Psychosocial and Quality of Life Issues in Prostate and Ovarian Cancer

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Psychosocial and Quality of Life Issues in Prostate and Ovarian Cancer

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in prostaat- en eierstokkanker

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CHAPTER 1

General introduction

INTRODUCTION

Cancer prevention and control have become important challenges for public health, since cancer is a major cause of mortality and morbidity in the industrialized world. Due to the aging of Western populations, the cancer burden is expected to increase substantially in the next 50 years, unless cancer prevention and treatment improve dramatically [1-3]. Screening for disease is increasingly being introduced as an integral part of medical practice. Historically, screening for cervical cancer with PAP smears and for lung cancer with thorax X-rays were the first screening practices that aimed at mortality reductions [4,5]. Mammographic screening for breast cancer has already been introduced as a national preventive program in many countries [6]. Population-based screening for other prevalent malignancies, e.g., prostate cancer, are still in the process of development and before being implemented at the level of a national preventive program, need to be thoroughly evaluated in terms of reduced mortality, costs and quality of life effects per life-year gained [7].

In the field of disease prevention and control, research efforts have also focused on understanding susceptibility to different types of cancers. The identification of risk factors, including environmental and hereditary factors, facilitate defining groups of high-risk individuals who would potentially benefit most from targeted prevention programs [8]. In the case of some cancers, e.g., breast and ovarian cancer, epidemiologic research has identified a positive family history as an important risk factor for developing the disease [9]. Following rapid advances in cancer genomics in recent years, DNA tests have been developed and introduced in clinical practice. By means of such tests, key gene mutations can be detected that are known to be responsible for increased risk of developing the disease. With the development of methods that allow for accurate identification of individuals at increased risk of developing breast and ovarian cancer, there is growing acceptance of prophylactic organ resection among high-risk individuals [10]. In the context of breast/ovarian cancer, high-risk women may opt for different preventive health measures targeted either at cancer risk reduction or early cancer detection [11].

Although disease-specific mortality reductions are the primary outcome when evaluating cancer prevention, patients' quality of life can be viewed as a complement of survival time in outcome research [12]. In the present context, quality of life relates to patients' functioning in the physical, psychological and social domains of health [13]. Applied preventive health strategies, including screening and early medical treatments either with prophylactic or curative intention, may substantially affect patients' quality of life [14,15]. In this thesis, two large investigations are presented that focus on the quality of life issues in cancer prevention and control, using the examples of two gender-specific cancers -- prostate and ovarian cancer -- that are among the leading

causes of death in Europe and in the United States. In the first investigation, the quality of life effects of the primary treatment of prostate cancer were studied in the context of a population-based screening trial. The second study focused on the population of women at increased hereditary risk of breast/ovarian cancer who sought preventive measures to manage their cancer risk. These investigations were conducted in order to provide both clinicians and patients with more complete information about the quality of life effects of the available preventive options for these diseases and thus to contribute meaningfully to decision-making at both the population and the individual patient level.

PROSTATE CANCER: EPIDEMIOLOGY, EARLY DETECTION AND PRIMARY TREATMENT

Prostate cancer is a major public health concern, with 6,900 new prostate cancer cases and 2,400 deaths in the Netherlands in 2000 [16]. Prostate cancer is the most common non-cutaneous malignancy, and the second leading cause of cancer death in men in Western countries [17]. Testing for prostate specific antigen (PSA), a protein produced by the cells of the prostate gland, has become a common method for detecting prostate cancer. The PSA test is usually able to detect prostate cancer at an early stage, but elevated levels of PSA may also be associated with other conditions, such as benign prostate enlargement or infection [18]. Physicians have applied PSA testing increasingly, since its introduction in the 1980s, which has resulted in increasing incidence rates of early-stage tumors, and a higher prevalence of prostate cancer [19]. Importantly, PSA testing may lead to overdiagnosis, i.e., detection of indolent cases of prostate cancer that would never have been diagnosed in the absence of such a diagnostic technique. Overdiagnosis often carries with it the risk of the overtreatment of slow-growing tumors that might not ever become of clinical significance during the patient's life [19-21].

