and thoughts related to the belief of personal responsibility of a traumatic past event (cancer diagnosis). The feelings of self-blame (i.e., "What could I have done to prevent this?"), and of counterfactual thinking (i.e., "If things had

gone differently, I wouldn't be in this situation") are usually linked with negative adjustment over time[95,185].

Breast cancer and melanoma

For both cancer, NCOP (i.e., behavioral disengagement, self-blame and denial) was also negatively associated with HRQoL over time, but in a different way. It affected almost all HRQoL dimensions for melanoma patients (except RF) and a fewer for breast cancer patients (EF, SF only). Our finding is in line with another longitudinal study in breast cancer patients in which negative coping, at 0-8 months' post diagnosis, was found to be negatively associated to the total score of HRQoL measured at 12–20 months' post-diagnosis[133]. As the Brennan's model of adjustment to cancer reported, the usage of negative coping can be maladaptive in the long term since it prevents from the traumatic information processing necessary to the positive adjustment over time[186]. Similarly, for both cancer, the higher the CONLOC level (perceived control over the course of illness LOC), the higher the changes in HRQoL over time. For reaching and maintaining control over time, patients use some adaptive cognitive compensation mechanisms, such as evaluating other domains in life or positive illusions, that seem to be beneficial for psychological functioning in cancer[89].

Age was positively associated with HRQOL changes for both cancer types; this has already been shown with EF and SF 2 years after treatments initiation for melanoma and breast cancer patients[135]. For breast cancer patients, this relation has been found during different phases after diagnosis and treatments[187], and it has been hypothesized that younger patients often report greater distress than older patients[66].

Moreover, living with a partner, was negatively associated with HRQoL change. As it was found in the literature, the HRQoL of the partners, psychologically affected by the illness as the patients, influences the patients' HRQoL and vice versa, since there is a "reciprocal influence" among them over time[182].

The levels of HRQoL at 1 mpd were mainly higher for breast cancer than melanoma (except for CF). It might be due to the different social support perceived by the patients[68]. This could be in line with the fact that usually in common language and risk communication breast cancer is fully recognized as a serious illness, whereas melanoma is often more trivialized at an early stage[135]. Hence, breast cancer patients might find more support from family and friends than melanoma patients at diagnosis.

Study limitations

Since the sample of breast cancer patients was composed only of women and the sample of melanoma patients included men and women (42.3% of women and 57.7% of men), gender and type of cancer effects might therefore be confounded.

Moreover, the study was based on a sample of breast cancer and melanoma patients at early stage, so the results' generalization to more severe stages cannot be made. Furthermore, as the data are from an observational longitudinal study, causal effects of the considered covariates on HRQoL change cannot be assessed. In further studies, the causal inferences could be tested using Marginal Structural Models.

All R^2 of the multivariate models were lower than 35%. Other cross-sectional studies looking also at the association of coping with HRQoL display similar **R²**, ranging between 22% and 40%[68,188,189]. In this work, R^2 ranged from 6 to 33%. Further studies are needed in order to increase the percentage of the variation of the explained HRQoL, considering other important variables such as specific treatments, distress, anxiety and depression as well as the perception of the illness by the partner. In particular, our study focused on the psychological constructs of coping and LOC that are within the domain of cognition on which Cognitive Behavioral Therapies can have an influence. However, cognition should be considered along with emotion such as distress, anxiety and depression to better understand the psychological progress at hand and take into account with targeted supportive therapies.

Clinical implications

According to our results, it seems that psychological therapies aiming at supporting HRQoL of breast cancer and melanoma patients over time, should take into account the differences and the similarities in the experience reported by the patients according to the type of cancer.

For breast cancer patients, the psychological therapy could be focused on helping patients who use ECOP strategies (i.e. venting, emotional and instrumental support, religion) that are negatively associated with HRQoL over time. It would be valuable to have a more comprehensive view of the link between ECOP strategies and HRQoL through patients' interviews, for example to explore whether emotional coping is an essential step to clarify information and understanding of the disease in order to mobilize, in the longer term, more positive strategies that could be beneficial in terms of HRQoL.

When facing cancer diagnosis, patients can experience several negative emotions (such as anger, shame, and frailty). The sense of self-blame that comes out from the belief of responsibility for the illness must be evaluated. Using a cognitive restructuring technique may

help the patients to identify some maladaptive automatic thoughts or to question the validity of negative automatic thoughts regarding perceived control over the situation or available coping skills in order to replace them by more realistic ones or change dysfunctional patterns[190]. In addition, using the problem-solving technique may help the patients to seek alternatives solutions or to define realistic goals to cope with the situation[191].

For both cancer types, psychological therapy could be focused on the behavioral and cognitive negative reactions to the event (e.g. negative coping strategies), since they have negative associations with HRQoL over time. It could be useful to help patients question the validity of their beliefs (using the cognitive restructuring and the problem-solving techniques), but also to work on the acceptance of experiencing negative emotions that patients may be avoiding. Moreover, for both cancer types, it seems important to maintain a sense of perceived control. Acceptance and Commitment Therapy which relies on the acceptance of emotional experiences (our results showed a negative association between behavioral disengagement and HRQoL and a positive relation between acceptance and HRQoL for both cancers) could be relevant as it may help to increase perceived control over the disease. Acceptance and Commitment Therapy aims at increasing the psychological flexibility (i.e. increasing the awareness and the openness to experience, acting in accordance with personal values) which can improve psychological adjustment and quality of life[192].

Furthermore, it is necessary to also take into consideration partners' mental state due to the illness, to propose dyadic social support for example. Psycho-educational approach could be relevant with interventions aiming at providing information about the disease and its consequences to patients and their relatives. One can assume that if the patient and his/her loved ones have a good knowledge and representation of the illness, they should manage it all the better. Notably because they will know how to share and speak about cancer and its treatments, to better understand and accept its consequences on their daily lives.

It seems that for both cancer types, psychological support is needed: for breast cancer patients during all the follow-up and particularly at time of diagnosis (we noticed a sharp decrease in HRQoL after diagnosis followed by a rebound effect afterwards); for melanoma patients, instead, a continuous psychological support could be proper (some HRQoL scores linearly decreased over time).

In conclusion, this study supports the evidence that for breast cancer and melanoma patients different coping strategies and LOC beliefs are associated with HRQoL changes. It seems that psychological therapies, that take into consideration the patients' coping strategies and beliefs, should be specific according to the type of cancer and time after diagnosis.

3.5. Ethical approval

This study was approved by an ethical French research committee (Comité de Protection des Personnes).

4. START STUDY

The second project of my thesis is based on the data collection of a bigger project as well. It is called START, italian acronym for Epidemiological multicentre study in the oncological network of Piemonte and Valle d'Aosta regions. This project was funded in the 2015 by the "Compagnia di San Paolo" in Italy.
The focus of this bigger project is on the prostate cancer and its treatments.

Surgery, radiotherapy, chemotherapy and hormonal therapy are the possible treatments for prostate cancer but they can have several side effects, such as urinary problems in case of surgery for prostate removal (see chapter 1.2).
Since today prostate carcinoma is begun the tumour with the highest incidence in men (see chapter 1.1), several efforts should be done to understand which can be the best treatments in term of psychological and physical impact on the patients. Unfortunately nowadays longitudinal studies focused on the treatments for prostate cancer are on a short follow-up or do not compare all the possible alternatives[193–195]. The main aim of this bigger project is to study what happens during the AS, comparing it with other treatments, whereas the second aim is to analyse the incidence of prostate cancer in the Piemonte and Valle d'Aosta regions.
The sample of the START study is composed by prostate cancer patients at low risk. At the time of diagnosis, enrolled patients could choose AS or different RTs (such as surgery, radiotherapy, chemotherapy, hormone therapy) with the physician's help. During the medical visit with the doctor, prostate cancer patients received one informative brochure with all the information regarding the project, the possible treatments and the related side effects. After the medical consultation, the patient could do his treatment choice. During the course of the illness, the patient had chance to change the treatment if medical conditions went worst or the patient changed idea.
The sample was collected in several clinical centres in Piemonte and Valle d'Aosta. The dimensions measured in the START study regard medical (PSA, Gleason score, erectile functioning, prostate symptoms) and psychological aspects (HRQoL, anxiety and depression, Locus of Control). The measures were taken at the time of diagnosis (0 mpd, months post-diagnosis), and at 6, 12, 18 and 24 mpd. The questionnaires used in the START project are the EORTC QLQ-C30[196] and the EORTC PR25[197] (for the measurement of several HRQoL sub-dimensions), the Hospital Anxiety and Depression Scale (HADS)[198] (for analysing anxiety and depression levels), the International Index for Erectile Functioning (IIEF-5)[199] (in order to

measure erectile functioning), the International Prostatic symptoms score (I-PSS)[200] (in order to measure prostate cancer symptoms), and the Multidimensional Health Locus of Control Form C (MHLC-C)[201] (for the measurement of the Locus of Control).

The shift from one treatment to any other was registered during the study.

This project is still an ongoing study. It was started in June 2015, will continue until June 2020 and is considering the following inclusion criteria: having the residence in Piemonte or Valle d'Aosta regions, giving a valid and informed consent for the participation to the study, being suitable for the RTs (such as the surgery or the radiotherapy), and having a diagnosis of localised prostate cancer at low risk or very low risk according to medical criteria (e.g., T1c or T2a clinic stadium, PSA $\leq$ 10 ng/ml, Gleason score 3+3, or 3+4 with patients more then 70 years old, etc.). The study was approved by the Ethics Committee of the A.O.U. Città della Salute e della Scienza di Torino – A.O. Mauriziano – A.S.L. TO1, and by the Ethics Committees of all the centres involved in the study (see Appendix 2).

4.1. Background

The prostate cancer is considered as the most diagnosed cancer in men: in 2015 worldwide, there were 17.5 million cases and 1.6 million new cases of prostate cancer[202,203].

Today several possible treatments are available, such as radical prostatectomy, hormone therapy, radiotherapy, chemotherapy, etc.. Although they represent a way to treat prostate cancer, the psychologically and physically heavy side effects of these treatments let think that they may not be the best option. For example, patients could feel emotional distress and fatigue during hormonal therapy[204], or loss of sexual interest and infertility[18,19] and urinary problems[18] during radiotherapy. Some patients may also experience fear[205] due to side effects on the sexual area, such as fear of "castration"[21].

When prostate cancer progression is low, physicians might propose AS, according to the patient medical condition. AS, a conservative approach that increasingly emerged since 2010[206], consists in the observation of the cancer evolution over the disease. It delays of several years or reduces the necessity of the active treatments for prostate cancer and so diminishes the health services costs[207]. Moreover, since the AS doesn't bring to the same heavy side effects as the RTs (e.g., hair loss), it lets the patients avoid treatments complications and continue with their daily lives as the cancer is not there.

AS seems a good choice in comparison with other active treatments also considering the patients' HRQoL level as it resulted in a comparative study between HRQoL of patients' under AS and RT: patients undergone AS had higher HRQoL comparing to patients who chose brachytherapy or radical prostatectomy (RTs) at the baseline[208].

It is possible to find differences between AS and RTs also over the pathology. In particular, patients under AS reported a better role, emotional and social functioning over 3.5 years follow-up[67] then patients undergone radical prostatectomy.

Nevertheless the strengths of choosing AS, patients under AS periodically underwent medical tests such as the prostate biopsies, that consist in the removal of small samples of the prostate, and that can be perceived as painful and uncomfortable[209]. On the other hand, patients may have an internal pressure to lower the fear of cancer progression, and feel the external pressure from the family and friends for "doing something" (i.e., active treatments) for their cancer[46].

Since each treatment choice has both negative and beneficial effects, the treatments decision making can be difficult and emotionally load[205]. Treatment decision is considered as a difficult choice since it regards prostate cancer management and may have life-altering consequences.

This choice can depend by physician suggestions since it is very often shared with the doctor during the medical visit after the cancer diagnosis.

The suggestions given by the physician depend on several medical factors related to the patient's condition, such as the PSA level and the biopsies results, incontinence, bowel symptoms, and age[163,164]. Moreover, the treatment choice can also depend by psychological factors that have a role in this decision, such as the patient's anxiety, and patients' and physicians' beliefs.

Among the psychological factors that can have a role in the shared treatment choice, there might be the LOC beliefs. It was found, indeed, that this type of beliefs are linked to the health situations. For example, in a study of Helmes et al.[212,213] powerful others LOC beliefs (the belief that others powerful can influence the health) resulted positively associated with trust in physicians regarding the tests for vulnerability to cancer. Moreover, the same beliefs seem to be associated with health-related behaviours, such as systematic and regular check-ups, patient compliance, etc.[214].

Although the relation between the health-related behaviours and LOC exists, there are no studies available in case of shared treatment decision-making. In addition, to the best of our knowledge, the studies conducted in prostate cancer have never considered the association between the treatment choice and both medical and psychological measures.

As first objective, it will be tested what are the factors associated with the treatment choice, AS or RTs, while as second objective, because of the different patients' experience in the two arms, the HRQoL and some other psychological variables will be analysed over time.

4.2. Methods

Participants

Prostate cancer patients (N=333) were recruited in the Urology and Radiotherapy services of several Italian clinical centres (see Appendix 2) from June 2015 to December 2017. A written informed consent was obtained from all the patients before the enrollment in the study. The recruited patients had a first diagnosis of prostate cancer at low risk. The sample was composed by patients that at the baseline chose AS (N=254) or RTs (N=79).

Measures

Patients completed self-administered questionnaires at the time of diagnosis, and 6, 12, 18 and 24 months later (mpd, months post-diagnosis).

Several clinical and psychological questionnaires have been administered to prostate cancer patients.

At each time two HRQoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-PR25), the IIEF, the IPSS, and the HADS were administered and sociodemographic variables were assessed, whereas the LOC questionnaire was administered only at the baseline.

The first HRQoL questionnaire, the EORTC QLQ-C30[145,196], has 30 items and the study focuses on its 6 functioning dimensions measuring physical (5 items), role (2 items), emotional (4 items), cognitive (2 items), social functioning (2 items), and global health (2 items). These dimensions are composed of four or seven point Likert items and all the dimension scores range from 0 to 100. A higher score represents a higher level of HRQoL.

The second HRQoL questionnaire, the EORTC QLQ-PR25[215], is instead composed by two functional scales, sexual activity (2 items) and sexual functioning (4 items), and 4 scales on symptoms: urinary symptoms (8 items), bowel symptoms (4 items), hormonal treatment-related symptoms (6 items), and incontinence aid (1 item). Patients could express their agreement on the sentences using a rating from "Not at all" to "Very much". All the scores of the EORTC QLQ-PR25 scales range from 0 to 100. A higher score represents higher level of symptoms or functioning, according to the type of scale.

For measuring the Health Locus of Control, the MHLC-Form C[81,201] was used. This instrument is composed by 4 dimensions: Internal LOC (6 items), Doctors LOC (3 items), Other people (3 items) and Chance LOC (6 items). Internal LOC represents the belief on the personal responsibility of the events (e.g., If my condition worsens, it is my own behaviour which determines how soon I will feel better again). The Doctors LOC is the belief that doctors can have the control of the health condition of the patient (e.g., If I see my doctor regularly, I am less likely to have problems with my condition). Other people, instead, is the belief that other people, family or friends for example, have the control of the health condition (e.g., Other people play a big role in whether my condition improves, stays the same, or gets worse). Chance LOC is the belief that the luck has the control of the pathology (e.g., I got ill because of I am unlucky).

The questionnaire International Index of Erectile Functioning (IIEF-5[216]) was used to measure the Erectile Functioning. The response scales are Likert scales on 5 points. The instrument is

composed by 5 items and it has only one final score. The final score may indicate no erectile dysfunction (score range 22-25), mild erectile dysfunction (score range 17-21), mild-moderate (score range 8-11), and severe erectile dysfunction (score range 5-7). Higher scores indicate higher erectile functioning.

The questionnaire International Prostatic Symptom scores (I-PSS[200,217]) was used to measure the prostatic symptoms. The questionnaire is composed by a score, indicating the prostatic symptoms level, and a single item score indicating the Quality of Life due to urinary symptoms. The score of prostatic symptoms is composed by 7 items on a Likert scale of 6 points. Higher scores indicate higher symptoms. In particular, final score range can indicate: mild symptoms (score range 0-7), moderate symptoms (score range 8-19), or severe symptoms (score range 20-35). The score indicating the Quality of Life due to urinary symptoms is composed only by the response to one item. This scale of this item can range from 0 to 6. Higher scores indicate worst Quality of Life.

To measure anxiety and depression, the Hospital Anxiety and Depression Scale (HADS[74,198]) was used. The anxiety and depression scores were composed by the sum of scores obtained on 7 items, respectively. All the items are on a Likert scale of 4 points. The final scores can indicate a normal or a pathologic level of anxiety/depression: Normal (score range 0-7), borderline abnormal (score range 8-10), or abnormal cases (score range 11-21)[74]. Higher levels indicate higher depression or anxiety.

To measure the comorbidities, the Charlson Comorbidity Index was used. It is a tool that gives the number of the total comorbidities (among, for example, vascular pathologies, AIDS, Leukemia, liver diseases, etc.). The range of this index goes from 0 to 37.

Statistical methods

To reach the first objective, so to test the variables associated with treatment choice, a logistic regression analysis has been made. As independent variables considered there were the physician type, sociodemographic variables (living with a partner, age, education level), medical variables (Charlson comorbidity index, PSA, Gleason score), psychological variables (anxiety, depression, perceptions of urinary symptoms and bowel symptoms, sexual activity), and all the LOC beliefs (chance, internal, others and doctors LOC). To test the association between the medical and the psychological variables, and the treatment choice, a Logistic Regression, modeled on the probability of choosing RTs at baseline, was performed.

To reach the second objective, so to test the differences over time between AS and RTs groups, mixed models have been used considering the time, the type of treatments and the interaction

between the time and the groups (1, AS; 2, RT) as independent variables. The interaction between group and time was used to check if any difference between groups exists over time. - One psychological and medical variable has been considered as dependent variable for each analysis (all the HRQoL functioning scales, anxiety and depression, sexual functioning, urinary symptoms, erectile functioning and prostate symptoms). For the analyses, SAS 9.2 proc logistic and proc mixed have been used.

4.3. Results

The sample was composed by 333 prostate cancer patients at low risk at baseline. The number of patients divided by arm at each time is presented below (see Figure 9).

Figure 9. Sample size at the different time points of the study
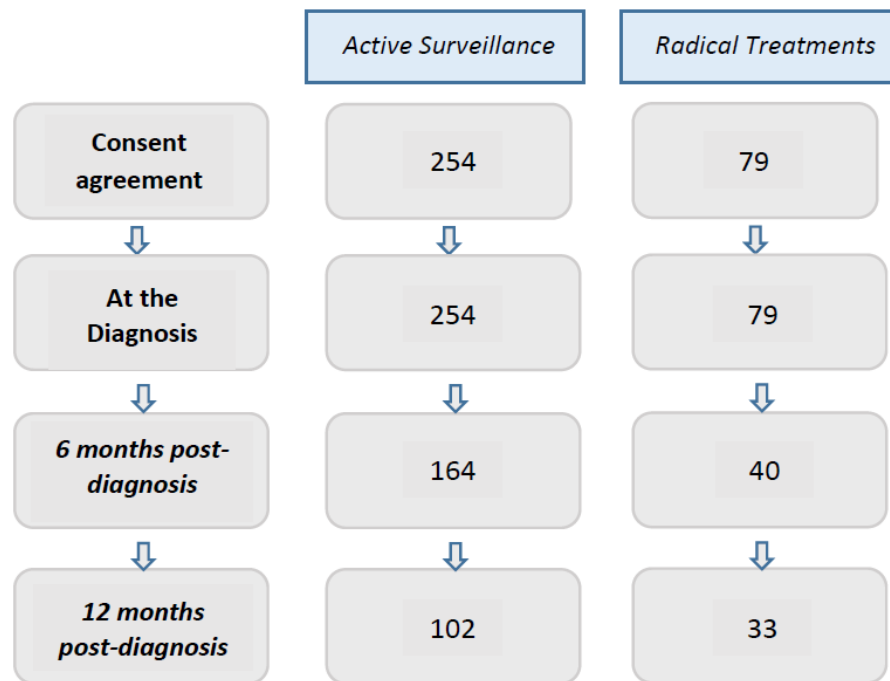
The majority of the sample chose AS, rather than RTs (254 prostate cancer patients in AS and 79 patients under RTs) at baseline. Among prostate cancer patients who chose RTs at baseline, there were 60 patients (75.9%) who chose surgery, 16 (20.2%) radiotherapy and 3 (3.8%) other treatments. Also over time, the sample was composed more by prostate cancer patients under AS rather than under RTs. Globally, 53 patients left the study after the baseline, and 48 after 6 months. The majority of them was composed by patients who chose AS at baseline. Among the patients that went out from the study, 8 went out because they withdraw the informed consent, 3 violated the protocol, 3 because of medical screening, 18 because of the progression of the illness and 3 for other reasons. There is no information regarding the reason why the remaining patients went out from the study. Since this study is ongoing, the other missing observations represent those cases for whom the time of the follow-up is not arrived yet.

In the second part of this study, only the first three times were considered for the longitudinal descriptive analyses (Baseline, 6 and 12 mpd) because of the small number of patients in the sample at 18 and 24 mpd (less than 20 in RT).

The characteristics of the participants divided by treatment choice at baseline (AS/RTs) are in tables 5-6. All the patients of the study had a prostate cancer at low risk, in particular, at T1c and T2a stages (see Table 5). Regarding the socio-demographic characteristics (type of physician, Charlson Comorbidity index, age, living with a partner and education level), no significant differences emerged between the groups of patients in AS and RTs (see Table 6).