The most common therapeutic options for localized prostate cancer are radical prostatectomy, primary radiotherapy and brachytherapy. Brachytherapy still accounts for a relatively small percentage of all primary treatment [22]. Men with well-differentiated prostate tumors may also opt for 'active surveillance' ('watchful waiting') consisting of periodic PSA-testing and prostatic biopsies. Although primary treatment for prostate cancer is potentially curative, it may result in urinary, bowel and sexual side-effects and functional impairment [23]. Data on the extent of side-effects and possible impairment of quality of life associated with each type of primary treatment are necessary in order to fully inform patients about the benefits and costs associated with each treatment, and to facilitate incorporating individual patient preferences in clinical decision-making.

Currently, it is not clear whether early detection of prostate cancer and consequent earlier treatment lead to any change in the natural history and outcome of the disease, including reduced mortality. Two large randomized controlled trials: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the U.S., and in the European Randomized Screening study for Prostate Cancer (ERSPC) in Europe are currently investigating these issues in the context of population-based screening [24,25]. Their outcomes regarding disease-specific mortality are expected, at the earliest, in 2007. A population-based prostate cancer screening program can only be introduced if the findings from both trials indicate substantial reductions in disease-specific mortality as a result of early prostate cancer detection, followed by earlier treatment. Other important conditions for the introduction of such a program relate to costs and quality of life effects. When the data on cancer-specific mortality reductions are available, cost per life year gained can be determined, using cost-effectiveness analyses. Unfavorable quality of life effects may occur during the screening procedure itself and the diagnosis phase (e.g., pain, discomfort, feelings of anxiety), during the primary treatment phase (e.g., urinary, bowel and sexual problems), and during stages of advanced disease in those men who have developed metastatic prostate cancer despite early primary treatment [26]. When evaluating public health effects of a prostate cancer screening program, the effects of screening and earlier treatment on both disease-specific mortality reductions and on quality of life have to be taken into account.

OVARIAN CANCER: EPIDEMIOLOGY, HEREDITARY CANCER AND PREVENTIVE HEALTH STRATEGIES

Ovarian cancer is the fourth most frequent cause of cancer death and the most lethal of all gynecologic tumors in women in Northern and Western Europe [17]. Despite recent advances in treatment (e.g., platinum-based, multi-agent chemotherapy), ovarian cancer remains a fatal disease for most women [3]. In 2000, there were 1,116 women diagnosed with ovarian cancer in the Netherlands, 910 of whom died of the disease [16]. Life-time cancer risk for women in industrialized countries is approximately 2%. A positive family history of breast/ovarian cancer is considered to be one of the strongest predictors of developing ovarian cancer [27]. Women who carry a BRCA 1/2 gene mutation have at least a 10-fold higher risk of developing ovarian cancer than women in the general population [28].

A growing number of women from hereditary breast/ovarian cancer (HBOC) families have access to genetic counseling, including DNA testing. In the Netherlands, women from HBOC families who are older than 35 years of age are also offered annual gynecological health care services focused on ovarian cancer prevention [29]. Principal preventive health strategies for women at increased risk of ovarian cancer include

periodic gynecological screening and prophylactic bilateral salpingo-oophorectomy. Screening, consisting of pelvic examination, transvaginal ultrasound and CA-125 serum, is a basic surveillance strategy. Since the efficacy of the currently available screening techniques is uncertain [30-32], oophorectomy remains a preferable preventive option in high risk women due to its established risk reducing benefits for both ovarian and breast cancer.

Generally, BRCA1/2 carriers who have completed their childbearing, women with a history of breast cancer, and in some cases, postmenopausal women who have received non-informative DNA test results are advised to undergo prophylactic surgery. Despite the clear cancer-protective effect of oophorectomy, surgery leads to hormonal deficiencies that are responsible for infertility and premature menopausal symptoms in younger women. Postoperative hormonal imbalance may affect women's functioning in several health domains. There is a clear need for better documentation of the physical and quality of life effects of preventive surgery for ovarian cancer.

OBJECTIVES AND STRUCTURE OF THE THESIS

The focus of this thesis is on the psychosocial issues, including quality of life, involved in the evaluation of early-detected and early-treated prostate cancer among men in the general population, and in the evaluation of preventive health strategies for ovarian cancer among women at increased hereditary risk of developing the disease. The main objectives of this thesis are:

To evaluate pretreatment quality of life among patients with localized prostate cancer detected by a population-based screening or in a regular clinical setting.