Table 5. Description of PSA and Gleason score at baseline

Gleason score	PSA (ng/ml)	Stage	N(%)
<3+3	<10	T1c	284(85.3)
3+4	<10	T2a	48(14.4)
<3+3	>10	T2a	1(0.3)
		Missing	0(0.0)
		N total	333

Table 6. Descriptive statistics of sociodemographic variables by choice type at baseline

Variables	AS (N=254)	RTs (N=79)	ALL (N=333)	Wilcoxon test
	N(%)	N(%)	N(%)	
Physician type				.054
Radiation Oncologist	20(7.9)	12(15.2)	32(9.6)	
Urologist	234(92.1)	67(84.8)	301(90.4)	
Missing	0(0.0)	0(0.0)	0(0.0)	
Charlson Comorbidity index				
None (0)	141(55.5)	45(57.0)	185(55.6)	.257
Mild (1-2)	87(34.2)	32(40.5)	120(36.0)	
Moderate (3-4)	19(7.5)	2(2.5)	21(6.3)	
Severe ($\geq$5)	7(2.7)	0(0.0)	7(2.1)	
Missing	0(0.0)	0(0.0)	0(0.0)	
Age				
<=65	59(23.2)	24(30.4)	83(24.9)	.352
66-70	69(27.2)	16(20.2)	85(25.5)	
71-75	69(27.2)	26(32.9)	95(28.5)	
>=76	57(22.4)	13(16.4)	70(21.0)	
Missing	0(0.0)	0(0.0)	0(0.0)	
Living with the partner				.359
Yes	176(69.3)	59(74.7)	235(70.6)	
No	78(30.7)	20(25.3)	98(29.4)	
Missing	0(0.0)	0(0.0)	0(0.0)	
Education				.224
Low	48(18.9)	15(19.0)	63(18.9)	
Middle	68(26.8)	34(43.0)	102(30.6)	
High	83(32.7)	19(24.0)	102(30.6)	
Missing	55(21.6)	11(13.9)	66(19.8)	

AS: Active Surveillance, RTs: Radical Treatments

Description of the sample over time according to choice at baseline

Globally, the means of the scales used in this study seem a bit different between patients under AS and RTs at 6 mpd (see Table 7). In physical (at 6 months), emotional (at 6 and 12 months) and cognitive (at 6 months) functioning the HRQoL seems higher for those patients who chose AS.

Regarding the sexual area, it seems there are different means in the two groups at all the three times.

The belief of the doctors' control on the own health (Doctors Locus of Control) seem to be the only difference at the baseline with higher score for patients who chose AS.

Table 7. Table with the means of all the scales of the patients under active surveillance or radical treatments

Variables	RTs M(SD)	AS M(SD)	RANGE
PF *0 mpd*	91.4(13.0)	93.2(10.9)	0-100
PF *6 mpd*	90.9(13.1)	95.9(6.5)	
PF *12 mpd*	92.5(10.9)	97.7(5.0)	
GH *0 mpd*	80.1(13.7)	81.2(13.8)	0-100
GH *6 mpd*	80.2(15.6)	84.0(11.7)	
GH *12 mpd*	79.0(15.1)	79.6(10.4)	
RF *0 mpd*	94.3(13.7)	94.9(12.2)	0-100
RF *6 mpd*	94.4(14.3)	96.0(11.2)	
RF *12 mpd*	94.1(12.4)	98.8(4.4)	
SF *0 mpd*	94.1(13.7)	96.4(9.0)	0-100
SF *6 mpd*	93.9(13.8)	97.4(7.3)	
SF *12 mpd*	94.1(13.7)	95.7(12.7)	
EF *0 mpd*	83.1(15.1)	86.2(13.8)	0-100
EF *6 mpd*	85.3(14.2)	91.2(10.4)	
EF *12 mpd*	85.6(13.7)	90.4(17.1)	
CF *0 mpd*	89.2(13.4)	90.8(14.1)	0-100
CF *6 mpd*	89.7(12.8)	94.7(8.7)	
CF *12 mpd*	88.2(14.5)	93.2(12.4)	
AX *0 mpd*	11.7(2.4)	11.4(2.2)	0-21
AX *6 mpd*	12.1(2.2)	11.9(2.2)	
AX *12 mpd*	11.8(2.6)	12.3(2.1)	
DP *0 mpd*	9.1(1.8)	9.4(1.9)	0-21
DP *6 mpd*	9.0(1.8)	9.2(1.3)	
DP *12 mpd*	8.9(1.9)	9.3(1.8)	
SXF *0 mpd*	73.8(15.5)	74.2(16.5)	0-100
SXF *6 mpd*	74.4(16.1)	64.3(18.5)	
SXF *12 mpd*	71.6(16.7)	63.8(21.6)	
SA *0 mpd*	37.7(22.5)	33.6(23.5)	0-100
SA *6 mpd*	36.4(21.9)	25.0 (19.7)	
SA *12 mpd*	36.0(24.1)	32.1(19.6)	
URI *0 mpd*	9.6(10.8)	9.5(12.0)	0-100
URI *6 mpd*	8.9(11.5)	9.3(10.8)	
URI *12 mpd*	8.4(9.3)	8.0(7.8)	
BOW *0 mpd*	2.6(5.1)	1.5(3.2)	0-100
BOW *6 mpd*	2.4(5.1)	1.7(4.3)	
BOW *12 mpd*	2.2(4.0)	1.3(3.7)	
IPSS *0 mpd*	7.1(5.8)	6.6(5.6)	0-35
IPSS *6 mpd*	6.0(5.5)	4.7(5.3)	

IPSS *12 mpd*	5.9(4.5)	3.7(3.3)	
IIEF *0 mpd*	18.3(8.2)	17.8(8.8)	5-25
IIEF *6 mpd*	17.1(8.6)	11.6(7.4)	
IIEF *12 mpd*	16.7(8.4)	14.4(7.8)	
Internal LOC *0 mpd*	19.8(5.6)	21.5(6.2)	6-36
Chance LOC *0 mpd*	18.1(6.3)	18.3(7.2)	6-36
Others LOC *0 mpd*	10.7(3.8)	11.5(3.4)	3-18
Doctors LOC *0 mpd*	12.4(3.8)	13.7(3.3)	3-18

PF: Physical Functioning, GH: Global Health, RF: Role Functioning, SF: Social Functioning, EF: Emotional Functioning, CF: Cognitive Functioning, AX: Anxiety, DP: Depression, SXF: Sexual Functioning, SA: Sexual Activity, URI: Urinary symptoms, BOW: Bowel symptoms, IPSS: International Prostatic Symptoms Score, IIEF: International Index of Erectile Functioning, *mpd*: months post-diagnosis, AS: Active Surveillance, RT: Radical Treatments, LOC: Locus of Control. *Statistically significant results.

Logistic Regression model to analyse the variables influencing the baseline treatment choice

Considering all the independent variables, the belief of the Doctors' control on the patients' health (Doctors LOC) (p=.01), the age (p<.05) and a low Gleason score (p<.03) were found negatively associated with the probability of choosing RT, whereas having a radiation oncologist as physician at the diagnosis resulted positively associated (p<.03) with this probability (see Table 8).

Table 8. Variables predicting the probability of choosing a radical treatment at baseline

Variables	Est.	SE	p-value
Doctors LOC	-0.2	0.1	.01*
Age	-0.4	0.2	.04*
Gleason (low)	-0.6	0.3	.02*
Radiation Oncologist	0.7	0.3	.02*
Living with a partner	-0.2	0.2	.37
Charlson comorbidity	-0.5	0.3	.09
PSA	.06	0.1	.55
Education level	0.3	0.2	.18
Anxiety	-.09	0.1	.24
Depression	.14	0.1	.19
Urinary symptoms	.02	0.1	.25
Sexual activity	.01	0.0	.23
Sexual functioning	-0.0	.01	.72
Bowel symptoms	-0.7	.04	.16
Internal LOC	-0.0	.04	.90
Chance LOC	0.0	.03	.30
Others LOC	0.0	.06	.99

Mixed models to study the HRQoL and psychological differences in the two arms over time

Over time, differences in the two groups emerged. Significant results are in Table 9 and they are graphically reported in the Figures 10-13. Sexual functioning resulted being higher for AS then RTs ($p=.003$), as well as erectile functioning ($p<.001$). Regarding the anxiety, it seems higher at 12 months in RTs then AS ($p<.03$). Prostate symptoms (urinary problems) are a little higher for patients under AS then for those under RTs ($p<.005$).

Table 9. Results of mixed models indicating different trends between the two groups

Mixed Models	Active Surveillance Mean(SD)	Radical Treatments Mean (SD)	Time*treatment Sign.	RANGE
Sexual functioning 0 mpd	26.2 (15.5)	25.8 (16.5)	.003*	0-100
Sexual functioning 6 mpd	25.6 (16.1)	35.6 (18.5)		
Sexual functioning 12 mpd	28.3 (16.7)	36.2 (21.6)		
Anxiety 0 mpd	11.7 (2.4)	11.4 (2.2)	.018*	0-21
Anxiety 6 mpd	12.1 (2.2)	11.9 (2.2)		
Anxiety 12 mpd	11.8 (2.6)	12.3 (2.1)		
Erectile Functioning 0 mpd	18.3 (8.1)	17.8 (8.8)	<.001*	5-25
Erectile Functioning 6 mpd	17.1 (8.6)	11.6 (7.4)		
Erectile Functioning 12 mpd	16.7 (8.4)	14.4 (7.8)		
Prostate Symptoms 0 mpd	7.1 (5.8)	6.7 (5.6)	.004*	1-35
Prostate Symptoms 6 mpd	6.0 (5.5)	4.7(5.3)		
Prostate Symptoms 12 mpd	5.9 (4.5)	3.7 (3.3)		

SD: Standard Deviation; mpd=months post-diagnosis.

Fig.10 Sexual Functioning in AS and RT
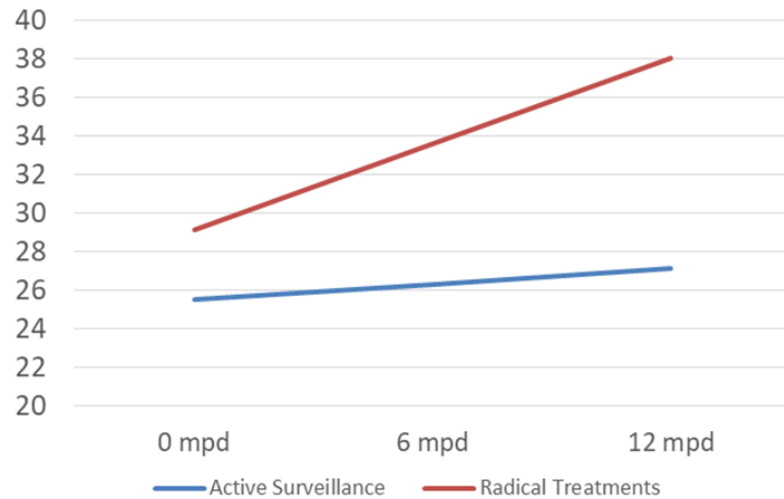
Fig.11 Anxiety over time in AS and RT
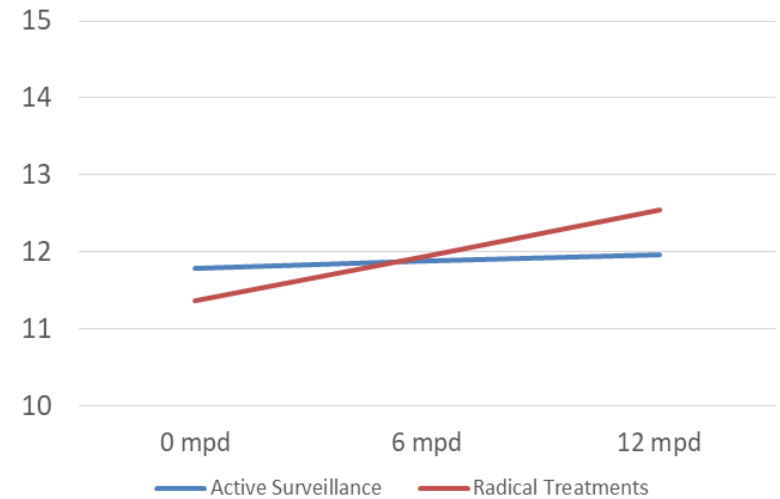
Fig.12 Erectile Functioning in AS and RT
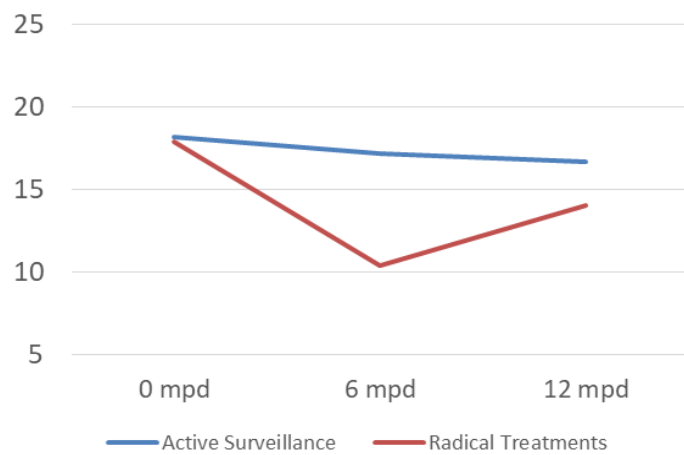
Fig.13 Prostatic symptoms in AS and RT
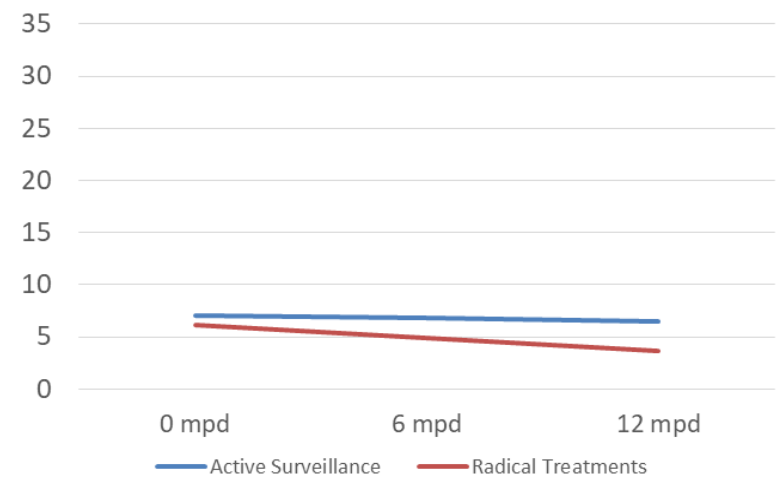
4.4. Discussion

The aim of the study was to test which are the variables that can be considered associated with the treatment choice at the time of diagnosis. The patient's decision regarding the best treatment for cancer is considered as a "shared" decision-making, since the patient tries to find the best solution with the physician's help. However, this choice is complex since the physician and the patient must take into account several factors such as the stage of disease, patient's age, and comorbid illnesses[218]. In this decisional process, not only the medical variables are relevant, but also the psychological ones, as the patient's beliefs, have an important role.

In order to achieve the goal of studying how the shared decision-making is done, the LOC beliefs have been considered. The LOC construct lets understand if the decision of the treatment could be perceived as under the control of the patient (so based on internal LOC beliefs) or, differently, under an external control (i.e., control of chance, doctors or others powerful).

In the results of this study, it emerged that the more the patients believe in the doctors' control on their health, the higher is the probability of choosing AS. As already reported, the treatment decision is often "not shared" in clinical practice. This can happen because in the patient-doctor relation, the doctor is placed in a position of power because of the medical knowledge. The doctor is expected to decide which is the best treatment option for the patient, and to make recommendations, whereas the patient is expected to comply with them (Model of Guidance-Cooperation[219,220]). Moreover, also the type of physician resulted to be associated with the probability of the RTs choice. In particular, having a radiation oncologist as physician at the time of diagnosis, increases the probability of choosing RTs. This can be explained by the fact that also the physicians' beliefs can have a role in the recommendations given to patients. As reported in literature indeed, urologists are more likely to agree that AS is effective than radiation oncologists, and report comfort by recommending it to low-risk prostate cancer patients[211]. Moreover, the fact that in our sample there are more urologists then radiation oncologists could partly explain the reason why (besides evaluations of the patients' medical conditions) our sample is mostly composed by prostate cancer patients under AS.

Moreover, other variables can be predictors of major probability of choosing AS.
Results indicate that higher age and low level of Gleason score can also predict higher probability of choosing AS. In clinical practice, indeed, AS is recommended especially for people who can't bear the side effects or that must avoid medical complications of the active

treatments, and this is the case of the elderly people. Moreover, as a semi-structured interview to 21 cancer patients (aged 48-70) have highlighted, prostate cancer patients' treatment choice (AS or watchful waiting or not) is based also on their beliefs regarding the age and which can be the best treatment. In particular, one of those beliefs is "WW/AS is only appropriate for older men." and if the person is "young" he should reject this option[46].

Moreover, high Gleason scores (that indicates how much the cancer is aggressive) is positively associated with the probability of choosing RTs. Maybe this result can be explained by the fact that the RTs can be the best choice in case of an aggressive cancer with a probable progression.

Furthermore, several dimensions have been measured in patients under AS or RTs over time. Regarding the HRQoL functional dimensions (EORTC QLQ C30 functioning scales), there are no differences in the two groups over time. This result can be explained by the fact that the sample is composed by prostate cancer patients at low risk and for this type of disease stage there cannot be an important HRQoL damage. Furthermore, also in a study on prostate cancer patients at low risk under radical prostatectomy or AS with 4 measurement times (baseline, 1, 2, and 3 years) it has been found a similar result: no differences were found between the two groups regarding the mental and physical HRQoL dimensions (measured with the SF-36) over time[26].

However, some differences have been found between the two groups of patients under AS or RTs over time.

Regarding the difference in the anxiety levels over time, it emerged that in both groups the anxiety is slightly significant (threshold ≥ 11[74]) but it is mostly stable under AS, whereas under RTs is not. For the patients under AS, the anxiety can be due to the monitoring of the disease including the PSA testing and the uncertainty of not knowing the progression of the illness[221]. So in this study the anxiety levels could be resulted stable because AS patients make PSA testing and biopsies over their illness at fixed time intervals (every 3 months). Psychological cognitive reframing techniques, based on the reconceptualization of the uncertainty during the illness (e.g., strategy focused on the acceptance), are often proposed to patients in order to provide them the psychological help to manage the uncertainty of their condition[221]. On the other hand, an increasing anxiety in the group of patients under RTs could be explained by the difficulty in the management of the treatments' side effects[222].

Regarding the prostate cancer symptoms, the urinary symptoms trends changed only a little bit in both groups over time and stayed mild over the first year, whereas the erectile dysfunction trend in the two groups evolved in a very different way. Both the AS and RTs groups showed

a symptomatic erectile dysfunction (score$\leq$21[223]), but in the radically treated prostate cancer patients the erectile dysfunction level is lower. Moreover, for these patients, a rebound trend at 6 months in erectile functioning has been observed. This result for patients under RTs could be explained by the fact that the sample of trained patients is composed mostly by patients under radiotherapy and surgery, and the erectile dysfunction is a side effect that can be observed in the post-surgery period or during the radiotherapy since it is induced by the radiations[224,225]. Regarding the last symptom, the sexual functioning, the trends over time resulted to be different but higher for the RTs group, which is a strange result since side effects of the radical treatments could involve the sexual area[19].

When the final database of the START study will be available, this result on the sexual functioning must be re-considered and re-tested. In this study, also because of the RTs sample size, all the radical treatments have been considered together and not analysed one by one.

Furthermore, since this study is not a randomised study but an observation one, it is unknown if the physician, considering some patients' medical characteristics (e.g., the level of sexual functioning), may have suggested a preference for one RTs arm. Specific characteristics of one group (e.g., surgery that mostly compose our RTs sample) may have influenced the increasing trend of the RTs patients' sexual functioning.

This study goes into the direction of taking into account both patients' and physicians' beliefs since they seem to have a role in the treatment decision-making. However, no questionnaires or information on the physicians' beliefs were available in this study. Further studies are needed to go more in depth into this patient-doctor relation and their communication during the visits for the treatment decision.

4.5. Ethical approval

This study received the approval of the ethics committee of the Molinette Hospital in Turin, and of the ethics committees of all the clinical centres involved.

5. THESIS DISCUSSION

HRQoL is a multidimensional construct on which several research protocols in oncology focus nowadays. During the thesis work, our attention has been focused on the cancer patients' HRQoL change and on which factors can be associated with it. We started from the assumption that the HRQoL changes could be different depending on cancer type, and we tried to see what could be the difference in the psychological factors possibly related to the HRQoL changes. Moreover, in the field of the shared treatment decision-making, we have investigated which psychological factors could be associated with the type of treatment chosen at baseline in prostate cancer. The study of the psychological factors in this field, could improve the understanding of the patient-physician relationship during the shared health-related decisions.

The first thematic deepened in the present thesis work is the study of the HRQoL change after cancer diagnosis (measured both in the ELCCA and START studies), which is linked in the literature with the psychological consequences of a traumatic event, i.e., the onset of cancer. After this traumatic event, patients may experience negative and positive changes reflecting patient's adaptation process to the illness and that can affect HRQoL. Indeed, as previous results[66] of the same cohort we studied showed us, rebound effects can appear in cancer, specific trajectories of HRQoL that decrease and increase to reach the beginning HRQoL level at the end of the measurements. The initial HRQoL decrease can be due to, as we have seen in the first chapters of thesis, the side effects of the treatments, and/or the psychological cancer trauma. Indeed, receiving a cancer diagnosis can lead to negative feelings such as anxiety and depression due to the shock of having a life-threatening illness.

However, cancer may also lead to positive changes and the literature about the adaptation and, in particular, on post-traumatic growth, have been evidenced it[226]. Positive changes can occur after traumatic events with high emotional impact as cancer (other examples are earthquake[227], child abuse[228], motor vehicle accidents[229]). More in depth, a resilient and adaptive process made of positive changes can start after the cancer diagnosis, and can positively affect the HRQoL[230,231]. The positive changes can consist in an increased appreciation of life in general, more meaningful interpersonal relationships, an increased sense of personal strength, changed priorities, and a richer existential and spiritual life (post-traumatic growth sub-dimensions)[232].

After a traumatic event, indeed, the person can start a process of positive changes at a psychological level (in cognitive schemas), called the post-traumatic growth. After having done this personal cognitive rebuilding, the person can be more resistant than before the trauma to possible future negative events[232].

However, the capacity of patients' adaptation and resilience (the capacity to maintain mental health also in stressful situations) can depend on personality (resilience is a personality trait), the level of optimism, hope or motivation, or your system characteristics (e.g., if the social system in which you live is supporting or not)[231,233–236]. Adaptation, indeed, is usually an individual process as the HRQoL.

The mixed models allow you to consider the fact that the HRQoL trends can change individually over time (because of the random effects), so in some way the fact that HRQoL can evolve in a different way among individuals can be considered. However, these analyses in the oncological field has often the aim to find similarities and differences between cancer groups. The researchers consider the HRQoL at a group level also to offer clinicians guidelines for better approaching different types of patients (according to type of cancer, treatments, age and so on…), which is useful for them from a practical point of view.

Is it possible to consider the HRQoL as individual phenomenon in the researches? What does it imply from a practical point of view? How to do it? And proceeding in this way, what can we transmit to physicians, who are not experts in psychology, for helping them in their work with patients?

Among the psychological factors that can be associated with HRQoL in cancer and that can be helpful tool for psychotherapies, there are LOC and coping.

The LOC, in particular, can be considered in different ways: was supposed to be a changing construct over time in the ELCCA study (Lazarus and Folkman's theory of reference[96]), and a stable personality trait in the START study (coming from another theory of reference, Rotter's social learning theory[85]). In the ELCCA study, indeed, the LOC has been measured at all the measurement times, whereas in the START study, the LOC has been measured only once at the diagnosis.

As we have seen in the ELCCA study, the LOC can change over time over the cancer illness. This result lets us imagine that even if the LOC is a personality trait and represents a predisposition, the cancer, as a traumatic event, can produce cognitive changes, in the habitual way of thinking.

In clinical practice, it is possible to find construct that indicate a general attitude for the explications of the events, or others that explicate a single event.

We can see this difference also in the items of the questionnaires chosen in the two studies. For example, for the same internal LOC sub-dimension, we have different items:
Belief situation-specific - "The beginning of my illness is mostly due to me" (IT. 17 of the Cancer LOC scale, ELCCA study), and
Belief as a general explication of a health event - "I am directly responsible if my condition will go better or worst" (IT. 6 of the MHLC-C Italian version, START study).
We can see that in the first item the belief is related to the "beginning of the illness" (situation), whereas the second item refers generally to the beliefs regarding the explication on the health. From a practical point of view, it means a different way of psychologically working on them.

In cognitive-behavioural therapy, the beliefs related to specific situations, are called situational automatic thoughts, a type of flexible beliefs, whereas the generalised belief, are called core beliefs and are inflexible[237,238]. The core beliefs form a cognitive schema that represents the base of the interpretation of the events and so the explication of certain behaviours[237,238]. Psychologists working with cancer patients can deal with both situational beliefs, such as "I have not the control in the situations related to the beginning of my cancer", or, more generalised beliefs, such as "I am not able to have control in any health situation" that are problematic for the patients since they create negative feelings.

To explain how this can happen we can propose here the Ellis's model ideated in 1957, the ABC model[120] where he explained that an event can activate a belief that can bring to emotional consequences. ABC stands for: A, the Activating event, B the Belief, and C the Consequences. For example, the belief of being the cause of the illness beginning (B), activated by the diagnosis (A) brings to negative emotions (C). It is true, indeed, that illness onset can bring negative feelings of self-blame and anxiety. This anxiety, added in a context in which the patient

is already scared, full of fear and anxiety can increase the probability of developing a post-traumatic stress disorder[239].

This is the reason why a belief can be dysfunctional, and psychologists have to work on them.

In case of dysfunctional situational automatic thought, the thoughts related to specific situations, psychologist could use a restructuring technique from the Cognitive-Behavioural Therapy, the dysfunctional thought record technique. Through this technique, it is possible to identify the dysfunctional thoughts linked with specific situations and negative feeling that the person has. The technique consists in asking the patient to think about the process situation-thought-emotion. For example, the psychologist can ask: "When you feel anxiety in this specific situation, what do you think?". Then the patient is invited to reflect on the dysfunctional belief linked to the feeling in the situation, and to propose alternative responses to the situations and the thoughts.

The psychologist, speaking with the patient about different situations, can find a patient's general themes of thought, a core belief[238].

The first step for psychologically working on a core belief is to recognise it, then, if it is dysfunctional, it must be decreased, and another much more helpful one must be increased.

Another way of identifying a core belief is the Downward Arrow Technique[238,240,241] that consists in a repeated questioning about the meaning of situational automatic thoughts till to arrive to the general belief.

For modifying the core beliefs, instead, a way is to examine critically the evidence that supports the old dysfunctional ones and to accumulate an increasing amount of evidence that supports the new good ones. If the patient identifies evidences that support the old dysfunctional beliefs, the psychologist can use the cognitive restructuring to disconfirm it. This procedure must be applied several times with the patient to be effective[238].

Sometimes the beliefs (situational or general core beliefs) are not irrational, and the patients have to accept them. For example, imagine that a woman with melanoma used to have unhealthy sun habits. In this case, the psychologist may let the patient accept the belief that her health behaviours can be partly responsible for the melanoma diagnosis, and accept the negative emotions related to this belief. The aim of this psychological intervention could be of structuring new healthy habits and letting the patient start to be more responsible for her health (develop the perceived personal control). A recent type of cognitive-behaviour therapy (CBT)

that focuses on the acceptance is the Acceptance and Commitment Therapy (ACT)[242]. This type of therapy has been tested successfully in case of breast cancer[242].

As we have seen in the START study's results, patients' beliefs also play a role in the field of the shared decision-making, not only in their adaptation over the illness.

The literature about the shared patient-doctor decision-making regards the patient-doctor relationship. This is an asymmetric relation where the physician has more medical knowledge of the therapies than the patient[243]. In clinical practice, this implies that very often the patients believe in the doctors' control on their health situations and usually follow the medical doctors' advices.

However, in the literature on shared medical decision-making, the situation in which the physicians' advices and the patients' preferences regarding treatments don't go in the same direction is reported[244]. For example, in the case of cancer, it can be the case if a patient have personal beliefs regarding the effectiveness and the personal tolerance to the treatments options, different from the physician's one[244]. For example, the patient can imagine that the side effects of a treatment can be too much for him, and he/she wants to choose the AS. On the other hand, the physician can think that the AS is not a good choice for the patient because of the patient's medical condition.

This type of situation leads to a mismatch between the physician's suggestion and the patient treatment preference[218], which could lead to dangerous consequences. Taking into account only the patient preferences and beliefs on a treatment, could mean planning an inappropriate treatment and potential medical problems during the illness for the patient.

A prostate cancer patient, for example, with an initial bowel dysfunction, should not choose the radiation therapy because the radiations to the prostate can cause acute and long-term bowel dysfunction[245]. In a study on early stage prostate cancer patients on the consequences of not shared treatment decisions, it has been shown that a mismatched brachytherapy and radiation therapy led to worsened urinary and bowel symptoms, respectively[245].

On the other hand, following only the doctors' advices without taking into consideration the patients' preferences and ideas, means that there can be possible risk of lack of patient compliance and adherence to the chosen therapy[246].

The patients' beliefs are very important in the decisions regarding the health, and they have to be taken into account.

Today several tools exist to help the patients clarify their preferences and beliefs, improve the patient-doctor communication, and so take the better medical decisions with the physician. Before the medical consultation for the treatment decision, for example, patients and their family/caregivers with a facilitator (any health professional), can identify and plan questions and concerns to speak about with the physician with the aid of a consultation planning[247]. Using this tool the patient can have clear beliefs and ideas on the several treatments options before entering to visit[247]. Actually, during the visit, the physician often gives to the patient a manual that explains the several possible treatments. For better explaining the different treatment options and improve the patient' understanding, the doctor can use decision boards, visual displays containing graphics and text with the different risks and benefit of each treatment. These tools can give to the patient both the possibility of having clear understanding and beliefs on the treatments and their side effects, and increase their sense of control on their health (since their feel to take part in the final decision).

Also from a psychological point of view, it is possible to take into account the beliefs related to the shared medical decisions. A technique to do this with early stage cancer patients can be the psychodrama, a role-play technique[248,249]. Using the psychodrama technique, the psychologist can allow the patient to change the role, as if he/she was the physician. In the role of the physician, the patient can understand the physician' point of view in the medical situation. This type of work can increase not only the trust in the patient for the physician, but also the comprehension of the physician's position regarding the advices given.

As we have seen, the beliefs are important tools to consider in psycho-oncology. And currently, the research is going to the direction of discovering the importance of these psychological variables (as the LOC for example), but this means an increasing in training for the physicians, and the allocation of more responsibilities, more than they already have. Reflecting on the fact that very often physicians don't have the time for taking care of the patients' beliefs and often the communication with them is based on their medical beliefs, maybe other roads might be possible. Maybe in the oncological division it should be better to increase the presence of the psychologists trained on the treatments, in order to intervene in the patient-doctor communication, and in the shared decision making, when the patient doesn't trust in the doctor. Moreover, the presence of the psychologists, trained on the way of working on the coping

strategies and patients' beliefs, remain essential for the patients' support and their adaptation during the illness.

Limitations and Perspectives

As we have seen in this thesis and in the results of the ELCCA study, it is important to consider both beliefs and the coping strategies together, since they both have an effect on the HRQoL; in the START study, however, we have taken into account the LOC beliefs and not the coping strategies.

In the field of the shared medical decision-making, the information seeking and the support of the families/caregiver, which both are coping strategies, take a role in the process that lead to the final treatment decisions. Cancer patients can find information on the Internet (active seeking information) or, in the patient-doctor exchange during the communication, asking to the physician (passive seeking information). The information seeking can help patients to form their explications on the health (LOC)[250,251], and to create the personal ideas (social representations) of the treatments, side effects, and symptoms that the patient has during the shared medical decision.

Regarding the family support, for example, this type of support has been studied at the time of diagnosis and during treatments[252]. Shaw et al. showed that the family support has a role in the shared treatment decision making process of prostate cancer patients [252]. This study let us think that the point of view of the families must be taken into consideration in the studies on treatment choice making, as well as the patient's point of view. Research could continue to analyse the type of communication between the partner, the patient and the physician during the visit, to understand in depth how and if the shared decision making is really "shared" or not. For doing this, maybe qualitative analysis can be done, using video to register the communication, with a software for video content analysis.

There are some variables that we didn't consider and that should be proposed in a further study, the measurement of the treatment and the psychological support of the patients. Regarding the treatments, for example, researchers should register the beginning/end of the treatments, and the type of treatment done, in order to see if the treatments influence the HRQoL over time and if there are influences according to the treatment type on the evolution of the HRQoL. Moreover, regarding the psychological support, it must consider that we actually don't know if the HRQoL trends in breast cancer and melanoma patients are also due to possible

psychotherapeutic interventions patients undergo. Regarding psychotherapies, it should be interesting to see if there are any difference in the HRQoL trends over time of cancer patients according to the type of psychotherapy done.

Moreover, a diagnosis of cancer is a very stressful episode for the patients and their families. Patients, partners and other family members can have stress reactions and can suffer from clinical levels of depression and severe levels of anxiety[253]. Because of the fact that, according to the biopsychosocial framework, the social area can influence the individual, and because of the fact that the family support has an effect on the patient's HRQoL, maybe the family's HRQoL should be taken into account in the study of the patients' HRQoL over time. In this case, the electronic tools to measure the HRQoL could be helpful and the families could fill the questionnaires during the patients' visits.

Moreover, it could be of interest to analyse the relationship between the HRQoL and other important variables in psycho-oncology, such as hopes and expectations. There are some models, indeed, that highlighted the relation between these variables and the HRQoL.

The expectation model of Calman[254], for example, defined the cancer patients' HRQoL considering the aims and goals in life, and the reality as well. For Calman[254] the HRQoL is defined as a measure of the difference between the hopes and the expectations (e.g. perceived future and current goals) and the reality. In particular, the HRQoL is assumed to get better as reality and hopes/expectations get closer. The hopes and the expectations are concepts studied in psycho-oncology, since during the oncological illness, the patient can have several types of hopes: "being cancer free", "being able to continue my life", "being close with the family", and so on[255]. Moreover, in clinical practice, distance between hopes, goal pursuit and reality can represent the objective of psychological support intervention for cancer patients in order to increase the HRQoL. The psychological work with cancer patients at early stage can consist in the definition of a possible goal, such as "being cancer free", and of possible ways to reach it: attending all the radiation appointments, for example, reading articles on cancer prevention and treatment, attending a cancer support group or clearly communicating any new symptoms to the oncologist. However, sometimes the patients' goals are not realistic because of their medical or psychological condition (e.g., the objective "being cancer free" for cancer patients at advanced stage). Thus, in this case, it is only possible to work on the acceptance of their condition or/and on the definition of new goals and expectancies. For example, during the patients' dying process, a psychological goal could be "achieving a good death", that can be reached defining and managing the best way for the patient to "say goodbye" to their loved

ones. Defining new objectives can be a way of reducing the distance between reality and hopes, and of taking care of the patients' HRQoL level.

Also patients' needs could be considered in the study of HRQoL[256]. This aspect has not been considered in the studies of the thesis. According to the model of Hunt and McKenna[256] about this relation, the more the individual needs are satisfied (such as self-esteem, status, identity, love, security, affection, enjoyment, food, creativity, pain avoidance, sleep, and activity), the higher the HRQoL.

Several unsatisfied needs, indeed, can appear for cancer patients during diagnosis and treatments: psychological (e.g., support for the feelings of sadness), health information (e.g., being given explanations on treatments), physical and daily living (e.g., support for the lack of energy and tiredness), sexuality (e.g., changes in sexual relationships), and patient care (e.g., hospital staff attending promptly to physical needs) needs[257–260].

In a research on the care and communication needs, it seems that different levels of needs can appear for different types of cancer: in melanoma and breast cancer patients for example, it has been found that more than 50 % of melanoma patients felt their doctors lacked concern for their ability to cope with the disease, whereas only a third of breast cancer patients expressed this complaint[135]. Slightly more melanoma patients than breast cancer patients experienced the lack of empathy and communication[135].

Not meeting the needs (e.g., psychological, health information, physical and daily living, patient care and sexuality) in cancer was found to be significantly associated with more psychological distress and lower level of Global Health status[260] at the diagnosis, and to the usage of negative coping strategies, such as avoidance at 6 months after cancer diagnosis (prostate, colorectal, female breast, lung, melanoma, non-Hodgkin's lymphoma, leukaemia, or head and neck)[257,261].

Maybe the patients can have different needs and hopes according to the types of cancer and type of prognosis. For example, researchers could compare the pancreatic cancer patients, who often have a poor prognosis[262], with another type of cancer which usually has a better prognosis, such as the melanoma at early stage, in order to have information regarding the specificity of each type of cancer regarding their needs and hopes, and to know how these factors are associated to the HRQoL over time.

Implications for clinical psychologists, oncologists and other professionals involved in the diagnosis and treatment of cancer

This thesis goes into the direction of considering the psychological aspects in the daily practice and during the management of the patients. This means not only that psychologists should be included in the multidisciplinary units of oncological services, but also that a psychological training for other professionals that work with cancer patients could be necessary. In this thesis, indeed, it has been shown that patients' and physicians' beliefs can determine the choices related to patients' health and how the patients feel during their illness. Furthermore, helping patients to manage properly their feelings and ideas on the illness could be really relevant in their perception of HRQoL over time. It is important to learn how to help patients using correct approach to the management of their illness in order to improve the HRQoL. In practice, professionals in oncological settings should take care of breast cancer and melanoma patients that are mostly young and live with a partner, asking them, for example, how they and their partners feel regarding the pathology and how they are managing it. If the professionals (e.g., trained nurses) see the need of psychological support, they should propose this in order to improve the HRQoL over time of their patients. The same attention should be given to those patients who vent their negative emotions in public (e.g., sadness or angry): it is important to hear and reassure them regarding their situation, let them feel that they have a hope and that their health situation will be better (in case of cancer at low risk. e.g., taking care of themselves and following doctors' advices). A good strategy could be to propose to patients or their families supportive groups with other people in the same situation and/or people that lived the same situation (e.g., people survived to cancer) in order to share their feelings and worries. Hearing that other people can have the same problems, and speaking with them about the possible solutions, maybe be very helpful for them and can help to maintain a good HRQoL over time. Moreover, in order to improve the positive coping strategies for the management of the illness (e.g., information seeking), nurses and oncological professionals should always give to patients brochures and suggest books to read before/during/after the visits with physicians to clarify their ideas on the illness. All the professionals that hear a patient having a possible wrong idea on the illness (e.g., it is my fault if I had a cancer diagnosis) should suggest him to seek information regarding the possible causes of his illness (positive active coping strategy) or explain his the actual possible causes. Training days in hospital with some experts could be proposed for melanoma/breast cancer patients, for example, in order to stimulate the information seeking and avoid the possible denial of the illness (which could be deleterious for the HRQoL over time). The information seeking is not only important for the general management of the illness, but also for the treatments decision making. It is common, indeed,

that patients deciding for the right treatment, are passive (they do not always actively form an idea on which treatment could be the best for them) and follow the doctors' advices.

So for physicians only, it is important that they are always aware of their beliefs on the possible cancer treatments efficacy and ask always themselves if their beliefs are scientifically supported or not, since they have an important role in the patients' treatment decisions. The patients, indeed, very are often compliant with physicians' suggestions.

Conclusions

The focus of this thesis work is the study of the psychological cognitive mechanisms that can be associated with the HRQoL evolution over time and with the shared treatment decision-making. In the ELCCA study, we started on the assumption that the HRQoL changed in different ways according to the type of cancer, and we tried to highlight the difference in the psychological variables that could be associated with these different trends of HRQoL in breast cancer and melanoma patients. Sometimes the generic term "cancer" lets the people forgive that this term include some different realities and illness experiences that can have different consequences on the HRQoL.

Also in the shared treatment decision-making with prostate cancer patients, we have seen that the psychological variables have a role. In particular, the patients' belief in the doctor's control seemed very important in this field. This result lets us think that today the decisions done during the illness by patients are not really shared, but they are mostly based on the trust on the physician's competence. Further studies are needed in order to understand more the decisional process.

The results of this thesis go into the direction of taking into account the beliefs and strategies used by the patients to face the situation related to the illness. This can be done for proposing a better support by psychological interventions or for better understand the shared decision-making at the diagnosis in the oncological setting.

6. BIBLIOGRAPHY

1. World Health Organization. Data and Statistics. *who.int* Available at: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics. (Accessed: 20th March 2018)

2. National Cancer Institute. Cancer staging. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/diagnosis-staging/staging. (Accessed: 20th March 2018)

3. National Cancer Institute. Risk Factors for Cancer. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk. (Accessed: 5th April 2018)

4. National Cancer Institute. Sunlight. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/sunlight. (Accessed: 5th April 2018)

5. Hecht, S. S. Lung carcinogenesis by tobacco smoke. *Int. J. Cancer* **131,** 2724–2732 (2012).

6. National Cancer Institute. Arsenic. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/arsenic. (Accessed: 5th April 2018)

7. National Cancer Institute. Human Immunodeficiency Virus (HIV). *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents#hiv. (Accessed: 5th April 2018)

8. National Cancer Institute. Helicobacter pylori (H. pylori). *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents#hiv. (Accessed: 5th April 2018)

9. National Cancer Institute. Schistosoma hematobium. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents#hiv. (Accessed: 5th April 2018)

10. ECIS - European Cancer Information System. Estimates of cancer incidence and mortality in 2018, for all countries. Available at: https://ecis.jrc.ec.europa.eu/explorer.php?$1-All$2-All$4-1,2$3-0$6-0,14$5-

null,null$7-7$0-0$CEstByCountry$X0_8-3$CEstRelative$X1_8-3$X1_9-AEE.
(Accessed: 15th May 2018)

11. United Nations. World population prospects. The 2010 Revision. (2011). Available at: http://www.un.org/en/development/desa/population/publications/pdf/trends/WPP2010/ WPP2010_Volume-I_Comprehensive-Tables.pdf. (Accessed: 24th July 2018)

12. Ferlay, J. *et al.* Cancer incidence and mortality patterns in Europe : Estimates for 40 countries in 2012. *Eur. J. Cancer* **49,** 1374–1403 (2013).