To determine the quality of life effects of primary treatment for localized prostate cancer detected by a population-based screening or in a regular clinical setting.

To identify psychosocial and clinical factors predicting use of prophylactic surgery versus gynecological screening among women with hereditary susceptibility for breast/ovarian cancer.

To determine the quality of life effects of prophylactic oophorectomy versus gynecological screening among high-risk women.

To establish the impact of postsurgical hormone replacement therapy (HRT) use on the levels of menopausal symptoms and sexual functioning among younger high-risk women.

The thesis consists of two parts. In part I, the results of the studies of the quality of life effects of early detected prostate cancer are presented. Chapter 2 describes the role of quality of life and cost-effectiveness studies within the framework of the two large population-based randomized screening trials in Europe and in the United States, respectively the ERSPC and PLCO trials. It also provides basic information about

different types of quality of life measures (generic, disease- or condition-specific and domain-specific) and quality of life assessment (description and valuation). Chapters 3 and 4 are based on a prospective cohort study conducted among men with localized prostate cancer, within the framework of the ERSPC trial. Pretreatment quality of life (Chapter 3) is evaluated in relation to the type of diagnosis (screen-detected or clinically diagnosed prostate cancer) and the subsequent primary treatment (radical prostatectomy or radiotherapy). Chapter 4 investigates the quality of life effects induced by radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed prostate cancer.

Part II comprises the studies investigating the impact of ovarian cancer prevention on psychosocial health and symptom experience, including quality of life, among women at hereditary risk of developing ovarian cancer. Chapter 5 provides an overview of factors predicting use of prophylactic oophorectomy versus gynecologic screening in the context of a prospective, nationwide study among high-risk women in the Netherlands. Chapter 6 presents the quality of life effects associated with prophylactic surgery versus gynecologic screening. Chapter 7 examines the impact of postsurgical use of hormone replacement therapy on the levels of endocrine symptoms and sexual functioning. Finally, in Chapter 8 we discuss the most important findings from the prostate and ovarian cancer studies, and their implications for clinical practice and future research.

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PART I:

STUDIES ON EARLY DETECTION AND TREATMENT OF PROSTATE CANCER

CHAPTER 2

Quality of life and cost-effectiveness issues in prostate cancer screening trials

Miller AB, Madalinska JB, Church T, Crawford D, Essink-Bot ML, Goel V, de Koning HJ, Maattanen L, Pentikainen T: Health-related quality of life and cost-effectiveness studies in the European Randomised Study of Screening for Prostate Cancer and the US Prostate, Lung, Colon and Ovary trial. European Journal of Cancer 37:2154-60, 2001

ABSTRACT

Decisions on policies for screening for prostate cancer require that information upon health-related quality of life (HRQL) and cost-effectiveness (CE) be available, as the lead time for some of the cases detected by screening will be very long and detriments in quality of life could have a major impact on the subjects remaining life span. A framework within both HRQL and cost-effectiveness of prostate cancer screening can be assessed is presented. Studies of both are ongoing in the European Randomized Study of screening for prostate cancer and the US Prostate, Lung, Colon and Ovary trial. Preliminary information confirms that it is important to study screened subjects and controls, and not to assume that inferences derived from study of prostate cancer outside screening trials can be extrapolated to the trials. However, it will require prolonged study to enable the overall effects on quality of life, and on cost-effectiveness to be determined. Such studies are ongoing for the two trials.

INTRODUCTION

The extent that prostate cancer screening improves or impairs overall health-related quality of life (HRQL), as well as the acceptability of its cost to the individual and the community, is an important evaluation measure [1]. Deciding the healthcare policy is only possible if information is available on HRQL and the health costs of screened and unscreened participants as well as the mortality reduction from screening. Modeling suggests that an 'optimistic' estimate of screening effectiveness is required in order for screening to be cost-effective [2,3]. HRQL and CE studies have been initiated within the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colon and Ovary (PLCO) trials. Collaboration between the trials will facilitate resolving the complex issues concerning HRQL and cost effectiveness.