13. Eurostat. Causes of death — standardised death rate, 2014 (per 100 000 inhabitants). (2017). Available at: http://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Causes_of_death_—_standardised_death_rate,_2014_(per_100_000_inhabitants)_YB17.png. (Accessed: 18th May 2018)

14. De Angelis, R. *et al.* Cancer survival in Europe 1999-2007 by country and age: Results of EUROCARE-5 - A population-based study. *Lancet Oncol.* **15,** 23–34 (2014).

15. Dickens, E. Principles of cancer treatment by chemotherapy. *Surgery* **36,** 134–138 (2017).

16. National Cancer Institute. Chemotherapy Can Cause Side Effects. Available at: https://www.cancer.gov/about-cancer/treatment/types/chemotherapy. (Accessed: 10th April 2018)

17. Sloan Memorial Kettering Cancer Center. Side Effects of Chemotherapy. Available at: https://www.mskcc.org/cancer-care/diagnosis-treatment/cancer-treatments/chemotherapy/side-effects-chemotherapy. (Accessed: 10th April 2018)

18. National Cancer Institute. Radiation Therapy to Treat Cancer. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy. (Accessed: 10th April 2018)

19. United Kingdom National Health Service. Radiotherapy. *nhs.uk* Available at: https://www.nhs.uk/conditions/radiotherapy/side-effects/. (Accessed: 10th April 2018)

20. American Society of Clinical Oncology (ASCO). Side Effects of Surgery. *cancer.net* Available at: https://www.cancer.net/navigating-cancer-care/how-cancer-treated/surgery/side-effects-surgery. (Accessed: 10th April 2018)

21. Mccullough, A. R. Sexual Dysfunction After Radical Prostatectomy. *Rev. Urol.* **7,** S3–S10 (2005).

22. Vomvolaki, E., Kalmantis, K., Kioses, E. & Antsaklis, A. The effect of hysterectomy on sexuality and psychological changes. *Eur. J. Contracept. Reprod. Heal. Care* **11,** 23–27 (2006).

23. European Society for Medical Oncology (ESMO). ESMO Patient Guide Series. Available at: http://www.esmo.org/content/download/124130/2352601/file/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf. (Accessed: 10th April 2018)

24. National Cancer Institute. Hormone Therapy to Treat Cancer. *cancer.gov* Available at: https://www.cancer.gov/about-cancer/treatment/types/hormone-therapy. (Accessed: 11th April 2018)

25. Cancer Research UK. Side effects of hormone therapy in men. Available at: http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/hormone-therapy/side-effects-men. (Accessed: 26th May 2018)

26. Banerji, J. S. *et al.* A prospective study of health-related quality-of-life outcomes for patients with low-risk prostate cancer managed by active surveillance or radiation therapy. *Urol. Oncol. Semin. Orig. Investig.* **35,** 234–242 (2017).

27. Dall'Era, M. A. The economics of active surveillance for prostate cancer. *Curr. Opin. Urol.* **23,** 278–282 (2013).

28. Jefford, M. *et al.* Patient-reported outcomes in cancer survivors : a population-wide cross-sectional study. *Support Care Cancer* **25,** 3171–3179 (2017).

29. Mohamed, S. & Baqutayan, S. Review Article The Effect of Anxiety on Breast Cancer Patients. *Indian J. Psychol. Med.* **34,** 119–123 (2012).

30. Pasquini, M. & Biondi, M. Clinical Practice and Epidemiology Depression in cancer patients : a critical review. *Clin. Pract. Epidemiol. Ment. Heal.* **3,** 1–9 (2007).

31. Badr, H. & Carmack Taylor, C. L. Sexual dysfunction and spousal communication in couples coping with prostate cancer. *Psychooncology.* **18,** 735–746 (2009).

32. Browall, M. *et al.* Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. *Eur. J. Oncol. Nurs.* **12,** 180–189 (2008).

33. Burgess, C. *et al.* Depression and anxiety in women with early breast cancer : five year observational cohort study. *BMJ* **3,** 1–4 (2005).

34. Fobair, P. *et al.* Body image and sexual problems in young women with breast cancer. *Psychooncology.* **15,** 579–594 (2006).

35. Boswell, E. N. & Dizon, D. S. Breast cancer and sexual function. *Transl Androl Urol* **4,** 160–168 (2015).

36. De Pedro, M., Otero, B. & Martín, B. Fertility preservation and breast cancer: A review. *ecancer* **9,** 1–20 (2015).

37. Rezaei, M., Elyasi, F., Janbabai, G. & Moosazadeh, M. Factors Influencing Body Image in Women with Breast Cancer : A Comprehensive Literature Review. *Iran. Red Crescent Med. J.* **18,** 1–9 (2016).

38. Koçan, S. & Gürsoy, A. Body Image of Women with Breast Cancer After Mastectomy : A Qualitative Research. *J Breast Heal.* **12,** 145–150 (2016).

39. Lichtenthal, W. G., Cruess, D. G., Clark, V. L. & Ming, M. E. Investment in body image among patients diagnosed with or at risk for malignant melanoma. *Body Image* **2,** 41–52 (2005).

40. Vurnek, M., Buljan, M. & Blaji, I. Psychological Status and Illness Perceptions in Patients with Melanoma. *Coll. Antropol.* **32,** 75–78 (2008).

41. Mujumdar, U. J. *et al.* Sun protection and skin self-examination in melanoma survivors. *Psychooncology* **18,** 1106–1115 (2009).

42. Pearce, S. M. *et al.* A Longitudinal Study of Predictors of Sexual Dysfunction in Men on Active Surveillance for Prostate Cancer. *Sex. Med.* **3,** 156–164 (2015).

43. Tavlarides, A. M. *et al.* Evaluation of the association of prostate cancer-specific anxiety with sexual function, depression and cancer aggressiveness in men 1 year following surgical treatment for localized prostate cancer. *Psychooncology* **22,** 1328–35 (2013).

44. Anderson, J. *et al.* Anxiety in the management of localised prostate cancer by active surveillance. *BJUI* **114,** 55–61 (2014).

45. Dale, W., Bilir, P., Han, M. & Meltzer, D. The Role of Anxiety in Prostate Carcinoma : *Cancer* **104,** 467–478 (2005).

46. Xu, J., Neale, A. V. & Dailey, R. K. Patient Perspective on Watchful Waiting / Active Surveillance for Localized Prostate Cancer. *JABFM* **25,** 763–770 (2012).

47. Torrance, G. W. Utility approach to measuring health-related quality of life. *J. Chronic Dis.* **40,** 593–603 (1987).

48. Post, M. Definitions of Quality of Life: What Has Happened and How to Move On. *Top. Spinal Cord Inj. Rehabil.* **20,** 167–180 (2014).

49. Bottolomey, A. The Cancer Patient and Quality of Life. *Oncologist* **7,** 120–125 (2002).

50. Taillerfer, M.-C., Dupuis, G., Roberge, M.-A. & Le May, S. Health-related quality of life models: systematic review of the literature. *Soc. Indic. Res.* **64,** 293–323 (2003).

51. Bakas, T. *et al.* Systematic review of health-related quality of life models. *Health Qual. Life Outcomes* **10,** 1–12 (2012).

52. Lavdaniti, M. & Tsitsis, N. Definitions and Conceptual Models of Quality of Life in Cancer Patients Theoretical Models Used in Quality of Life Research for Cancer Patients. *Heal. Sci. J.* **9,** 1–5 (2015).

53. Pigou, A. C. *The economics of welfare*. (McMillan, 1920).

54. Testa, M. & Simonson, D. C. Assessment of Quality-of-Life Outcomes. *Curr. Concepts* **334,** 835–840 (1996).

55. Alvarez-Diaz, A., Gonzalez, L. & Radcliff, B. The politics of happiness: on the political determinants of quality of life in the american states. *J. Polit.* **72,** 894–905 (2010).

56. Bagdonienė, D. Gyvenimo kokybės ir gyventojų kokybės sąvokų apibrėžimas. *Ekon. ir Vadyb. 2000 Aktual. ir Metodol. tarptautinės Konf. pranešimų medžiaga* 46–48 (2000).

57. Susniene, D. & Jurkauskas, A. The Concepts of Quality of Life and Happiness – Correlation and Differences. *Inz. Ekon. Econ.* 58–66 (2009).

58. Engel, G. L. The need for a new medical model: a challange for biomedicine. *Science (80-.).* **196,** 129–136 (1977).

59. Wilson, I. B. & Cleary, P. D. Linking Clinical Variables With Health-Related Quality of Life : A Conceptual Model of Patient Outcomes. *J. Am. Med. Assoc.* **4,** 59–65 (1995).

60. Fayers, P. M. & Machin, D. *Quality of Life: the assessment, analysis and interpretation of patient-reported outcomes*. (Wiley & Sons, 2007).

61.   Quality of Life Research Unit. The Quality of Life Model. Available at: http://sites.utoronto.ca/qol/qol_model.htm. (Accessed: 12th April 2018)

62.   Raphael, D., Brown, I., Renwick, R. & Rootman, I. Assessing the Quality of Life of Persons with Developmental Disabilities: Description of a New Model, Measuring Instruments, and Initial Findings. *Int. J. Disabil. Dev. Educ.* **43,** 25–42 (1996).

63.   Ashing-giwa, K. T. The contextual model of HRQoL : A paradigm for expanding the HRQoL framework. *Qual. Life Res.* **14,** 297–307 (2005).

64.   Ferrans, E. C., Zerwic, J. J., Wilbur, E. J. & Larson, J. L. Conceptual Model of Health-Related Quality of Life. *J. Nurs. Scholarsh.* **37,** 336–342 (2005).

65.   Sosnowski, R. *et al.* Basic issues concerning health-related quality of life. *Cent. Eur. J. Urol.* **70,** 206–211 (2017).

66.   Bourdon, M. *et al.* Changes in quality of life after a diagnosis of cancer: a 2-year study comparing breast cancer and melanoma patients. *Qual. Life Res.* **25,** 1969–1979 (2016).

67.   Ansmann, L. *et al.* Health-related quality of life in active surveillance and radical prostatectomy for low-risk prostate cancer: a prospective observational study. *BJU Int.* **122,** 401–410 (2018).

68.   Lehto, U. S., Ojanen, M. & Kellokumpu-Lehtinen, P. Predictors of quality of life in newly diagnosed melanoma and breast cancer patients. *Ann. Oncol.* **16,** 805–816 (2005).

69.   Sosnowski, R. *et al.* Quality of life in penile carcinoma patients – post-total penectomy. *Cent. Eur. J. Urol. 204 Androl. Cent Eur J Urol* **69,** 204–211 (2016).

70.   Schapira, M. M., Lawrence, W. F., Katz, D. A. & Mcauliffe, T. L. Effect of Treatment on Quality of Life among Men with Clinically Localized Prostate Cancer. *Med. Care* **39,** 243–253 (2001).

71.   Breastcancer.org.   Lymphedema.   (2018).   Available   at: https://www.breastcancer.org/treatment/lymphedema. (Accessed: 8th July 2018)

72.   Fowler, F. J., Wennberg, J. E. & Timothy, R. P. Symptom status and quality of life following prostatectomy. *Jama* **259,** 3018–3022 (1988).

73.   Snyder, C. R. *et al.* The development and validation of the State Hope Scale. *J. Pers. Soc. Psychol.* **70,** 321–335 (1996).

74. Zigmond, A. S. & Snaith, R. P. The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* **67,** 361–370 (1983).

75. Ware, J. E. J. & Sherbourne, C. D. The MOS 36-ltem Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med. Care* **30,** 473–83 (1992).

76. Ferrans, C. E. Development of a quality of life index for patients with cancer. *Oncol. Nurs. Forum* **17,** 9–15 (1990).

77. Leidy, N. Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nurs. Res.* **43,** 196–202 (1994).

78. Sprangers, M. A. . & Schwartz, C. E. Integrating response shift into health-related quality of life research: a theoretical model. *Soc. Sci. Med.* **48,** 1507–1515 (1999).

79. Rotter, J. B. Generalized expectancies for internal versus external control of reinforcement. *Psychol. Monogr. Gen. Appl.* **80,** 1–28 (1966).

80. Levenson, H. Activism and Powerful Others: Distinctions Within the Concept of Internal-External Control. *J. Pers. Assess.* **38,** 377–383 (1974).

81. Wallston, K. A., Stein, M. J. & Smith, C. A. Form C of the MHLC Scales: A Condition-Specific Measure of Locus of Control. *J. Pers. Assess.* **63,** 534–553 (1994).

82. Pruyn, J. *et al.* De Locus of Control-Schaal voor Kankerpatienten. *Tijdschift voor Soc. Gezondheidszorj* **66,** 404–408 (1988).

83. Cousson-Gèlie, F., Irachbal, S., Bruchon-Schweitzer, M., Dilhuydy, J. M. & Lakdja, F. Dimensions of cancer Locus of Control scale as predictors of psychological adjustment and survival in breast cancer patients. *Psychol. Rep.* **97,** 699–711 (2005).

84. Lazarus, R. S. & Folkman, S. *Stress, coping and adaptation.* (Springers, 1984).

85. Wallston, K. a, Wallston, B. S. & Devellis, R. Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Educ. Monogr.* **6,** 160–170 (1978).

86. Rodríguez, V. M. *et al.* What Women Think: Cancer Causal Attributions in a Diverse Sample of Women. *J Psychosoc Oncol.* **33,** 48–65 (2015).

87. Hay, J. *et al.* Personal attributions for melanoma risk in melanoma-affected patients and family members. *J. Behav. Med.* **34,** 53–63 (2011).

88. Peuker, A. C. W. B., Armiliato, M. J., de Souza, L. V. & de Castro, E. K. Causal

attribution among women with breast cancer. *Psicol. Reflexão e Crítica* **29,** 4 (2016).

89. Ranchor, A. V. *et al.* The adaptive role of perceived control before and after cancer diagnosis: A prospective study. *Soc. Sci. Med.* **70,** 1825–1831 (2010).

90. Thompson, S., Sobolew-Shubin, A., Galbraith, M., Schwankovsky, L. & Cruzen, D. Maintaining perceptions of control: Finding perceived control in low-control circumstances. *J. Pers. Soc. Psychol.* **64,** 293–304 (1993).

91. McVey, J., Madill, A. & Fielding, D. The relevance of lowered personal control for patients who have stoma surgery to treat cancer. *Br. J. Clin. Psychol.* **40,** 337–360 (2001).

92. Maddi, S. R. The Story of Hardiness: Twenty Years of Theorizing, Research, and Practice. *Consult. Psychol. J.* **54,** 173–185 (2002).

93. Helmreich, I. *et al.* Psychological interventions for resilience enhancement in adults (Protocol). *Cochrane Database Syst. Rev.* 1–43 (2017).

94. Gendlin, E. *Focusing*. (Bantam, 1978).

95. Pagnini, F., Bercovitz, K. & Langer, E. Perceived Control and Mindfulness: Implications for Clinical Practice. *J. Psychother. Integr.* **26,** 91–102 (2016).

96. Lazarus, R. & Folkman, S. *Stress, appraisal and coping*. (Springer, 1984).

97. Šprah, L. & Šoštarič, M. Psychosocial coping strategies in cancer patients. *Radiol Oncol* **38,** 35–42 (2004).

98. Cramer, P. Coping and defense mechanisms: What's the difference? *J. Pers.* **66,** 919–946 (1998).

99. Alker, H. A. Coping, defense and socially desirable responses. *Psychol. Rep.* **22,** 985–988 (1968).

100. Freud, S. in *The standard edition of complete works of Sigmund Freud. Transl. by James Strachey* 157–185 (The Hogart Press and the Institute of Psychoanalysis, 1896).

101. Freud, S. in *The standard edition of complete works of Sigmund Freud. Transl. by James Strachey* 43–61 (The Hogart Press and the Institute of Psychoanalysis, 1894).

102. Chabrol, H. & Callahan, S. *Mécanismes de défense et coping*. (Dunod, 2013).

103. Grebot, E., Paty, B. & Girard Dephanix, N. Styles défensifs et stratégies d'ajustement ou coping en situation stressante. *Encephale* **32,** 315–324 (2006).

104. Kramer, U. Coping and defence mechanisms: What's the difference? - Second act. *Psychol. Psychother. Theory, Res. Pract.* **83,** 207–221 (2010).

105. Carver, C. S., Scheier, M. F. & Weintraub, J. K. Assessing coping startegies: A theoretically based approach. *J. Pers. Soc. Psychol.* **56,** 267–283 (1989).

106. Coyne, J. C., Tennen, H. & Ranchor, A. V. Positive psychology in cancer care: A story line resistant to evidence. *Ann. Behav. Med.* **39,** 35–42 (2010).

107. Telch, C. F. & Telch, M. J. Group coping skills instruction and supportive group therapy for cancer patients: a comparison of strategies. *J. Consult. Clin. Psychol.* **54,** 802–808 (1986).

108. Kashani, F. L. *et al.* Stress Coping Skills Training and Distress in Women with Breast Cancer. *Procedia - Soc. Behav. Sci.* **159,** 192–196 (2014).

109. Daniels, S. Cognitive Behavior Therapy for Patients With Cancer. *J. Adv. Pract. Oncol.* **6,** 54–56 (2015).

110. Arch, J. J. & Mitchell, J. L. An Acceptance and Commitment Therapy (ACT) group intervention for cancer survivors experiencing anxiety at re-entry. *Psychooncology.* **25,** 610–615 (2015).

111. Folkman, S., Lazarus, R. S., Dunkel-Schetter, C., DeLongis, A. & Gruen, R. J. Dynamics of a Stressful Encounter. Cognitive Appraisal, Coping, and Encounter Outcomes. *J. Pers. Soc. Psychol.* **50,** 992–1003 (1986).

112. Dumont, M. in *Stress et adaptation chez l'enfant* (eds. Dumont, M. & Plancherel, B.) 53–68 (Presses de l'Université du Québec, 2001).

113. Tarquinio, C. & Spitz, E. *Psychologie de l'adaptation*. (De boech, 2012).

114. Moos, R. & Schaefer, J. *Coping with life crises An integrated approach*. (Plenum Press, 1986).

115. Moos, R. & Schaefer, J. in *Coping with physical illness* (Springer, 1984).

116. Moos, R. *Coping with physical illness*. (Springer Science & Business Media, 2012).

117. Oleson, M. & Shadick, K. M. G. Application of Moos and Schaefer's (1986) model to

nursing care of elderly persons relocating to a nursing home. *J. Adv. Nurs.* **18,** 479–485 (1993).

118. Bruchon-Schweitzer, M. *Psychologie de la santé. Modèles, concept et mèthodes.* (Dunod, 2002).

119. Paulhan, I. & Bourgeois, M. *Stress et coping, les stratégies d'ajustement à l'adversité.* (P.U.F., 1995).

120. Ellis, A. Rational psychotherapy and individual psychology. *J. Individ. Psychol.* **13,** 38–44 (1957).

121. Koolaee, A. K., Falsafinejad, M. R. & Akbari, M. E. The Effect of Stress Management Model in Quality of Life in Breast Cancer Women. *Iran. J. cancer Prev.* **8,** e3435 (2015).

122. Phelps, A. C. *et al.* Association between religious coping and use of intensive life-prolonging care near death among patients with advanced care. *J. Am. Med. Assoc.* **301,** 1140–1147 (2010).

123. Sood, A., Prasad, K., Schroeder, D. & Varkey, P. Stress management and resilience training among department of medicine faculty: A pilot randomized clinical trial. *J. Gen. Intern. Med.* **26,** 858–861 (2011).

124. Pahlevan Sharif, S. Locus of control, quality of life, anxiety, and depression among Malaysian breast cancer patients: The mediating role of uncertainty. *Eur. J. Oncol. Nurs.* **27,** 28–35 (2017).

125. Helgeson, V. S. & Cohen, S. Social support and adjustment to cancer: Reconciling descriptive, correlational, and intervention research. *Heal. Psychol.* **15,** 135–148 (1996).

126. Friedman, L. C. *et al.* Attribution of Blame, Self-forgiving Attitude and Psychological Adjustment in Women with Breast Cancer. *J. Behav. Med.* **30,** 351–357 (2007).

127. Gibbons, A., Groarke, A. M. & Sweeney, K. Predicting general and cancer-related distress in women with newly diagnosed breast cancer. *BMC Cancer* **16,** 1–9 (2016).

128. Farajzadegan, Z., Khalili, N. & Mokarian, F. Coping skill improve quality of life in women with breast cancer and maladaptive coping style. *Psychooncology.* **24,** 212–213 (2015).

129. Goli, F., Scheidt, C. E., Gholamrezaei, A. & Farzanegan, M. The Role of Locus of

Control and Attributional Style in Coping Strategies and Quality of Life among Iranian Breast Cancer and Colorectal Cancer Patients : A Pilot Study. *Int J Body Mind Cult.* **1,** 65–72 (2014).

130. Carver, C. S. *et al.* How important is the perception of personal control? Studies of early stage breast cancer patients. *Personal. Soc. Psychol. Bull.* **26,** 139–149 (2000).

131. Li, J. & Lambert, V. A. Coping strategies and predictors of general well-being in women with breast cancer in the People's Republic of China. *Nurs. Health Sci.* **9,** 199–204 (2007).

132. Ferrucci, L. M. *et al.* Causal attribution among cancer survivors of the ten most common cancers. *J. Psychosoc. Oncol.* **29,** 121–140 (2011).

133. Paek, M.-S., Ip, E. H., Levine, B. & Avis, N. E. Longitudinal Reciprocal Relationships Between Quality of Life and Coping Strategies Among Women with Breast Cancer. *Ann. Behav. Med.* **50,** 775–783 (2016).