The principal endpoint for the trials is a reduction in mortality from prostate cancer. The only valid surrogate for mortality is believed to be a reduction in clinically advanced or metastatic cancer [4]. However, surveillance may bring forward the time of diagnosis of such disease among men found to have prostate cancer by prostate-specific antigen (PSA) screening, resulting in an excess of advanced disease in a screened group compared with an unscreened one. Thus, basing cost effectiveness on cancer detection, especially if they are small stage 1 tumors, or even all cancers irrespective of stage, would be wrong, as each of these are expected to be influenced by screening but are affected by lead-time, length, selection and over-diagnosis biases.

There is a similar problem related to the time cost-effectiveness and HRQL events occur. Many cancers will be diagnosed earlier in the screening arm, and thus at a younger age than in the control arm. Given that the costs of the screening tests, and the costs and adverse HRQL associated with false-positives and from treating the cancers that occur relatively early, it could be concluded that the HRQL issues are overwhelming [5]. It will require a prolonged follow-up before the detrimental effects on HRQL associated with advanced cancer late in life, which may be prevented in the screened group, appear in the control group. Therefore, long-term follow-up of participants in the trials will be required to determine the late quality of life effects.

Factors that are detrimental for HRQL and that are related to therapy can be estimated in non-trial participants, as can costs. The quality of life of patients with advanced prostate cancer has already been measured in several studies [6-13]. However, the spectrum and distribution of disease identified as a result of screening is not the same as in the absence of screening, it is therefore necessary to measure HRQL and determine the costs directly from samples of subjects in the trials to permit an accurate modeling of the late effects and their consequences. Thus, the ERSPC and

PLCO trials are being conducted with the intent of evaluating the comprehensive value of screening.

FRAMEWORK FOR HRQL AND COST-EFFECTIVENESS

HRQL and cost-effectiveness studies are imbedded in a framework such as Fig. 1. The framework helps to facilitate decisions on the measures and timing that may be required. Each numbered node indicates a point in the screening, diagnosis, treatment, follow-up, and final endpoint (death) process when HRQL changes and cost expenditures occur. In non-compliant participants allocated to the screened group, no screening costs are incurred; likewise, some control group participants will incur screening costs because of contamination. Because of this self-selection, the analysis must primarily make an intention-to-treat comparison of the allocated screened and control groups.

For simplicity, the different nodes are described below in relation to HRQL and cost-effectiveness studies separately, although it is recognized that they are closely integrated, since HRQL is often incorporated into cost-effective studies, usually as preference-based measures.

HRQL studies

(1) Eligible participants have a baseline quality of life that should be estimated from representative samples. In several ERSPC or PLCO HRQL studies, measurements are being performed on a sampling basis within strata of age, race, centre and previous screening history.

(2) There appears to be an immediate, short-lived, (decrement in quality of life following screening. It is important to measure the HRQL effects of the tests, including pain, discomfort and anxiety [14], before the results of the tests are available.

(3) Those participants allocated usual care (UC) in (the volunteer-based trials may be disappointed, and some may seek PSA testing to substitute for the lack of screening. Studies to estimate the frequency of such contamination and assess the impact on HRQL of randomizing to UC are being done.

(4) Participants with positive screening tests experience anxiety [14]. It would be preferable to measure this in advance of the diagnostic tests that follow, but in most instances it is only possible to measure such effects retrospectively.

(5) Participants with negative screening tests are reassured [14]. The majority of those with negative results will be true-negatives. The false-negatives are not initially identifiable; some of them will appear later as interval or screen-detected cancers.

(6) Diagnostic tests heighten anxiety, and also affect HRQL through their interference with normal life [14]. Ideally, HRQL should be measured before the outcome is known, as there is a risk of recall bias if measurements are attempted later.

(7) Reaction to screen-detected cancers will vary in relation to whether their 'earlier' detection is perceived as a benefit derived from the trial. Such reactions should be captured before therapy is started, as in the Rotterdam HRQL study [15].

(8) A non-cancer outcome to positive diagnostic tests (false-positive) is likely to be reassuring, with a rapid reduction in anxiety. Measurement of HRQL at several points after the non-cancer outcome is feasible. There is some evidence that compliance with subsequent screen-related events is higher than for those with negative test results [16].

(9) HRQL should be measured soon after completion (of therapy for screen-detected cancers, and during it also if treatment is prolonged, to detect adverse consequences such as impotence, incontinence, impaired bowel functioning, etc. [17].