134. Holzner, B. *et al.* Quality of Life in Breast Cancer Patients—Not Enough Attention for Long-Term Survivors? *Psychosomatics* **42,** 117–123 (2001).

135. Engel, J., Schlesinger-Raab, A., Emeny, R., Hölzel, D. & Schubert-Fritschle, G. Quality of life in women with localised breast cancer or malignant melanoma 2 years after initial treatment: a comparison. *Int. J. Behav. Med.* **21,** 478–486 (2014).

136. Schneider, A. *et al.* Impact of age, health locus of control and psychological co-morbidity on patients' preferences for shared decision making in general practice. *Patient Educ. Couns.* **61,** 292–298 (2006).

137. Deshpande, P., Sudeepthi, Bl., Rajan, S. & Abdul Nazir, C. Patient-reported outcomes: A new era in clinical research. *Perspect. Clin. Res.* **2,** 137 (2011).

138. Likert, R. A technique for the measurement of attitudes. *Arch. Psychol.* **22,** 5–55 (1932).

139. Weldring, T. & Smith, S. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Heal. Serv. Insights* **6,** 61 (2013).

140. Refolo, P., Minacori, R., Mele, V., Sacchini, D. & Spagnolo, A. G. Patient-reported outcomes (PROs): The significance of using humanistic measures in clinical trial and clinical practice. *Eur. Rev. Med. Pharmacol. Sci.* **16,** 1319–1323 (2012).

141. Basch, E. Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. *N. Engl. J. Med.* **376,** 103–105 (2017).

142. Fayers, P. M. & Machin, D. *Quality of Life: the assessment, analysis and interpretation of patient-reported outcomes*. (Wiley & Sons, 2007).

143. Greenhalgh, J. The applications of PROs in clinical practice: What are they, do they work, and why? *Qual. Life Res.* **18,** 115–123 (2009).

144. Snyder, C. F. & Aaronson, N. K. Use of patient-reported outcomes in clinical practice. *Lancet* **374,** 369–370 (2009).

145. Aaronson, N. K. *et al.* The European Organization for Research and Treatment for Use in International Clinical Trials in Oncology. *J. Natl. Cancer Inst.* **85,** 365–376 (1993).

146. Novick, M. R. The axioms and principal results of classical test theory. *J. Math. Psychol.* **3,** 1–18 (1966).

147. Smith, R. M. *Introduction to Rasch measurement: theory, models and applications*. (JAM Press, 2004).

148. Van der Linden, W. *Handbook of Item Response Theory*. (Chapman and Hall/CRC, 2018).

149. Kline, R. B. *Principles and practice of structural equation modeling*. (Guilford publications, 2015).

150. Jiang, S., Wang, C. & Weiss, D. J. Sample Size Requirements for Estimation of Item Parameters in the Multidimensional Graded Response Model. *Front. Psychol.* **7,** 1–10 (2016).

151. Embretson, S. & Reise, S. in *Item Response Theory for psychologists* (Lawrence Erlbaum Associates Inc., 2000).

152. Blanchin, M., Hardouin, J., Guillemin, F. & Falissard, B. Power and Sample Size Determination for the Group Comparison of Patient-Reported Outcomes with Rasch Family Models. **8,** (2013).

153. Fitzmaurice, G. M., Laird, N. M. & Ware, J. H. *Applied Longitudinal analysis*. (John Wiley & Sons, Ltd., 2004).

154. Pusponegoro, N. H., Rachmawati, R. N., Notodiputro, K. A. & Sartono, B. Linear Mixed

Model for Analyzing Longitudinal Data: A Simulation Study of Children Growth Differences. *Procedia Comput. Sci.* **116,** 284–291 (2017).

155. Verbeke, G. & Molenberghs, G. *Linear Mixed Models for Longitudinal Data*. (Springer, 2000).

156. Akaike, H. A new look at the statistical model identification. System identification and time-series analysis. *IEEE Trans. Automat. Contr.* **19,** 716–723 (1974).

157. Kenward, M. & Roger, J. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* **53,** 983–997 (1997).

158. Satterthwaite, F. Synthesis of variance. *Psychometrika* **6,** 309–316 (1941).

159. Orelien, J. G. & Edwards, L. J. Fixed-effect variable selection in linear mixed models using R2 statistics. *Comput. Stat. Data Anal.* **52,** 1896–1907 (2008).

160. Edwards, L. J., Muller, K., Wolfinger, R. D., Qaqish, B. F. & Schabenberger, O. An R2 statistic for fixed effects in the linear mixed model. *Stat. Med.* **27,** 6137–6157 (2008).

161. Cox, D. R. The Regression Analysis of Binary Sequences. *J. R. Stat. Soc.* **20,** 215–242 (1958).

162. Ghoncheh, M., Pournamdar, Z. & Salehiniya, H. Incidence and Mortality and Epidemiology of Breast Cancer in the World. *Asian Pacific J. Cancer Prev.* **17,** 43–46 (2016).

163. National Cancer Institute. Le cancer du sein en chiffres. Available at: http://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-du-sein. (Accessed: 1st February 2018)

164. World Health Organization. Skin cancer. Available at: http://www.who.int/uv/faq/skincancer/en/index1.html. (Accessed: 1st February 2018)

165. Schmidt, J. L., Wetzel, C. M., Lange, K. W., Heine, N. & Ortmann, O. Patients' experience of breast reconstruction after mastectomy and its influence on postoperative satisfaction. *Arch. Gynecol. Obstet.* **296,** 827–834 (2017).

166. Lepore, S. J. & Revenson, T. A. Social Constraints on Disclosure and Adjustment to Cancer. *Soc. Personal. Psychol. Compass* **1,** 313–333 (2007).

167. Brandão, T., Schulz, M. S. & Matos, P. M. Psychological adjustment after breast cancer: A systematic review of longitudinal studies. *Psychooncology.* **26,** 917–926 (2017).

168. Stanton, A. L. *et al.* Emotionally expressive coping predicts psychological and physical adjustment to breast cancer. *J. Consult. Clin. Psychol.* **68,** 875–882 (2000).

169. Avis, N. E., Crawford, S. & Manuel, J. Quality of life among younger women with breast cancer. *J. Clin. Oncol.* **23,** 3322–3330 (2005).

170. Danhauer, S. C., Crawford, S. L., Farmer, D. F. & Avis, N. E. A longitudinal investigation of coping strategies and quality of life among younger women with breast cancer. *J. Behav. Med.* **32,** 371–379 (2009).

171. Bonnaud-Antignac, A., Bourdon, M., Dréno, B. & Quéreux, G. Coping Strategies at the Time of Diagnosis and Quality of Life 2 Years Later. *Cancer Nurs.* **40,** E45–E53 (2017).

172. Danhauer, S. C. *et al.* Predictors of posttraumatic growth in women with breast cancer. *Psychooncology.* **22,** 2676–2683 (2013).

173. Watson, M., Greer, S., Pruyn, J. & Van den Borne, B. Locus of control and adjustment to cancer. *Psychol. Rep.* **66,** 39–48 (1990).

174. Carver, C. S. You want to measure coping but your protocol' too long: Consider the brief cope. *Int. J. Behav. Med.* **4,** 92–100 (1997).

175. Muller, L. & Spitz, E. Multidimensional assessment of coping: validation of the Brief COPE among French population. *Encephale* **29,** 507–518 (2003).

176. Vigneau, E. & Qannari, E. M. Clustering of Variables Around Latent Components. *Commun. Stat. -Simulation Comput.* **32,** 1131–1150 (2003).

177. Cheng, J. Real Longitudinal Data Analysis for Real People: Building a Good Enough Mixed Model Jing. *Stat Med* **29,** 504–520 (2010).

178. Gilbertson-White, S., Campbell, G., Ward, S., Sherwood, P. & Donovan, H. HHS Public Access. *Cancer Nurs.* **40,** 117–123 (2017).

179. Narjes Khalili, Ziba Farajzadegan, Fariborz Mokarian, F. & Bahrami, F. Coping strategies, quality of life and pain in women with breast cancer. *Iran J Nurs Midwifery Res.* **18,** 105–111 (2013).

180. Boinon, D. *et al.* Changes in psychological adjustment over the course of treatment for

breast cancer : the predictive role of social sharing and social support. *Psychooncology.* **23,** 291–298 (2014).

181. Ginter, A. C. & Braun, B. Social support needs of breast cancer patients without partners. *J. Soc. Pers. Relat.* 1–20 (2017).

182. Li, Q. & Yuen, A. A literature review on the mutual impact of the spousal caregiver-cancer patients dyads : ' Communication ' , ' reciprocal influence ' , and ' caregiver-patient congruence '. *Eur. J. Oncol. Nurs.* **18,** 58–65 (2014).

183. Else-quest, N. M., Loconte, N. K., Schiller, J. H. & Hyde, J. S. Perceived stigma, self-blame, and adjustment among lung, breast and prostate cancer patients. *Psychol. Health* **24,** 949–964 (2009).

184. Kulik, L. & Kronfeld, M. Adjustment to Breast Cancer: The Contribution of Resources and Causal Attributions Regarding the Illness. *Soc. Work Health Care* **41,** 37–57 (2005).

185. Frazier, P., Berman, M. & Steward, J. Perceived control and posttraumatic stress : A temporal model. *Appl. Prev. Psychol.* **10,** 207–223 (2002).

186. Brennan, J. Adjustment to cancer—coping or personal transition? *Psychooncology.* **10,** 1–18 (2001).

187. Howard-Anderson, J., Ganz, P. A., Bower, J. E. & Stanton, A. L. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: A systematic review. *J. Natl. Cancer Inst.* **104,** 386–405 (2012).

188. Kershaw, T. *et al.* Utility of the Rorschach technique for suicide risk evaluation in depressed women. *Psychol. Heal.* **19,** 139–155 (2004).

189. Zamanian, H. *et al.* Religious Coping and Quality of Life in Women with Breast Cancer. *Asian Pacific J. Cancer Prev.* **16,** 7721–7725 (2015).

190. Willard, M. in *Aide-mémoire: Thérapies Comportementales et Cognitives en 37 notions* (eds. Chapelle, F., Monié, B., Poinsot, R. & Willard, R. and M.) 218–223 (2014).

191. Poinsot, R. in *Aide-mémoire: Thérapies Comportementales et Cognitives en 37 notions* (eds. Chapelle, F., Monié, B., Poinsot, R. & Willard Rusinek and M.) 224–228 (Dunod, 2014).

192. Monié, B. in *Aide-mémoire: Thérapies Comportementales et Cognitives en 37 notions*

(eds. Chapelle, F., Monié, B., Poinsot, R. & Willard, R. and M.) 205–211 (Dunod, 2014).

193. Couper, J. W. *et al.* The psychological aftermath of prostate cancer treatment choices: a comparison of depression, anxiety and quality of life outcomes over the 12 months following diagnosis. *Med. J. Aust.* **190,** S86–S89 (2009).

194. Matthew, A. G. *et al.* Psychological distress and lifestyle disruption in low-risk prostate cancer patients: Comparison between active surveillance and radical prostatectomy. *J. Psychosoc. Oncol.* **7332,** 1–16 (2017).

195. Sciarra, A. *et al.* Psychological and functional effect of different primary treatments for prostate cancer: A comparative prospective analysis. *Urol. Oncol. Semin. Orig. Investig.* 1–15 (2018). doi:10.1016/j.urolonc.2018.03.022

196. Apolone, G., Filiberti, A., Cifani, S., Ruggiata, R. & Mosconi, P. Evaluation of the EORTC QLQ-C30 questionnaire: A comparison with SF-36 Health Survey in a cohort of Italian long-survival cancer patients. *Ann. Oncol.* **9,** 549–557 (1998).

197. van Leeuwen, M. *et al.* International evaluation of the psychometrics of health-related quality of life questionnaires for use among long-term survivors of testicular and prostate cancer. *Health Qual. Life Outcomes* **15,** 1 (2017).

198. Costantini, M. *et al.* Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support. Care Cancer* **7,** 121–7 (1999).

199. Rosen, R. C. *et al.* The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* **49,** 822–830 (1997).

200. Badia, X., Garcia-Losa, M. & Dal-Ré, R. Ten-language translation and harmonization of the international prostate symptom score: developing a methodology for multinational clinical trials. *Eur. Urol.* **31,** 129–140 (1997).

201. Ubbiali, A. *et al.* The usefulness of the multidimensional health locus of control form C (MHLC-C) for HIV+ subjects: An Italian study. *AIDS Care - Psychol. Socio-Medical Asp. AIDS/HIV* **20,** 495–502 (2008).

202. Fitzmaurice, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer

groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden . *JAMA Oncol.* **3,** 524–548 (2017).

203. Pernar, C. H., Ebot, E. M., Wilson, K. M. & Mucci, L. A. The Epidemiology of Prostate Cancer. *Cold Spring Harb. Perspect. Med.* (2018). doi:10.1101/cshperspect.a030361

204. Roth, A. J., Weinberger, M. I. & Nelson, C. J. Prostate Cancer: Quality of Life, Psychosocial Implications and Treatment Choices. *Futur. Oncol.* **4,** 561–568 (2009).

205. Klotz, L. Active surveillance, quality of life, and cancer-related anxiety. *Eur. Urol.* **64,** 37–39 (2013).

206. Prostate Cancer Foundation. What is active surveillance. (2018). Available at: https://www.pcf.org/c/active-surveillance/. (Accessed: 25th May 2018)

207. Chung, M. S. & Lee, S. H. Current status of active surveillance in prostate cancer. *Investig. Clin. Urol.* **57,** 14 (2016).

208. Hayes, J. H. *et al.* Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *Jama* **304,** 2373–2380 (2010).

209. Skriapas, K., Konstandinidis, C., Samarinas, M., Kartsaklis, P. & Gekas, A. Pain level and anal discomfort during transrectal ultrasound for guided prostate biopsy. Does intrarectal administration of local anesthetic before periprostatic anesthesia makes any difference? *Ital. J. Urol. Nephrol.* **61,** 137–142 (2009).

210. Sidana, A. *et al.* Treatment decision-making for localized prostate cancer:what younger men choose and why. *Prostate* **72,** 58–64 (2012).

211. Kim, S. P. *et al.* Perceptions of active surveillance and treatment recommendations for low-risk prostate cancer: Results from a national survey of radiation oncologists and urologists. *Med. Care* **52,** 579–585 (2014).

212. Helmes, A. W., Bowen, D. J. & Bengel, J. Patient preferences of decision-making in the context of genetic testing for breast cancer risk. *Genet. Med.* **4,** 150–157 (2002).

213. Brincks, A. M., Feaster, D. J., Burns, M. J. & Mitrani, V. B. The Influence of Health Locus of Control on the Patient-Provider Relationship. *Psychol. Health Med.* **15,** 720–728 (2010).

214. Koscielak, R. Cognitive determinants of health behaviour in women with breast cancer.

27–41 Available at: http://www.euh-e.edu.pl/media/_js/filemanager/userfiles/wydawnictwo/Polish_13/02_Cognitive_determinants_of_health_behaviour_in_women_27-41.pdf. (Accessed: 20th May 2018)

215. Van Andel, G. *et al.* An international field study of the EORTC QLQ-PR25: A questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur. J. Cancer* **44,** 2418–2424 (2008).

216. Rosen, R. C. *et al.* The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* **49,** 822–830 (1997).

217. Barry, M. J. *et al.* The American urological association symptom index for benign prostatic hyperplasia. *J. Urol.* **148,** 1549–1557 (1992).

218. Zafar, S. Y., Alexander, S. C., Weinfurt, K. P., Schulman, K. A. & Abernethy, A. P. Decision making and quality of life in the treatment of cancer: A review. *Support. Care Cancer* **17,** 117–127 (2009).

219. Chipidza, F. E., Wallwork, R. S. & Stern, T. A. Impact of the Doctor-Patient Relationship. *Prim Care Companion CNS Disord* **17,** (2015).

220. Szasz, T. S. & Hollender, M. H. A contribution to the philosophy of medicine: the basic models of the doctor-patient relationship. *AMA Arch Intern Med* **97,** 585–592 (1956).

221. Pickles, T. *et al.* Psychosocial barriers to active surveillance for the management of early prostate cancer and a strategy for increased acceptance. doi:10.1111/j.1464-410X.2007.06981.x

222. Watts, S. *et al.* Depression and anxiety in prostate cancer: A systematic review and meta-analysis of prevalence rates. *BMJ Open* **4,** 1–9 (2014).

223. Rosen, R. C., Cappelleri, J. C., Smith, M. D., Lipsky, J. & Peñ, B. M. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int. J. Impot. Res.* **11,** 319–326 (1999).

224. Albaugh, J. A. Addressing and managing erectile dysfunction after prostatectomy for prostate cancer. *Urol Nurs* **30,** (2010).

225. Mahmood, J. *et al.* Radiation-induced erectile dysfunction: Recent advances and future

directions. *Adv. Radiat. Oncol.* **1,** 161–169 (2016).

226. Scrignaro, M., Barni, S. & Magrin, M. E. The combined contribution of social support and coping strategies in predicting post-traumatic growth: a longitudinal study on cancer patients. *Psychooncology.* **20,** 823–831 (2011).

227. Karanchi, N. A. & Acarturk, C. Post-Traumatic Growth among Marmara Earthquake Survivors Involved in Disaster Preparedness as Volunteers. *Traumatology (Tallahass. Fla).* **11,** 307–323 (2005).

228. Woodward, C. & Joseph, S. Positive change processes and post-traumatic growth in people who have experienced childhood abuse: Understanding vehicles of change. *Psychol. Psychother. Theory, Res. Pract.* **76,** 267–283 (2003).

229. Zoellner, T., Rabe, S., Karl, A. & Maercker, A. Post-traumatic growth as outcome of a cognitive-behavioural therapy trial for motor vehicle accident survivors with PTSD. *Psychol. Psychother. Theory, Res. Pract.* **84,** 201–213 (2011).

230. Rowland, J. H. & Baker, F. Introduction: Resilience of cancer survivors across the lifespan. *Cancer* **104,** 2543–2548 (2005).

231. Ristevska-Dimitrovska, G., Filov, I., Rajchanovska, D., Stefanovski, P. & Dejanova, B. Resilience and Quality of Life in Breast Cancer Patients. *Open access Maced. J. Med. Sci.* **3,** 727–731 (2015).

232. Tedeschi, R. G. & Calhoun, L. G. Posttraumatic Growth: Conceptual Foundations and Empirical Evidence. *Psychol. Inq.* **15,** 1–18 (2004).

233. Connor, K. M. Assessment of Resilience in the Aftermath of Trauma. *J Clin Psychiatry* **67,** 46–49 (2006).

234. Richardson, G. E. The metatheory of resilience and resiliency. *J. Clin. Psychol.* **58,** 307–321 (2002).

235. Snyder, C. R. *et al.* The will and the ways: Development and validation of an individual-differences measure of hope. *J. Pers. Soc. Psychol.* **60,** 570–585 (1991).

236. Herth, K. Abbreviated instrument to measure hope: development and psychometric evaluation. *J. Adv. Nurs.* **17,** 1251–1259 (1992).

237. Beck, J. S. *Cognitive behavior therapy: Basics and beyond*. (Guilford Press, 2011).

238. Wenzel, A. in *Standard and Innovative Strategies in Cognitive Behavior Therapy* 17–34 (Intechopen, 2012).

239. Menhert, A. & Koch, U. Prevalence of acute and post-traumatic stress disorder and comorbid mental disorders in breast cancer patients during primary cancer care: A prospective study. *Psychooncology.* **16,** 181–188 (2007).

240. Beck, J. S., Rush, A. J., Shaw, B. F. & Emery, G. *Cognitive theraphy of depression.* (Guilford Press, 1979).

241. Burns, D. D. *Feeling good: The new mood theraphy*. (Signet, 1980).

242. Dehghani Najvani, B., Neshatdoost, H. T., Abedi, M. R. & Mokarian, F. The Effect of Acceptance and Commitment Therapy on Depression and Psychological Flexibility in Women With Breast Cancer. *Zahedan J. Res. Med. Sci.* **17,** 0–5 (2015).

243. Robinson, A. & Thomson, R. Variability in patient preferences for participating in medical decision making: implication for the use of decision support tools. *Qual. Heal. care* **10,** i34–i38 (2001).

244. Showalter, T. N., Mishra, M. V. & Bridges, J. F. P. Factors that influence patient preferences for prostate cancer management options: A systematic review. *Patient Prefer. Adherence* **9,** 899–911 (2015).

245. Chen, R. C., Clark, J. A., Manola, J. & Talcott, J. A. Treatment 'mismatch' in early prostate cancer: Do treatment choices take patient quality of life into account? *Cancer* **112,** 61–68 (2008).

246. Schaede, U. *et al.* Shared Decision-Making in Patients With Prostate Cancer in Japan: Patient Preferences Versus Physician Perceptions. *J. Glob. Oncol.* **4,** 1–9 (2017).

247. Politi, M. C., Studts, J. L. & Hayslip, J. W. Shared decidion making in oncology practice: What do oncologists need to know? *Oncologist* **17,** 91–100 (2012).

248. Moreno, J. L. & Moreno, Z. T. in *Action and Principles of Practice* (Beacon House, 1969).

249. Menichetti, J., Giusti, L., Fossati, I. & Vegni, E. Adjustment to cancer: exploring patients' experiences of participating in a psychodramatic group intervention. *Eur. J. Cancer Care (Engl).* **25,** 903–915 (2016).

250. Longo, D. R. Understanding health information, communication, and information seeking of patients and consumers: A comprehensive and integrated model. *Heal. Expect.* **8,** 189–194 (2005).