(10) Measurements during follow-up should capture long-term increments and decrements of HRQL, as well as interference with life events caused by diagnostic testing for cancer recurrence. If there is recurrence, there will be further decrements of HRQL.

(11) Interval cancers will probably be similar to clinically detected cancers in the UC group (12). However, the fact that they occurred after a negative screening test may result in a different emotional reaction. Hence, they need study in their own right.

(12) Apart from those detected by opportunistic (spontaneous or self-selected) screening, the majority of cancers in the UC group will be symptomatic. They require careful study as they form the controls for (7).

(13) The HRQL decrements associated with treatment should also be measured. Measurement will be facilitated in the centers that provide diagnosis and therapy for UC participants.

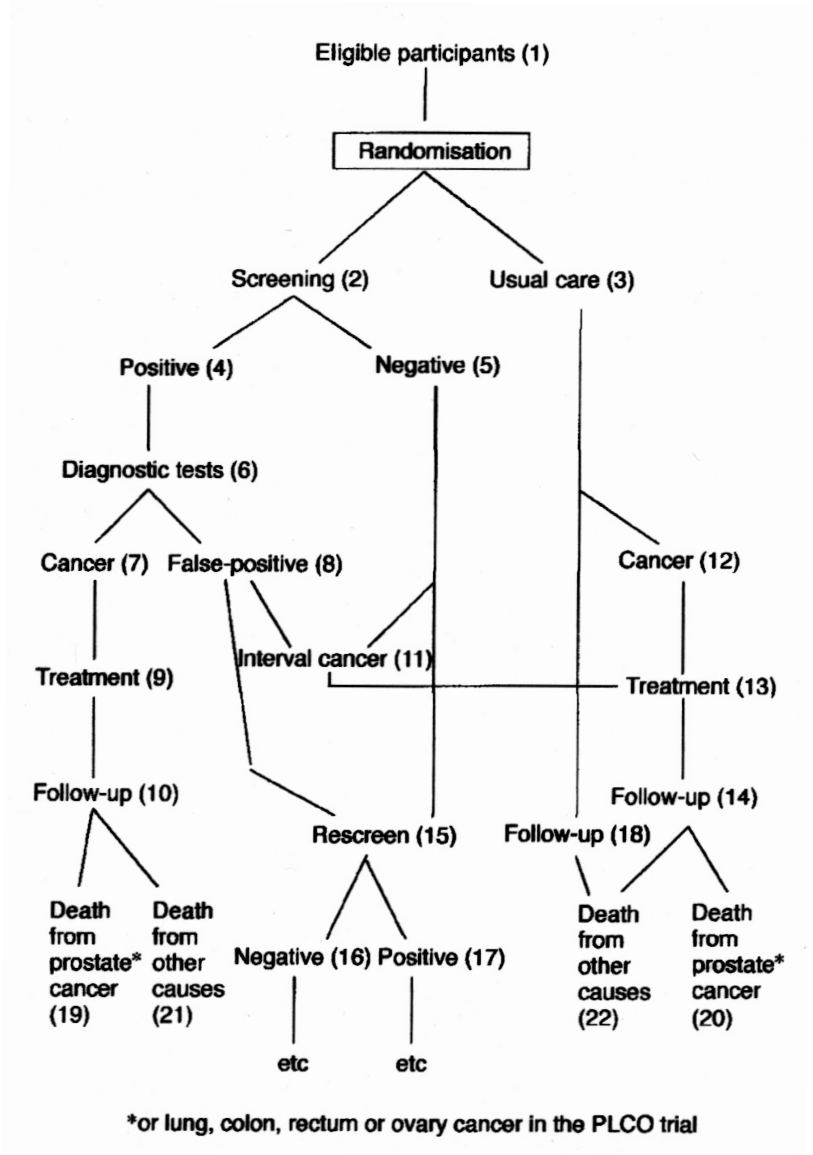
(14) For comparison purposes, follow-up assessments should be scheduled at the same frequency as for (10).

(15) The routinely scheduled re-screens will induce changes in HRQL that will resemble those that follow the initial (prevalence) screen. Thus, there are similar measurement requirements as for (2).

(16)/(17) Negative and positive results from re-screening will induce measurement requirements similar to (4) and (5), to be followed by similar requirements to (6), etc.

(18) The follow-up requirements for the UC group are periodic, perhaps annual, for the duration of the follow-up in the trial.

Figure 1. Framework for cost-effectiveness and health-related quality of life (HRQL) measurements



(19)/(20) HRQL during the terminal illness will be assessed by proxy ratings, as obtaining these data directly from patients may be emotionally too burdensome for them or the screening centre may learn of the terminal illness after the death of the

patient. Previous studies [18,19] showed that at the individual level, patient-proxy agreement was generally moderate to good. Although at the group level systematic differences between the patient and proxy mean scores were observed, with a tendency of relatives to report more impairments of patients' HRQL, the bias tended to be limited. Despite these limitations, when employing significant others as the proxy respondents of cancer patients' quality of life the proxy is a viable and acceptable method for obtaining HRQL data [18].

(21)/(22) Deaths from other causes will also have decrements associated with HRQL that contribute to the total HRQL burden for study subjects. If screening is effective there will eventually be more of them in the screen arm than in the UC group.

CE studies

(1) There is a cost associated with identifying subjects eligible for screening. However, the processes required for a trial usually differ from routine screening. This cost element will have to be acknowledged, but not necessarily evaluated in the trials.

(2) The costs associated with the screening tests are important, as they may be the major cost of the screening process. Some costs could be obtained from the budgets of the trials, but the costs incurred in routine practice, and the costs incurred by the participants in attending the screen, require special study.

(3) There is a cost associated with UC, including physician visits for symptoms associated with cancer, and any diagnostic tests.

(4)/(5) There are costs associated with notifying screen-test results.

(6)/(8) The costs of distinguishing true- from false positives and managing false-positives require special study, as these may not be not under the control of the screening centers. Both insurance (HMO) and MEDICARE costs have to be considered, since costs vary by insurance status as well as by age.

(7)/(9)/(10) The costs of treating true-positives will vary by stage. It cannot be assumed that the costs of treatment by stage for a screen-detected cancer are the same as for a non-screen-detected cancer.

(11)/(12)/(13)/(14) The costs of identifying, treating and managing interval and non-screen-detected cancers should be the same by stage, age and centre as for the general population. However, special study may be needed to obtain the detail required for trial purposes.

(15)/(16)/(17) Re-screening costs will be similar to the initial screening, although they involve costs associated with ensuring compliance.

(18) There are the study-associated costs of follow-up of the UC group. These will probably not require special documentation.

(19)/(20) The costs associated with terminal illness from fatal cancers may be incurred earlier in life in the UC than the study group. Therefore, costs associated with both (19) and (20) will have to be separately determined.

(21)/(22) The costs of caring for people dying of other causes will also require study. The time these events occur, and thus the influence of discounting, may be critical.

Difficulties in applying the framework

One of the major difficulties investigators will have in determining HRQL for many of the steps in the framework, is that they may learn of an event after much delay. This particularly affects items nos. (2), (4), (6), (7), (8), (9), (11), (12) and (13). However, the main concern in the trials has to be with long-term, persistent decrements of HRQL.

Costs related to the treatment of prostate cancer are available for the US [20]. However, they may differ from the costs of treating screen-detected or interval cancers. Although administrative data for costs may be available, it is nearly impossible to determine from routine medical records which costs are screen-related and which are not. Thus, the only unbiased way of comparing costs is by intention-to-treat, accruing costs to each allocated group and determining the difference. For a complete accounting, both indirect and intangible costs should be estimated, as well as direct costs. For several of the CE measures, costs in the trials will not directly reflect future costs. Diagnosis and treatment will change in the future, and to guide policy in the future, the costs in the future will have to be included in the CE models. This can be partly overcome by ensuring that health care utilization data are collected on all subjects. The unit costs for specific utilization can then be indexed to a reference year when the CE analysis is done.

Several items, such as numbers (2), (4), (6), (7), (8), (9) and perhaps (19), require screening to be undertaken to determine the costs. Comparable costs in the UC group will have to be estimated over a similar time period.