251. Longo, D. R., P, T. B. & Kruse, R. L. in *Proceedings of the AMIA Symposium* 413–417 (Americal Medical Informatics Association, 2001).

252. Shaw, E. K., Scott, J. G. & Ferrante, J. M. The Influence of Family Ties on Men's Prostate Cancer Screening, Biopsy, and Treatment Decisions. *Am. J. Mens. Health* **7,** 461–471 (2013).

253. Edwards, B. & Clarke, V. The psychological impact of cancer diagnosis on families: The influence of family functioning and patients' illness characteristics on depression and anxiety. *Psychooncology.* **13,** 562–576 (2004).

254. Calman, K. C. Quality of life in cancer patients -an hypothesis. *J. Med. Ethics* **10,** 124–127 (1984).

255. Sanatani, M., Schreier, G. & Stitt, L. Level and direction of hope in cancer patients: An exploratory longitudinal study. *Support. Care Cancer* **16,** 493–499 (2008).

256. Hunt, S. M. & Mckenna, S. P. The QLDS : A scale for the measurement quality of life in depression. *Health Policy (New. York).* **22,** 307–319 (1992).

257. Okediji, P. T., Salako, O. & Fatiregun, O. O. Pattern and Predictors of Unmet Supportive Care Needs in Cancer Patients. *Cureus* **9,** 3–13 (2017).

258. Abdollahzadeh, F. *et al.* Un-met Supportive Care Needs of Iranian Breast Cancer Patients. *Asian Pacific J. cancer Prev.* **15,** 3933–3938 (2014).

259. Rutten, L. J. F., Arora, N. K., Bakos, A. D., Aziz, N. & Rowland, J. Information needs and sources of information among cancer patients: A systematic review of research (1980-2003). *Patient Educ. Couns.* **57,** 250–261 (2005).

260. Akechi, T. *et al.* Patient ' s perceived need and psychological distress and / or quality of life in ambulatory breast cancer patients in Japan. *Psychooncology.* **20,** 497–505 (2011).

261. Boyes, A. W., Girgis, A., Este, C. D. & Zucca, A. C. Prevalence and correlates of cancer survivors ' supportive care needs 6 months after diagnosis : a population-based cross-sectional study. *BMC Cancer* **12,** 1–10 (2012).

262. Bilici, A. Prognostic factors related with survival in patients with pancreatic adenocarcinoma. *World J. Gastroenterol.* **20,** 10802–10812 (2014).

263. Rodriguez, A. M., Mayo, N. E. & Gagnon, B. Independent contributors to overall quality of life in people with advanced cancer. *Br. J. Cancer* **108,** 1790–1800 (2013).

264. Innominato, P. F. *et al.* Circadian Rhythm in Rest and Activity: A Biological Correlate of Quality of Life and a Predictor of Survival in Patients with Metastatic Colorectal Cancer. *Cancer Res.* **69,** 4700–4708 (2009).

SCIENTIFIC OUTPUT

Original articles published in international peer-reviewed journals

Testa, S., Toscano, A., Rosato, R. **Distractor efficiency in an item pool for statistics classroom exam: assessing its relation with items' cognitive level classified according to Bloom's Taxonomy.** *Frontiers in Psychology, section Quantitative Psychology and Measurement*. DOI: 10.3389/fpsyg.2018.01585

Other article in international peer-reviewed journal about the Health-Related Quality of Life

Rosato, R., Testa, S., Bertolotto, A., Scavelli, F., Giovannetti, A. M., Confalonieri, P., Patti, P., Chisari, C.G., Lugaresi, A., Pietrolongo, E., Grasso, M. G., Rossi, I., Toscano, A., Loera, B., Giordano, A., Solari, A. (2018). **eMSQOL-29: Prospective validation of the abbreviated, electronic version of MSQOL-54**. *Multiple Sclerosis Journal*. DOI: 10.1177/1352458518774935.

Rosato R., Testa S., Bertolotto A., Confalonieri P., Patti F., Lugaresi A., Grasso M. G., Toscano A., Giordano A., Solari A. (2016). **Development of a short version of the MSQOL-54 using factor analysis and item response theory**". *PlosOne.* DOI:10.1371/journal.pone.0153466

Communications (Oral)

Toscano, A, Blanchin, M, Bonnaud-Antignac, A, Bourdon, M, Sebille, V. (2017). **Longitudinal associations between locus of control, coping, and Health-related quality of life changes in patients with breast cancer or melanoma**. Oral Communication at the 9th European Conference in Positive Psychology in Budapest, 27-30 June 2018.
Speaker: Anna Toscano

Toscano, A, Blanchin, M, Bonnaud-Antignac, A, Bourdon, M, Sebille, V. (2017). **Longitudinal associations between locus of control, coping, and Health-related quality of life changes in patients with breast cancer or melanoma**. Oral communication at the 10th Conference in Health Psychology in Metz, France, 12-15 June 2018.
Speaker: Anna Toscano

Collaboration to works presented during Conferences

Vanier, A, Toscano, A, Sebille, V, Hardouin, JB. (2017). **What are all the proposed methods to estimate the Minimal Clinically Important Difference of a Patient-Reported Outcomes Measure? A systematic review**. *Quality of Life Research*, 26(1).

Work presented at the 24th ISOQOL (International Society for Quality of Life Research) annual Conference, 18-21 October 2017, Philadelphia, United States, America.
Speaker: Antoine Vanier

Posters

Toscano, A, Blanchin, M, Bonnaud-Antignac, A, Sebille, V. (2017). **Locus of control and coping as predictors of the change of Health-Related Quality of Life over time in breast cancer and melanoma patients**. *Quality of Life Research*, 26(1).

Poster presented at the 24th ISOQOL (International Society for Quality of Life Research) annual Conference, 18-21 October 2017, Philadelphia, United States, America.

Solari A., Testa S., Bertolotto A., Confalonieri P., Patti F., Lugaresi A., Grasso M.G., Vickrey B., Toscano A., Giordano A., Rosato R. (2015). **Development of a shortened version of the MSQOL-54 using factor analysis and item response theory**. *Journal of the Neurological Sciences*, 357, e295–e323. DOI:10.1016/j.jns.2015.08.1117

Poster presented at the World Neurology Congress in 2015 in Santiago, Chile.

APPENDIX 1
(ELCCA study)

Linear mixed models

Mixed models are widely used for the analysis of data from longitudinal studies. They allow dealing with repeated measurements by specifying a structure for the correlation between measurements from a same patient. Mixed models can also handle incomplete data. A mixed model is composed of both fixed effects and random effects, that is mixed effects. The mean response is modeled as a combination of fixed effects characterizing the population mean and random effects characterizing the subject-specific effects that are unique to a particular individual.

Let

n_i be the number of observations on patient i, $i=1...N$ and $M = \sum_{i=1}^{N} n_i$ be the total number of observations

p and k be the number of fixed and random parameters respectively

Y_i be the (n_i x 1) vector containing the responses for the patient i

X_i and Z_i be the (n_i x p) design matrix characterizing the fixed part of the model and (n_i x k) design matrix characterizing the random variation in the model due to among-unit sources

β be the (p x 1) vector of fixed effects parameters

b_i be the (k x 1) vector of random effects parameters, $b_i \sim N_k(0, \mathbf{D})$

e_i be the (n_i x 1) vector of error terms, characterizing variation due to within-unit and measurement error sources, $e_i \sim N_{ni}(0, \mathbf{R_i})$

Σ_i be the (n_i x n_i) covariance matrix

$$Y_i = \left(Y_i^{(1)} Y_i^{(2)} Y_i^{(3)}\right)' = X_i\beta + Z_i b_i + e_i$$
$$var(Y_i) = Z_i D Z_i' + R_i = V_i$$
$$Y_i \sim N_{n_i}(X_i\beta, V_i)$$

The parameters to be estimated in the model are the mean parameters β that characterize the mean and the covariance parameters ω, the parameters that makes up V_i. In this study, they were estimated using the REstricted Maximum Likelihood (REML) method in order to reduce the bias on covariance parameters in comparison to the use of Maximum Likelihood (ML) estimation.

F-test

In order to perform a test of nullity of some parameters of the fixed effects, a F-test can be performed.

For a contrast matrix L, the F-test can be written as:

$$H_0: L\beta = 0 \; versus \; H_1: L\beta \neq 0$$

$$W = (\hat{\beta} - \beta)'L'\left[L\left(\sum_{i=1}^{N} X_i' V_i^{-1}(\widehat{\omega}) X_i\right)^{-1} L' \right] L(\hat{\beta} - \beta)$$

Under H_0, W/rank(L) has an approximate F distribution with rank(L) being the numerator degrees of freedom and ν denominator degrees of freedom. The number of denominator degrees of freedom for the tests of fixed effects can be approximated by Satterthwaite[158] or Kenward-Roger[157] methods amongst others with SAS Proc MIXED.

R² statistic for linear mixed models

Contrary to the linear regression, the evaluation of goodness-of-fit of fixed-effect covariates in linear mixed models using R² statistic is relatively new. Amongst different R² statistics in linear mixed models[159], the R² statistic proposed by Edwards et al.[160] is simple to implement as it can be computed with results from the model of interest. This R² measures multivariate association between the repeated measures of HRQoL and the fixed effects for a given covariance structure and helps comparing mean models (i.e. different fixed effects) with the same covariance structure. In fact, the proposed R² is simply defined using an approximate F statistic for a Wald test of fixed effects.

$$R^2 = \frac{(q-1)\nu^{-1}F}{1 + (q-1)\nu^{-1}F}$$

The model of interest (full model) with q-1 predictors in the fixed effects is compared to a null model with only the intercept in the fixed effects and the same covariance structure so that R² relies on a F-test of the null hypothesis H0: $\beta 1 = \beta 2 = \cdots = \beta q-1 = 0$. F is the statistic of the Kenward-Roger F-test computed during the fitting of the model of interest and ν are the associated denominator degrees of freedom.

APPENDIX 2
(START study)

Centres involved in the START study:

Candiolo Institute (IRCCS),

"Ospedale degli infermi" in Rivoli,

Cardinal Massaia Hospital in Asti,

SS. Anunziata Hospital in Savigliano,

S. Lazzaro Hospital in Alba,

Umberto Parini Hospital in Aosta,

S. Giovanni Bosco Hospital in Turin,

Maria Vittoria Hospital in Turin,

S. Luigi Gonzaga Hospital in Orbassano,

S. Croce e Carle Hospital in Cuneo,

ASL TO4 of Cirié-Lanzo",

ASL TO4 of Chivasso,

ASL TO4 of Ivrea-Cuorgné-Castellamonte,

Martini Hospital in Turin,

"SS. Antonio e Biagio e Cesare Arrigo" Hospital in Alessandria,

"Ospedale degli Infermi" in Biella,

S. Biagio Hospital in Domodossola,

Maggiore della Carità Hospital in Novara,

San Giacomo Hospital in Novi Ligure,

Regina Montis Regalis Hospital of Mondovì-Ceva,

Santo Spirito Hospital in Casale Monferrato,

S. Andrea Hospital in Vercelli.

Longitudinal associations between Coping strategies, Locus of Control, and Health-Related Quality of Life changes in patients with Breast Cancer or Melanoma

SCHOLARONE™
Manuscripts

Title

Longitudinal associations between Coping strategies, Locus of Control and Health-Related Quality of Life changes in patients with Breast Cancer or Melanoma

Anna Toscano[a,b], Myriam Blanchin[a], Marianne Bourdon[a], François Dravet[c], Gaëlle Quéreux[d], Rosalba Rosato[b], Angélique Bonnaud Antignac[a,c], Véronique Sébille[a,e]

[a]UMR INSERM 1246, SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch", University of Nantes, University of Tours, Nantes, France; [b]Department of Psychology, University of Turin, Turin, Italy; [c]Surgical Oncology Service, ICO Nantes, Saint Herblain, France; [d]CHU of Nantes, UMR INSERM 892, Nantes, France; [e]Biostatistics unit, CHU of Nantes, Nantes, France.

*Corresponding author: Email: veronique.sebille@univ-nantes.fr Véronique Sébille, UMR INSERM 1246, SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch", Nantes University, Tours University, 22 boulevard Benoni Goullin, Nantes, France.

133

Abstract

Objective

Helping identifying the best supportive strategies and the best timing for initiating them, according to the type of cancer, is essential for patient care. The objective of this study was to assess the association of coping and locus-of-control (LOC) changes, with change in Health-Related Quality-of-Life (HRQoL) over time in breast cancer (BC) and melanoma patients.

Design & Main Outcome Measures

The Brief Cope, Cancer Locus-of-Control Scale, EORTC QLQ-C30 were administered to newly-diagnosed BC (N=215) and melanoma (N=78) patients at 1, 6, 12 and 24-months post-diagnosis.

Results

At baseline, HRQoL levels were often higher for BC compared to melanoma patients. The pattern of change of HRQoL was different for BC and melanoma patients with a rebound effect (steep decrease and slight increase after 6-months) for the former and a linear increase or decrease over the follow-up for the latter. For BC and melanoma patients, negative coping strategies and perceived control were negatively and positively associated with HRQoL, respectively. For BC patients only, a negative association with HRQoL was evidenced for emotional coping.

Conclusion

It seems that psychological therapies or support, that consider the patients' coping strategies and beliefs, should be specific according to the type of cancer and time post-diagnosis.

Keywords

Cancer; coping; health locus of control; health-related quality of life; longitudinal data.

Introduction

Breast cancer is the most common cancer in women. Worldwide nearly 1.7 million of new breast cancer cases were diagnosed in 2012 (Ghoncheh et al., 2016), and in France, almost 60000 new

2

cases were observed in 2017 (Institut National du cancer). In comparison, melanoma is not as frequent (132.000 melanoma skin cancers occur globally each year (World Health Organization), although its incidence is increasing each year. A better understanding of the experience of cancer patients using Patient-reported outcomes (PRO) to investigate perceived Health-related Quality of Life (HRQoL) is now deemed essential to assess treatment and health care effectiveness. Previous research, including one on the same sample of patients, suggests that breast cancer and melanoma patients do not experience the same level of HRQoL (Engel et al., 2014; Bourdon et al., 2016). Melanoma patients seem to have higher levels regarding functioning dimensions (global health, physical, role, emotional, cognitive, social functioning) as compared to breast cancer patients 2 years after treatments initiation (Engel et al., 2014). Moreover, the patterns of HRQoL change differ between these two cancer types with a delayed increase in global health, physical and role functioning dimensions for melanoma as compared to breast cancer patients (Bourdon et al., 2016). Some hypotheses might be put forward. From a medical viewpoint, breast cancer patients undergo treatments that may cause potential physical disabilities, while melanoma patients often have less invasive treatments and side-effects. From a psychological viewpoint, breast cancer involves a part of the body that usually represents the femininity and sexuality of women (Schmidt et al., 2017), which might not be the case for melanoma patients (e.g. spots on the hand's surface). Hence the supportive care needs might differ during the course of illness for breast cancer and melanoma patients.

A diagnosis of cancer is a traumatic life event that can lead patients to question beliefs about themselves and about the future (Lepore, 2001). Patients will try to decrease, control or accept the impact of the disease on their physical and psychological well-being and make the reality more acceptable via the domains of cognitions, affects and behaviors (Bruchon-Schweitzer, 2002; Paulhan & Bourgeois, 1995). Cancer patients' HRQoL is often related to psychological variables (Brandão et al., 2017), like coping strategies and locus of control (LOC) beliefs (Stanton et al., 2000; Avis et al., 2005; Cousson-Gélie et al., 2005; Lehto et al., 2005; Danhauer et al., 2009;

3

135

Bonnaud-Antignac et al., 2017; Paek et al., 2016) which are relevant variables to consider in psychological therapies for cancer support. Targeting perceived control and coping strategies may help patients to interpret their personal and interpersonal context, promote the adoption of adaptive behaviors and by extension improve their HRQoL.

Positive (e.g. acceptance) and negative coping (e.g. cognitive escape-avoidance) strategies were found to be positively and negatively associated with HRQoL respectively, in breast cancer patients (Stanton et al., 2000; Avis et al., 2005; Lehto et al., 2005). The same associations with negative coping (e.g. behavioral disengagement) were evidenced for melanoma patients; active coping and religious coping strategies were also negatively associated with negative cognitive functioning 2 years after diagnosis (Bonnaud-Antignac et al., 2017). A high belief of internal causal attribution (i.e. self-attribution for illness beginning) at diagnosis was related to higher social functioning 2 years later for breast cancer patients (Cousson-Gélie et al., 2005); perceived control over the course of the illness at time of diagnosis was positively associated to HRQoL 2 years later for melanoma patients (Bonnaud-Antignac et al., 2017).

These studies, however, did not consider coping, LOC and HRQoL longitudinally (Stanton et al., 2000; Avis et al., 2005; Cousson-Gélie et al., 2005; Lehto et al., 2005; Bonnaud-Antignac et al., 2017) although coping and control variables are situational process that might not be stable over time (Lazarus et al., 1984).

Longitudinal studies remain rather scarce and sometimes the short follow-up period does not allow assessing how variables change over time, how they are related to change in HRQoL, and so how to support cancer patients' psychological needs that can take time to appear. In the study of Paek et al. (Paek et al., 2016) in breast cancer, the measures were taken from the diagnosis to almost until 2 years later, but, as in Danhauer et al. (Danhauer et al., 2009), the authors considered the associations between coping and HRQoL at two distinct time points. It means that the analyses did not allow understanding changes in coping strategies and HRQoL and identifying how they are related. The results of the work of Peak et al. (Paek et al., 2016) suggested that the more the patients used

4

negative coping strategies (denial, behavioral disengagement, and self-blame) in the first 0-8 months from the diagnosis the less their HRQoL at 12–20 months' post-diagnosis was. To our knowledge, no similar longitudinal studies focusing on coping or locus of control, and HRQoL have been conducted in early stage melanoma patients.

Assessing the association between coping, LOC, and HRQoL changes over time could help identifying the coping strategies and the cognitions that might be targeted in supportive therapies and their best timing for improvement of HRQOL in breast cancer and melanoma patients. It is also likely that breast cancer and melanoma patients should not be managed in the same way but in a more personalized manner for effective support.

The aim of this study is to assess the association between changes in coping and LOC with HRQoL changes in breast cancer and melanoma patients.

Methods

Participants

The longitudinal ELCCA study aims at assessing the changes experienced by patients since diagnosis of breast cancer or melanoma in the Department of Onco-Dermatology (for melanoma patients) and a Cancerology Institute (for breast cancer patients) in Nantes, France. Patients diagnosed with a stage I or II (early stage, non-metastatic) cancer were eligible for the study. Among them, 220 breast cancer patients and 82 melanoma patients agreed to participate. Patients completed self-administered questionnaires within 1-month post-diagnosis (mpd), and 6, 12, and 24 months later. At each time point, HRQoL, coping, LOC, and sociodemographic variables (age, gender, living with a partner, education level and perceived standard of living) were assessed as well as medical information.

Measures

5

137

The EORTC quality of life questionnaire (QLQ-C30) (Aaronson et al., 1993) was used to assess HRQoL. This scale has 30 items and we focused on the 6 functioning dimensions measuring physical (5 items), role (2 items), emotional (4 items), cognitive (2 items), social functioning (2 items), and global health (2 items). These dimensions are composed of four or seven point Likert items and all the dimension scores range from 0 to 100. A higher score represents a higher level of HRQoL.

The Cancer Locus of Control scale (Cousson-Gélie et al., 2005; Pruyn et al., 1988) assesses the perceived control over the illness. This 14-item scale has 3 dimensions composed of four-point Likert items: perceived control over the course of the illness (6 items), internal causal attribution (5 items), and religious control (3 items). A higher score indicates a higher agreement (e.g. If I follow the advice of my doctor).

Coping strategies were assessed with the 28-item Brief Cope questionnaire (Carver et al., 1997; Muller et al., 2003) which measures 14 coping dimensions: active coping, planning, using instrumental support, using emotional support, venting, behavioral disengagement, self-distraction, self-blame, positive reframing, humor, denial, acceptance, religion, and substance use. Each dimension is composed of two four-point Likert items with a higher score indicating a higher use of a given strategy to deal with stressful life events.

Statistical Methods

The coping dimensions which were strongly related to each other were first grouped together using the clustering around latent variables method (Vigneau et al., 2003) to assemble the 14 dimensions into homogeneous clusters representing different latent variables. The coping dimensions which were strongly related to each other were grouped together. The possible number of clusters was therefore between 1 and 14. The number of clusters for our analysis was determined by inspecting the dendrogram and identifying clinically meaningful clusters of coping dimensions. All coping

6

138

dimensions' clusters and LOC scores were subsequently standardized between 0 and 100 to be on the same metric as HRQoL scores.

Changes of each LOC and clusters of coping dimensions were investigated with linear mixed models (Verbeke et al., 2000) by cancer type (see Appendix 1 for details). These models include fixed effects that characterize the mean behavior of the sample over time (intercept as mean value at 1 mpd and time variable to assess change) as well as random effects to model individual variation around the mean trajectory (possibly intercept and/or time in our study to model a different value at 1 mpd and/or change for each patient from the mean of the sample). The correlation between measurements of the same patient measured across different occasions is taken into account by specifying the structure of the variance-covariance matrix (see Appendix). For each variable (LOC dimension and coping dimensions' clusters) and each type of cancer, the addition of random effects and/or the choice of the structure for the variance-covariance matrix were based on the Akaike Information Criteria (AIC) (Akaike, 1974) to choose the best fitting model. A significant time effect resulted in considering the corresponding LOC or coping variable as a time-dependent covariate in the following multivariate analyses, otherwise, their values at 1 mpd were used.

To assess the effect of coping strategies, LOC and sociodemographic variables on HRQoL changes, a linear mixed model was fitted on each dimension score for melanoma and breast cancer separately. In addition to coping and LOC dimensions, age, level of education, perceived standard of living, living with a partner or not at 1 mpd were included into the fixed-effect part of the mixed model. As recommended, the fixed-effect part also included time and all potential interactions between LOC or coping covariates and time (Cheng et al., 2010). The inclusion of the main effects as well as interactions allow distinguishing between the mean effect of the covariate on HRQOL over time (main effect) and a change from the mean effect at a given time (interaction with time). The strategy for statistical analysis was as follows. First, the addition of a random intercept and/or time and the choice of the structure of the covariance matrix were based on the AIC. Second, the fixed-effect part of the best fitting model was reduced by deleting first non-significant interactions

7

and last non-significant main effects using the AIC, p-value of the Wald test and a specific R^2 statistic developed for mixed models (Edwards et al., 2008) (see Appendix for more details). SAS 9.2 Proc MIXED was used for the analyses.

Results

Participants' characteristics at 1 mpd are presented in Table 1 . Overall, 78 melanoma patients and 215 breast cancer patients completed the questionnaires at 1 mpd. Patients were on average 51 and 53 years old, mostly lived with a partner (82.8% and 79.5%) for breast cancer and melanoma patients, respectively. Most patients had an education level higher than elementary school (83.6%) and declared to have an intermediate standard of living (80.5%).

Clusters of coping dimensions

According to the clustering around latent variables method, the 14 dimensions of coping were grouped into 4 clusters. The first cluster, Negative COPing (NCOP), included behavioral disengagement, self-blame and denial. The second cluster Emotional COPing (ECOP) included using instrumental support, using emotional support, venting and religion. The third cluster Positive COPing (PCOP) included active coping, planning, self-distraction, positive reframing, humor and acceptance. Substance use alone constituted the fourth cluster.

Usage of coping and LOC dimensions

At 1 mpd, among the coping and LOC dimensions (Table 1), the perceived CONtrol over the course of illness LOC (CONLOC) seemed the strongest belief (on average 67.2 for breast cancer and 69.1 for melanoma) and the PCOP the most used coping strategy (on average 50.7 for breast cancer and 50.6 for melanoma). As substance use was very rarely used (on average 6.0 for breast cancer and 7.7 for melanoma), this strategy was not considered for the subsequent analyses.

TABLE 1

Longitudinal change in coping and LOC dimensions

8

140

The first analyses, stratified by cancer type, assessed whether coping and LOC changed over time (Table 2). For breast cancer patients, ECOP and CONLOC scores both significantly decreased over time (-2.2 and -1.0 on average from one time to another, respectively), whereas INTernal LOC (INTLOC) significantly increased (1.4 on average over time). For melanoma patients, NCOP significantly increased over time, whereas ECOP, PCOP and CONLOC significantly decreased.

All these covariates were considered as time-dependent for all further analyses. The variables not changing over time were considered as time-independent variables; their values at 1 mpd were used for all further analyses.

TABLE 2

Longitudinal change in Health-Related Quality of Life

The results of the multivariate analyses on emotional functioning (EF), physical functioning (PF), global health (GH), cognitive functioning (CF), role functioning (RF), social functioning (SF), dimensions of the QLQ-C30, are presented in Table 3. The levels of all HRQoL dimensions at 1 mpd were always higher for breast cancer than melanoma patients indicating an overall better HRQoL for breast cancer patients at 1 mpd (except for CF, estimated intercepts: 66.6 and 91.0 for breast cancer and melanoma, respectively).

Time effect

Regarding change over time, rebound effects were observed for some dimensions of HRQoL for breast cancer patients: the PF, GH, RF and SF scores decreased steeply from 1 to 6 mpd, then increased slightly from 6 to 12 mpd, and remained stable from 12 to 24 mpd. Globally, during the 2-year follow-up (24 vs 1 mpd in Table 1), breast cancer patients' PF, RF, SF scores had an average decrease of -5.3, -7.5, and -4.9 points, respectively whereas GH and EF remained globally stable. In contrast, melanoma patients' EF linearly increased (+3.3 points on average between each visit) and melanoma patients' PF linearly decreased (-2.6 points on average between each visit) over time.

Covariates' effects: common to breast cancer and melanoma

9

141

For both cancer types, NCOP and living with a partner were negatively associated with changes in EF, SF, and RF, SF, respectively. For example, an increase of 10 points in the NCOP score was associated with an average decrease of 3 points in EF score for breast cancer patients and of 5 points for melanoma patients. Moreover, CONLOC and age were positively associated with changes in GH, RF, and SF, EF, respectively. In particular, an increase of 10 points of CONLOC was associated with an average increase of 2 points in GH for melanoma patients, and of 1 point for breast cancer patients.

Covariates' effects: breast cancer

For breast cancer patients only, PCOP was positively associated with EF changes (+ 1 points of EF for each 10 points of PCOP increase). ECOP and INTLOC were negatively associated with changes in PF, GH, SF, and EF, GH, CF, RF, respectively. In addition, ECOP was negatively associated with breast cancer patients' EF but only at 1 mpd. Change in The EF mean scores depending on the level of ECOP are shown in Figure 1. The patients with higher scores of ECOP (observed third quartile of ECOP scores) had a lower mean level of EF at 1 mpd compared to the patients with lower ECOP scores (first quartile). From 6 mpd, the EF mean scores were higher than 1 mpd scores and similar whatever the level of ECOP.

Covariates' effects: melanoma

For melanoma patients only, PCOP was positively associated with PF changes (+ 2 points increase in PF for each 10 points of PCOP increase). RELLOC was negatively associated with changes in EF and SF (both -2 points for each 10 points of RELLOC increase).

Explained variance

For breast cancer patients, the ECOP scores at 1 mpd and the time variable explained 30% of the variance in PF over time ($R^2=30\%$). For melanoma patients, NCOP, CONLOC, RELLOC, age, living with a partner and the time variable all contribute to 33% of the explanation of the variance of EF over time ($R^2=33\%$). For both cancer types, the lowest R^2 was observed for CF (R^2, <10%).

10

142

TABLE 3

Discussion

This study assessed the association of change in coping and LOC dimensions with change in HRQoL over time for breast cancer and melanoma patients.

Breast cancer

For breast cancer patients, ECOP had a negative association with HRQoL over time (EF, PF, GH, and SF dimensions). ECOP was mainly composed of coping strategies that consist in the sharing of thoughts and feelings with others (i.e. instrumental support, venting, using emotional support). Emotionally expressive strategies, aiming at managing negative emotions, can be relatively ineffective in improving HRQoL (Gilbertson-White et al., 2017; Khalili et al., 2013). The use of emotionally expressive coping can indeed be associated with the perception that quality of life is poor, i.e the coping efforts may then contribute to decrease rather than increase HRQoL. The social sharing of thoughts and feelings may indeed not facilitate psychological adjustment in case of a perceived unsupportive social context (Lepore et al., 2007; Boinon et al., 2014). In fact, the patients' social environment (friends, relatives, partner, etc.) may find it difficult to face the illness of their friend or partner over time (Ginter et al., 2017; Li et al., 2014) and have negative supportive attitudes, that can influence the way people will cope with the situation (Lepore, 2001).

Also, reverse causality cannot be ruled out and it is also possible that poorer scores in HRQoL contribute to a greater use of emotionally expressive strategies. When HRQoL of patients is threatened, expressing and sharing their emotions may help them to get a better understanding of the disease and its treatments, reinterpret the situation, decrease anxiety and motivate problem-focused coping strategies to gain reassurance of disease control. (Gilbertson-White, Campbell, Ward, Sherwood, & Donovan, 2017; Helgeson & Cohen, 1996).

The negative association between INTLOC (self-attribution for illness onset) and HRQoL changes (EF, GH, CF, RF) in breast cancer patients, suggest that the more patients think of having the

11

143

responsibility for the illness, the more negative their change of HRQoL is. It seems in line with the results of previous studies that found a negative association between internal causal attributions and psychological adjustment or HRQoL (Else-Quest et al., 2009; Friedman et al., 2007; Kulik et al., 2005). Nevertheless, most of these studies were cross-sectional and did not take into consideration the psychological change over time (Else-Quest et al., 2009; Friedman et al., 2007), apart from the longitudinal work of Kulik et al. (Kulik et al., 2005) that considered 2 time points to test this negative association. The negative association between INTLOC and HRQoL change over time can be due to negative feelings and thoughts related to the belief of personal responsibility of a traumatic past event (cancer diagnosis). The feelings of self-blame (i.e., "What could I have done to prevent this?"), and of counterfactual thinking (i.e., "If things had gone differently, I wouldn't be in this situation") are usually linked with negative adjustment over time (Frazier et al., 2001; Pagnini et al., 2016).

Breast cancer and melanoma

For both cancer, NCOP (i.e., behavioral disengagement, self-blame and denial) was also negatively associated with HRQoL over time, but in a different way. It affected almost all HRQoL dimensions for melanoma patients (except RF) and a fewer for breast cancer patients (EF, SF only). Our finding is in line with another longitudinal study in breast cancer patients in which negative coping, at 0-8 months' post diagnosis, was found to be negatively associated to the total score of HRQoL measured at 12–20 months' post-diagnosis (Paek et al., 2016). As the Brennan's model of adjustment to cancer reported, the usage of negative coping can be maladaptive in the long term since it prevents from the traumatic information processing necessary to the positive adjustment over time (Brennan, 2001). Similarly, for both cancer, the higher the CONLOC level (perceived control over the course of illness LOC), the higher the changes in HRQoL over time. For reaching and maintaining control over time, patients use some adaptive cognitive compensation mechanisms,

12

144

such as evaluating other domains in life or positive illusions, that seem to be beneficial for psychological functioning in cancer (Ranchor et al., 2010).

Age was positively associated with HRQOL changes for both cancer types; this has already been shown with EF and SF 2 years after treatments initiation for melanoma and breast cancer patients (Engel et al., 2014). For breast cancer patients, this relation has been found during different phases after diagnosis and treatments (Howard-Anderson et al., 2012), and it has been hypothesized that younger patients often report greater distress than older patients (Bourdon et al., 2016).

Moreover, living with a partner, was negatively associated with HRQoL change. As it was found in the literature, the HRQoL of the partners, psychologically affected by the illness as the patients, influences the patients' HRQoL and vice versa, since there is a "reciprocal influence" among them over time (Li et al., 2014).

The levels of HRQoL at 1 mpd were mainly higher for breast cancer than melanoma (except for CF). It might be due to the different social support perceived by the patients (Lehto et al., 2005). This could be in line with the fact that usually in common language and risk communication breast cancer is fully recognized as a serious illness, whereas melanoma is often more trivialized at an early stage (Engel et al., 2014). Hence, breast cancer patients might find more support from family and friends than melanoma patients at diagnosis.

Study limitations

Since the sample of breast cancer patients was composed only of women and the sample of melanoma patients included men and women (42.3% of women and 57.7% of men), gender and type of cancer effects might therefore be confounded.

Moreover, the study was based on a sample of breast cancer and melanoma patients at early stage, so the results' generalization to more severe stages cannot be made. Furthermore, as the data are from an observational longitudinal study, causal effects of the considered covariates on HRQoL change cannot be assessed.

13

145

All R^2 of the multivariate models were lower than 35%. Other cross-sectional studies looking also at the association of coping with HRQoL display similar R^2, ranging between 22% and 40% (Lehto et al., 2005; Kershaw et al., 2004; Zamanian et al., 2015). In this work, R^2 ranged from 6 to 33%. Further studies are needed in order to increase the percentage of the variation of the explained HRQoL, considering other important variables such as specific treatments, distress, anxiety and depression as well as the perception of the illness by the partner. In particular, our study focused on the psychological constructs of coping and LOC that are within the domain of cognition on which Cognitive Behavioral Therapies can have an influence. However, cognition should be considered along with emotion such as distress, anxiety and depression to better understand the psychological progress at hand and take into account with targeted supportive therapies.

Clinical implications

According to our results, it seems that psychological therapies aiming at supporting HRQoL of breast cancer and melanoma patients over time, should take into account the differences and the similarities in the experience reported by the patients according to the type of cancer.

For breast cancer patients, the psychological therapy could be focused on helping patients who use ECOP strategies (i.e. venting, emotional and instrumental support, religion) that are negatively associated with HRQoL over time. It would be valuable to have a more comprehensive view of the link between ECOP strategies and HRQoL through patients' interviews, for example to explore whether emotional coping is an essential step to clarify information and understanding of the disease in order to mobilize, in the longer term, more positive strategies that could be beneficial in terms of HRQoL.

When facing cancer diagnosis, patients can experience several negative emotions (such as anger, shame, and frailty). The sense of self-blame that comes out from the belief of responsibility for the illness must be evaluated. Using a cognitive restructuring technique may help the patients to identify some maladaptive automatic thoughts or to question the validity of negative automatic thoughts regarding perceived control over the situation or available coping skills in order to replace

14

146

them by more realistic ones or change dysfunctional patterns (Willard, 2014). In addition, using the problem-solving technique may help the patients to seek alternatives solutions or to define realistic goals to cope with the situation (Poinsot, 2014).

For both cancer types, psychological therapy could be focused on the behavioral and cognitive negative reactions to the event (e.g. negative coping strategies), since they have negative associations with HRQoL over time. It could be useful to help patients question the validity of their beliefs (using the cognitive restructuring and the problem-solving techniques), but also to work on the acceptance of experiencing negative emotions that patients may be avoiding. Moreover, for both cancer types, it seems important to maintain a sense of perceived control. Acceptance and Commitment Therapy which relies on the acceptance of emotional experiences (our results showed a negative association between behavioral disengagement and HRQoL and a positive relation between acceptance and HRQoL for both cancers) could be relevant as it may help to increase perceived control over the disease. Acceptance and Commitment Therapy aims at increasing the psychological flexibility (i.e. increasing the awareness and the openness to experience, acting in accordance with personal values) which can improve psychological adjustment and quality of life (Monié, 2014).

Furthermore, it is necessary to also take into consideration partners' mental state due to the illness, to propose dyadic social support for example. Psycho-educational approach could be relevant with interventions aiming at providing information about the disease and its consequences to patients and their relatives. One can assume that if the patient and his/her loved ones have a good knowledge and representation of the illness, they should manage it all the better. Notably because they will know how to share and speak about cancer and its treatments, to better understand and accept its consequences on their daily lives.

It seems that for both cancer types, psychological support is needed: for breast cancer patients during all the follow-up and particularly at time of diagnosis (we noticed a sharp decrease in HRQoL after diagnosis followed by a rebound effect afterwards); for melanoma patients, instead, a

15

147

continuous psychological support could be proper (some HRQoL scores linearly decreased over time).

In conclusion, this study supports the evidence that for breast cancer and melanoma patients different coping strategies and LOC beliefs are associated with HRQoL changes. It seems that psychological therapies, that take into consideration the patients' coping strategies and beliefs, should be specific according to the type of cancer and time after diagnosis.

Ethical approval

This study was approved by an ethical French research committee (Comité de Protection des Personnes).

References

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Flechtner, H., Fleishman, S.B., de Haes, J.C., et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute, 85(5)*, 365-376.

Akaike, H. (1974). A new look at the statistical model identification. System identification and time-series analysis. *IEEE Transactions on Automatic Control, 19(6)*, 716-723.

Avis, N.E., Crawford, S., & Manuel, J. (2005). Quality of life among younger women with breast cancer. *J of Clinical Oncology, 23(15)*, 3322-3330. DOI: 10.1200/JCO.2005.05.130

Boinon, D., Sultan, S., Charles, C., Stulz, A., Guillemeau, C., Delaloge, S., Dauchy, S. (2014). Changes in psychological adjustment over the course of treatment for breast cancer: the

16

148

predictive role of social sharing and social support. *Psycho-oncology, 23(3)*, 291-298. DOI: 10.1002/pon.3420

Bonnaud-Antignac, A., Bourdon, M., Dréno, B., Quéreux, G. (2017). Coping Strategies at the Time of Diagnosis and Quality of Life 2 Years Later: A Study in Primary Cutaneous Melanoma Patients. *Cancer Nursing, 40(1)*, E45-E53. DOI: 10.1097/NCC.0000000000000337

Bourdon, M., Blanchin, M., Tessier, P., Campone, M., Quéreux, G., Dravet, F., Sebille, V., Bonnaud-Antignac, A. (2016). Changes in quality of life after a diagnosis of cancer: a 2-year study comparing breast cancer and melanoma patients. *Quality of Life Research, 25(8)*,1969-1979. DOI: 10.1007/s11136-016-1244-3

Brandão, T., Schulz, M.S., & Matos, P.M. (2017). Psychological adjustment after breast cancer: a systematic review of longitudinal studies. *Psycho-oncology, 26(7)*,917-926. DOI: 10.1002/pon.4230

Brennan, J. (2001). Adjustment to cancer—coping or personal transition? *Psycho-oncology, 10(1)*, 1-18.

Bruchon-Schweitzer, M. (2002). *Psychologie de la santé. Modèles, concepts et méthodes*. Paris: Dunod.

Carver, C.S. (1997). You want to measure coping but your protocol's too long: consider the brief COPE. *International Journal of Behavioral Medicine, 4(1)*, 92-100. DOI: 10.1207/s15327558ijbm0401_6

Cheng J., Edwards L.J., Maldonado-Molina M.M., Komro K.A., Muller K.E. (2010). Real Longitudinal Data Analysis for Real People: Building a Good Enough Mixed Model. *Statistics in Medicine, 29(4)*, 504-520. DOI: 10.1002/sim.3775

Cousson-Gélie, F., Irachabal, S., Bruchon-Schweitzer, M., Dilhuydy, J.M., & Lakdja, F. (2005). Dimensions of cancer locus of control scale as predictors of psychological adjustment and

17

149

survival in breast cancer patients. *Psychological Reports, 97(3)*, 699-711. DOI: 10.2466/pr0.97.3.699-711

Danhauer, S.C., Crawford, S.L., Farmer, D.F., & Avis, N.E. (2009). A longitudinal investigation of coping strategies and quality of life among younger women with breast cancer *Journal of Behavioral Medicine, 32(4)*, 371-379. DOI: 10.1007/s10865-009-9211-x

Edwards, L.J., Muller, K.E., Wolfinger, R.D., Qaqish, B.F., Schabenberger, O. (2008). An R2 Statistic for Fixed Effects in the Linear Mixed Model. *Statistics in Medicine, 27(29)*, 6137-6157. DOI: 10.1002/sim.3429

Else-Quest, N.M., LoConte, N.K., Schiller, J.H., Hyde, J.S. (2009). Perceived stigma, self-blame, and adjustment among lung, breast and prostate cancer patients. *Psychology & health, 24(8)*, 949-964. doi: 10.1080/08870440802074664

Engel, J., Schlesinger-Raab, A., Emeny, R., Hölzel, D., & Schubert-Fritschle, G. (2014). Quality of life in women with localised breast cancer or malignant melanoma 2 years after initial treatment: a comparison. *International journal of behavioral medicine, 21(3)*, 478-486. DOI: 10.1007/s12529-013-9334-x

Frazier, P., Berman, M., Steward, J. (2001). Perceived control and posttraumatic stress: A temporal model *Applied and Preventive Psychology, 10(3)*, 207-223. https://doi.org/10.1016/S0962-1849(01)80015-9

Friedman, L.C., Romero, C., Elledge, R., Chang, J., Kalidas, M., Dulay, M.F., Lynch, G.R., Osborne, C.K. (2007). Attribution of blame, self-forgiving attitude and psychological adjustment in women with breast cancer; *Journal of Behavioral Medicine, 30(4)*, 351-357. DOI: 10.1007/s10865-007-9108-5

Ghoncheh, M., Pournamdar, Z., & Salehiniya, H. (2016). Incidence and mortality and epidemiology of breast cancer in the world. *Asian Asian Pacific Journal of Cancer Prevention, 17(S3)*, 43-6. http://dx.doi.org/10.7314/APJCP.2016.17.S3.43

18

150

Gilbertson-White, S., Campbell, G., Ward, S., Sherwood, P., & Donovan H. (2017). Coping with pain severity, distress, and consequences in women with ovarian cancer. *Cancer Nursing, 40*(2), 117-123.

Ginter, A.C., Braun, B. (2017). Social support needs of breast cancer patients without partners. *Journal of Social and Personal Relationships*, 1-10. https://doi.org/10.1177/0265407517718390

Helgeson, V. S., & Cohen, S. (1996). Social support and adjustment to cancer: reconciling descriptive, correlational, and intervention research. *Health Psychology, 15*(2), 135-148.

Howard-Anderson, J., Ganz, P.A., Bower, J.E., Stanton, A.L. (2012). Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *Journal of the National Cancer Institute, 104*, 386–405. DOI: 10.1093/jnci/djr541

Institut National du cancer. Le cancer du sein en chiffres. Available from: http://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-du-sein [Accessed 1st February 2018].

Kenward, M.G., Roger, J.H. (1997). Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics, 53(3)*:983-997.

Kershaw, T., Northouse, L., Kritpracha, C., Schafenacker, A., Mood, D. (2004). Coping strategies and quality of life in women with advanced breast cancer and their family caregivers. *Psychology & Health, 19(2),* 139-155. https://doi.org/10.1080/08870440310001652687

Khalili N., Farajzadegan, Z., Mokarian, F., & Bahrami F. (2013). Coping strategies, quality of life and pain in women with breast cancer. *Iranian Journal of Nursing and Midwifery Research, 18*(2), 105-11.

Kulik, L., Kronfeld, M. (2005). Adjustment to breast cancer: the contribution of resources and causal attributions regarding the illness. *Social Work in Health Care, 41(2),* 37-57. DOI: 10.1300/J010v41n02_03

Lazarus, R.S., & Folkman, S. (1984). *Stress, appraisal, and coping.* New York: Springer.

19

151

Lehto, U.S., Ojanen, M., & Kellokumpu-Lehtinen, P. (2005). Predictors of quality of life in newly

 diagnosed melanoma and breast cancer patients. *Annals of Oncology, 16(5)*, 805-816. DOI:

 10.1093/annonc/mdi146

Lepore, S. J. (2001). A social–cognitive processing model of emotional adjustment to cancer. In A.

 Baum & B. L. Andersen (Eds.), Psychosocial interventions for cancer (pp. 99-116). Washington,

 DC, US: American Psychological Association.

Lepore, S.J., Revenson, T.A. (2007). Social constraints on disclosure and adjustment to cancer.

 Social and Personality Psychology Compass., 1(1):313-333. https://doi.org/10.1111/j.1751-

 9004.2007.00013.x

Li, Q., Loke, A.Y. (2014). A literature review on the mutual impact of the spousal caregiver–cancer

 patients dyads: 'Communication', 'reciprocal influence', and 'caregiver–patient congruence'.

 European journal of oncology nursing, 18(1), 58-65. doi: 10.1016/j.ejon.2013.09.003

Monié, B. (2014). Acceptance and Commitment Therapy. In F. Chapelle, B. Monié, R. Poinsot,

Rusinek and M. Willard (Eds.). *Aide-mémoire: Thérapies Comportementales et Cognitives en 37

 notions* (pp.205-211). Paris: Dunod.

Muller, L., Spitz, E. (2003). Multidimensional assessment of coping: validation of the Brief COPE

 among French population. *Encephale, 29(6)*, 507-518.

Orelien, J.G., Edwards, L.J. (2008). Fixed effect variable selection in linear mixed models using R2

 statistics. *Computational Statistics & Data Analysis, 52*, 1896-1907.

 https://doi.org/10.1016/j.csda.2007.06.006

Paek, M.S., Ip, E.H., Levine, B., & Avis, N.E. (2016). Longitudinal reciprocal relationships

 between quality of life and coping strategies among women with breast cancer. *Annals of

 Behavioral Medicine, 50(5)*, 775-783. DOI: 10.1007/s12160-016-9803-y

Pagnini, F., Bercovitz, K., Langer, E. (2016). Perceived control and mindfulness: Implications for

 clinical practice. *Journal of Psychotherapy Integration, 26(2)*, 91-102.

 http://dx.doi.org/10.1037/int0000035

20

152

Paulhan, I., & Bourgeois, M. (1995). *Stress et coping, les stratégies d'ajustement à l'adversité.* Paris: P.U.F.

Poinsot, R. (2014). Résolution de problèmes. In F. Chapelle, B. Monié, R. Poinsot, Rusinek and M. Willard (Eds.). *Aide-mémoire: Thérapies Comportementales et Cognitives en 37 notions* (pp.224-228). Paris: Dunod.

Pruyn, J. F. A., Van den Borne, H. W., De Reuver, R. S. M., De Boer, M. F., Bosman, L. J., Ter Pelkwijk, M. A,, & De Jong, P. C. (1988). De Locus of Control-Schaal voor kankerpatienten [The Locus of Control Scale for Cancer Patients]. Tzjdschift voor Sociales Gezondheidszorj, 66, 404-408.

Ranchor, A.V., Wardle, J., Steptoe, A., Henselmans, I., Ormel, J., Sanderman, R. (2010). The adaptive role of perceived control before and after cancer diagnosis: A prospective study. *Social Science & Medicine, 70(11)*: 1825-1831. https://doi.org/10.1016/j.socscimed.2009.10.069

Satterthwaite, F. (1941). Synthesis of variance. *Psychometrika, 6*:309–316.

Schmidt, J.L., Wetzel, C.M., Lange, K.W., Heine, N., & Ortmann, O. (2017). Patients' experience of breast reconstruction after mastectomy and its influence on postoperative satisfaction. *Archives of gynecology and obstetrics, 296(4)*, 827-834. DOI: 10.1007/s00404-017-4495-5

Stanton, A.L., Danoff-Burg, S., Cameron, C.L., Bishop, M., Collins, C.A., Kirk, S.B., Sworowski, L.A., & Twillman, R. (2000). Emotionally expressive coping predicts psychological and physical adjustment to breast cancer. *Journal of Consulting and Clinical Psychology, 68(5),* 875-882. http://dx.doi.org/10.1037/0022-006X.68.5.875

Verbeke, G., Molenberghs, G. (2000). *Linear Mixed Models for Longitudinal Data.* New York, Springer.

Vigneau, E., Qannari, E.M. (2003). Clustering of Variables Around Latent Components. *Communications in Statistics - Simulation and Computation, 32(4),* 1131-1150. DOI: 10.1081/SAC-120023882

21

153

Willard, M. (2014) Restructuration cognitive. In F. Chapelle, B. Monié, R. Poinsot, Rusinek and M. Willard (Eds.). *Aide-mémoire: Thérapies Comportementales et Cognitives en 37 notions* (pp.218-223). Paris: Dunod.

World Health Organization. Skin cancers. Available from: http://www.who.int/uv/faq/skincancer/en/index1.html [Accessed 1st February 2018].

Zamanian, H, Eftekhar-Ardebili, H, Eftekhar-Ardebili, M, Shojaeizadeh, D, Nedjat, S, Taheri-Kharameh, Z, Daryaafzoon, M. (2015). Religious coping and quality of life in women with breast cancer. *Asian Pacific Journal of Cancer Prevention, 16(17)*, 7721-7725. http://dx.doi.org/10.7314/APJCP.2015.16.17.7721

154

Table 1. Characteristics of breast cancer and melanoma patients within 1 month post-

	All the patients (N=293)	Breast cancer patients (N=215)	Melanoma patients (N=78)
	n(%)	n(%)	n(%)
Gender			
Female	246 (83.9%)	213 (99.1%)	33 (42.3%)
Male	45 (15.3%)	0 (0.0%)	45 (57.7%)
Missing data	2 (0.7%)	2 (0.9%)	0 (0.0%)
Living with a partner			
Yes	240 (81.9%)	178 (82.8%)	62 (79.5%)
No	51 (17.4%)	35 (16.3%)	16 (20.5%)
Missing data	2 (0.7%)	2 (0.9%)	0 (0.0%)
Education			
$\leq$ Elementary school	44 (15.0%)	30 (13.9%)	14 (17.9%)
> Elementary school	245 (83.6%)	181 (84.2%)	64 (82.0%)
Missing data	4 (1.4%)	4(1.9%)	0 (0.0%)
Standard of living			
High	36 (12.3%)	24 (11.2%)	12 (15.4%)
Intermediate	236 (80.5%)	175 (81.4%)	61 (78.2%)
Low	16 (5.5%)	12 (5.6%)	4 (5.1%)
Missing data	5 (1.7%)	4 (1.9%)	1 (1.3%)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	52.2 (9.9)	53.0 (8.6)	51.3 (12.7)
Coping dimensions			
NCOP	16.0 (15.6)	16.6 (16.6)	14.4 (12.1)
ECOP	36.0 (17.8)	38.2 (18.2)	30.4 (15.4)
PCOP	50.6 (16.6)	50.7 (17.4)	50.6 (14.4)
SUBUSE	6.5 (15.6)	6.0 (14.9)	7.7 (17.3)
LOC dimensions			
INTLOC	31.6 (21.2)	32.4 (21.9)	29.4 (19.5)
CONLOC	67.8 (19.6)	67.2 (20.5)	69.1 (16.8)
RELLOC	13.3 (21.2)	13.7 (21.4)	12.1 (21.0)

NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; SUBUSE: substance use; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control. Range of the coping and locus of control scores: 0-100

diagnosis

1

155

Table 2. Changing over time of the dimensions of coping and locus of control

Dimensions	Breast		Melanoma	
	Estimate	SE	Estimate	SE
NCOP	-0.1	0.3	0.2*	0.1
ECOP	-2.2**	0.4	-0.2*	0.1
PCOP	0.1	0.4	-1.4*	0.6
INTLOC	1.4*	0.4	0.0	0.7
CONLOC	-1.0*	0.4	-1.7*	0.7
RELLOC	-0.1	0.0	-0.6	0.6

* p-value for the test of nullity of the coefficient <0.05; ** p value for the test of nullity of the coefficient <0.0001. SE: Standard Error. NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control.

156

Table 3. Results of the multivariate analyses of the coping, locus of control and sociodemographic variables on the dimensions of Health-Related Quality of Life

	Emotional Functioning (EF)				Physical Functioning (PF)				Global Health (GH)			
	Breast cancer		Melanoma		Breast cancer		Melanoma		Breast cancer		Melanoma	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
Intercept	59.58**	8.18	33.74*	9.75	95.57**	2.05	88.04**	3.80	67.71**	2.94	33.16**	7.76
NCOP	-0.27*	0.07	-0.50***†	0.10	--	--	-0.57***†	0.13	--	--	-0.23*†	0.08
ECOP	-0.30**†	0.05	--	--	-0.06*†	0.03	--	--	-0.11*†	0.04	--	--
PCOP	0.15*	0.07	--	--	--	--	0.19*†	0.05	--	--	--	--
INTLOC	-0.12*†	0.04	--	--	--	--	--	--	-0.13*†	0.03	--	--
CONLOC	--	--	0.28*†	0.08	--	--	--	--	0.15*†	0.04	0.21*†	0.07
RELLOC	--	--	-0.24*	0.08	--	--	--	--	--	--	--	--
Age	0.34*	0.13	0.42*	0.14	--	--	--	--	--	--	0.41*	0.12
Living with a partner	--	--	-13.50*	4.28	--	--	--	--	--	--	-10.16*	3.66
Standard of living	--	--	--	--	--	--	--	--	7.34*	2.76	--	--
Time	--	--									--	--
6 vs 1 mpd			3.30*	1.20	-12.37**	1.15	-2.62*	0.97	-6.87*	1.74		
12 vs 6 mpd			3.30*	1.20	5.28**	0.94	-2.62*	0.97	6.88**	1.32		
24 vs 12 mpd			3.30*	1.20	1.76*	0.66	-2.62*	0.97	0.45	1.24		
24 vs 1 mpd			9.89*	3.59	-5.33**	0.92	-7.85*	2.91	0.46	1.63		
Interactions between ECOP and time	0.22**(6 mpd) 0.26**(12 mpd) 0.22**(24 mpd)	0.04 0.04 0.05	--	--	--	--	--	--	--	--	--	--
Interactions between NCOP and time	--	--	--	--	--	--	0.13*	0.05	--	--	--	--
R²	18%		33%		30%		19%		15%		18%	

1

157

Table 3 (Continued)

	Cognitive Functioning (CF)				Role Functioning (RF)				Social Functioning (SF)			
	Breast cancer		Melanoma		Breast cancer		Melanoma		Breast cancer		Melanoma	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
Intercept	66.59**	7.18	91.01**	2.10	92.72**	4.47	23.91	12.35	87.55**	7.26	38.13*	10.72
NCOP	--	--	-0.36**†	0.08	--	--	--	--	-0.20*	0.06	-0.31*†	0.12
ECOP	--	--	--	--	--	--	--	--	-0.13*†	0.04	--	--
INTLOC	-0.14*†	0.04	--	--	-0.12*†	0.05	--	--	--	--	--	--
CONLOC	--	--	--	--	0.10*†	0.05	0.25*†	0.10	--	--	0.25*†	0.09
RELLOC	--	--	--	--	--	--	--	--	--	--	-0.19*	0.09
Age	0.37*	0.13	--	--	--	--	0.61*	0.19	0.31*	0.12	0.52*	0.16
Living with a partner	--	--	--	--	-8.79*	3.05	-13.38*	5.78	-6.73*	2.80	-17.53*	4.95
Time	--	--	--	--			--	--			--	--
6 vs 1 mpd					-17.79**	2.21			-14.39**	1.76		
12 vs 6 mpd					10.17**	2.00			7.58**	1.90		
24 vs 12 mpd					0.10	1.63			1.94	1.71		
24 vs 1 mpd					-7.52*	2.02			-4.87*	1.57		
R²	6%		9%		17%		15%		18%		14%	

* p value for the test of nullity of the coefficient <0.05
** p value for the test of nullity of the coefficient <0.0001
†=Time-dependent variable.

Reference levels: household living standard: low intermediate, education: ≤ certificate of elementary school, living with a partner: no, time: time 1.
mpd: months post-diagnosis; NCOP: negative coping; ECOP: emotional coping; PCOP: positive coping; INTLOC: internal locus of control; CONLOC: control over the course of the illness; RELLOC: religious locus of control.

2

158

Figure 1. Mean scores of emotional functioning over time according to the level of emotional coping in breast cancer patients

EF: emotional functioning; ECOP: emotional coping; mpd: months post-diagnosis.

Observed levels of emotional coping in the sample:

- mean: 39.9

- 1st quartile: 25

- 3rd quartile: 50

159
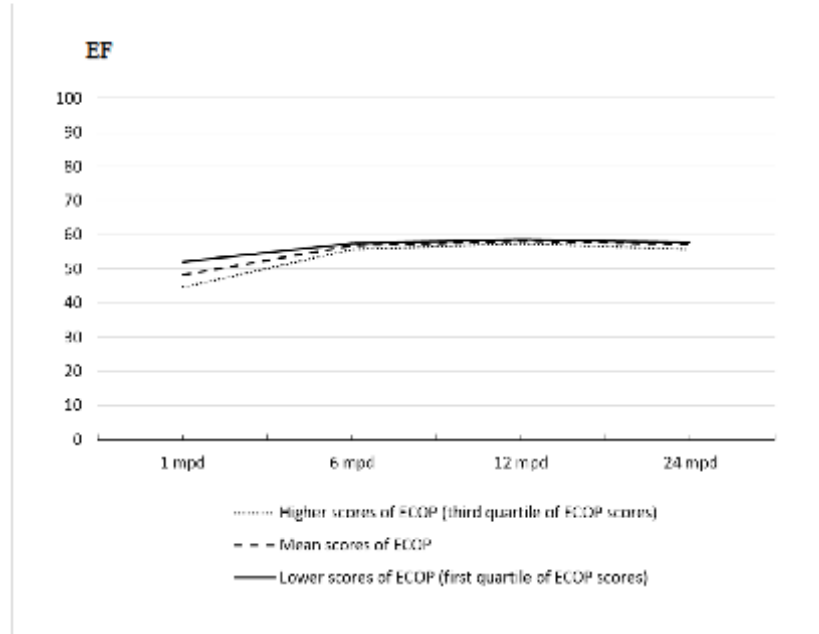
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Appendix

Linear mixed models

Mixed models are widely used for the analysis of data from longitudinal studies. They allow dealing with repeated measurements by specifying a structure for the correlation between measurements from a same patient. Mixed models can also handle incomplete data. A mixed model is composed of both fixed effects and random effects, that is mixed effects. The mean response is modeled as a combination of fixed effects characterizing the population mean and random effects characterizing the subject-specific effects that are unique to a particular individual.

Let

$-n_i$ be the number of observations on patient i, $i=1...N$ and $M = \sum_{i=1}^{N} n_i$ be the total number of observations

$-p$ and k be the number of fixed and random parameters respectively

$-Y_i$ be the $(n_i \, x \, 1)$ vector containing the responses for the patient i

$-X_i$ and Z_i be the $(n_i \, x \, p)$ design matrix characterizing the fixed part of the model and $(n_i \, x \, k)$ design matrix characterizing the random variation in the model due to among-unit sources

$-\beta$ be the $(p \, x \, 1)$ vector of fixed effects parameters

$-b_i$ be the $(k \, x \, 1)$ vector of random effects parameters, $b_i \sim N_k(0, \mathbf{D})$

$-e_i$ be the $(n_i \, x \, 1)$ vector of error terms, characterizing variation due to within-unit and measurement error sources, $e_i \sim N_{ni}(0, \mathbf{R}_i)$

$-\Sigma_i$ be the $(n_i \, x \, n_i)$ covariance matrix

$$Y_i = \left(Y_i^{(1)} Y_i^{(2)} Y_i^{(3)} \right)' = X_i\beta + Z_i b_i + e_i$$
$$var(Y_i) = Z_i D Z_i' + R_i = V_i$$
$$Y_i \sim N_{n_i}(X_i\beta, V_i)$$

The parameters to be estimated in the model are the mean parameters β that characterize the mean and the covariance parameters ω, the parameters that makes up V_i. In this study, they were estimated using the REstricted Maximum Likelihood (REML) method in order to reduce the bias on covariance parameters in comparison to the use of Maximum Likelihood (ML) estimation.

160

F-test

In order to perform a test of nullity of some parameters of the fixed effects, a F-test can be performed.

For a contrast matrix L, the F-test can be written as:

$$H_0: L\beta = 0 \; versus \; H_1: L\beta \neq 0$$

$$W = (\hat{\beta} - \beta)'L' \left[L \left(\sum_{i=1}^{N} X_i'V_i^{-1}(\widehat{\omega})X_i \right)^{-1} L' \right] L(\hat{\beta} - \beta)$$

Under H_0, W/rank(L) has an approximate F distribution with rank(L) being the numerator degrees of freedom and ν denominator degrees of freedom. The number of denominator degrees of freedom for the tests of fixed effects can be approximated by Satterthwaite (Satterthwaite, 1941) or Kenward-Roger (Kenward et al., 1997) methods amongst others with SAS Proc MIXED.

R^2 statistic for linear mixed models

Contrary to the linear regression, the evaluation of goodness-of-fit of fixed-effect covariates in linear mixed models using R^2 statistic is relatively new. Amongst different R^2 statistics in linear mixed models (Orelien, et al., 2008), the R^2 statistic proposed by Edwards et al. (Edwards et al., 2008) is simple to implement as it can be computed with results from the model of interest. This R^2 measures multivariate association between the repeated measures of HRQoL and the fixed effects for a given covariance structure and helps comparing mean models (i.e. different fixed effects) with the same covariance structure. In fact, the proposed R^2 is simply defined using an approximate F statistic for a Wald test of fixed effects.

$$R^2 = \frac{(q-1)\nu^{-1}F}{1 + (q-1)\nu^{-1}F}$$

The model of interest (full model) with q-1 predictors in the fixed effects is compared to a null model with only the intercept in the fixed effects and the same covariance structure so that R^2 relies on a F-test of the null hypothesis H0: $\beta1 = \beta2 = \cdots = \beta q-1 = 0$. F is the statistic of the Kenward-Roger F-test computed during the fitting of the model of interest and ν are the associated denominator degrees of freedom.

161

Résumé : Les progrès thérapeutiques et le diagnostic plus rapide ont permis d'améliorer le taux de survie de nombreux cancers. Il est donc de plus en plus nécessaire de trouver un moyen d'aider les patients à maintenir une bonne santé psychologique et à améliorer leur Qualité de Vie Liée à la Santé (QVLS). Les croyances des patients (Locus De Contrôle, LDC) et les stratégies de coping sont des variables psychologiques pouvant influer sur la QVLS des patients. Les liens entre l'évolution de la QVLS et du LDC et du coping ont été étudiés chez des patients atteints d'un cancer du sein ou d'un mélanome au cours des deux ans suivant le diagnostic. Afin d'évaluer si les croyances des patients jouent également un rôle dans les choix thérapeutiques, l'association entre le choix du traitement au moment du diagnostic d'un cancer de la prostate et les croyances des patients et d'autres variables médicales et psychologiques, a été étudiée.

Certains types de LDC ou stratégies de coping ont une influence sur l'évolution de la QVLS pour le cancer du sein et le mélanome alors que certains ont une influence uniquement pour l'un des deux cancers. De plus, la QVLS n'évolue pas de la même façon pour ces deux cancers. La croyance que les médecins peuvent avoir le contrôle sur la santé du patient était négativement associée au choix d'un traitement plus invasif au moment du diagnostic d'un cancer de la prostate. Il semble que les psychothérapies basées sur le coping ou le LDC devraient être spécifiques au type de cancer et au temps depuis le diagnostic. Ce travail renseigne également sur l'importance de considérer les aspects psychologiques de la relation médecin-patient dans la décision médicale partagée.

Abstract: Advances in treatment and faster diagnosis have helped improve the survival rate for many cancers. Therefore, the need to find a way to help patients to maintain good psychological health and to increase Health-Related Quality of Life (HRQoL) has become essential. The patients' beliefs (Locus of Control, LOC) and the coping strategies are psychological variables can have an impact on patients' HRQoL. The association of changes in HRQoL over time and coping and LOC was assessed in breast cancer and melanoma patients during 2 years post-diagnosis. In order to study if the patients' beliefs also play a role in treatment decision making, the association between the treatment choice at diagnosis and patients' beliefs and other medical and psychological variables was assessed.

Some LOC sub-dimensions or coping strategies have an association with HRQoL change for breast cancer and melanoma, whereas some of them have an association only with one cancer type. Moreover, HRQoL does not evolve in the same way for both types of cancer. The belief of the control of the doctors on patient's health was negatively associated with radical treatment choice. It seems that psychological therapies, that consider the patients' coping strategies and beliefs, should be specific according to the type of cancer and time post-diagnosis. This work has also highlighted the importance of considering the psychological aspects of the doctor-patient relationship in shared medical decision making.