ASSESSMENT OF HRQL

HRQL is a multidimensional construct incorporating patients' functioning in physical, psychological and social domains. A clear distinction must be made between the description and evaluation of HRQL. Descriptive measures generate a profile of scores across different dimensions of HRQL and provide a detailed description of HRQL during different phases of screening and disease. Evaluative measurement yields a single summary index ('utility') that is obtained for each profile of HRQL scores (health state). Health state utilities are necessary for calculation of quality-adjusted life years (QALYs). A QALY is a composite health outcome measure, combining both

duration and quality of life. Time lived with disease is made 'equivalent' to a shorter period in full health using a utility weight between 0 (death) and 1 (full health). QALYs are suited to the overall evaluation of a screening program.

To assess HRQL effects, generic, disease-specific or domain-specific measures can be used. Generic questionnaires (e.g. Short Form-36 (SF36), Short Form-12) are comprehensive, non-specific HRQL measures. They allow for comparisons across diseases and between disease stages. Although generic measures are used mainly for descriptive purposes, some instruments provide a direct link to health state utilities. Measures with a link to utilities (EuroQoL-5D, Quality of Well-Being Scale, Health Utility Index) provide a 'tariff' or scoring formula to transform descriptions of a patient's health status into a summary figure ('utility'). Preferences from the general public are commonly used to reflect the societal perspective in a decision-making context [21,22]. Recently, efforts have been made to derive utilities from the SF-36 [23,24].

Disease- and domain-specific measures are used to complement generic measures. The early ones (e.g. UCLA Prostate Cancer Index) assessed the extent of symptoms related to prostate cancer and its treatment (e.g. urinary incontinence, sexual dysfunction, gastrointestinal symptoms). Later ones (e.g. State-Trait Anxiety Inventory, Centre for Epidemiologic Studies Depression Scale) concentrate on the impact of the disease on a specific psychosocial domain of a patient's HRQL (e.g. anxiety, depression). Disease-specific instruments seem to be capable of detecting longitudinal differences in functioning of patients who undergo radical prostatectomy or primary radiotherapy [17], as well as differences between disease stages (localized versus metastatic prostate cancer). Whether posttreatment decrements in functional status have an impact on generic HRQL is unclear. Some studies could not detect significant changes between pre- and posttreatment SF-36 scores [25].

In ERSPC and PLCO, a commonly applied combination consists of descriptive generic, generic with link to utilities, disease-specific and domain-specific instruments. The studies explore the relationship between disease-specific and generic HRQL in prostate cancer patients. These efforts may result in the development of more sensitive instruments for capturing relevant HRQL changes in all phases of screening.

PRELIMINARY FINDINGS IN THE ERSPC AND PLCO TRIALS

On HRQL

In general, the screening process itself does not seem to result in appreciable differences between screened subjects and controls, nor between participants and non-participants, although participants with pre-existing anxiety tend to remain anxious [14]. Considerable attention is therefore being paid to the HRQL decrements associated

with false-positive screening test results and to those with a positive screen who are found to have cancer. Those deemed to have a false-positive screen after a negative biopsy of the prostate are an important risk group for subsequent cancer diagnosis, as some may later be diagnosed with prostate cancer, whether as an interval finding or after a subsequent screen. In the group who come for re-screening, HRQL decrements could become more important as they age. In the Rotterdam HRQL study, patients with screen-detected prostate cancer reported significantly better pre-treatment generic HRQL (physical aspects), compared with patients diagnosed in a clinical setting [15]. Nevertheless, HRQL scores of the latter group remained in the range of the population norm. No differences were found in patients' self-reported levels of urinary, bowel and sexual functioning. Pre-treatment comparison of patients scheduled either for prostatectomy or radiotherapy revealed that the radiotherapy patients were significantly older and had more co-morbidity. Problems with urinary, bowel and sexual functioning were uncommon; however, radiotherapy patients older than 65 years appeared to be less sexually active prior to the diagnosis. Radiotherapy patients also reported poorer levels of generic HRQL. These results indicate that patients with screen-detected prostate cancer come from a distinct, relatively healthy population, presumably due to some self-selection when responding to invitations to be screened.

On cost-effectiveness

Costs are being determined at many steps in the framework, especially in the screened arm, in both trials. Cost implications of advanced prostate cancer have been determined from non-trial participants in Rotterdam [26]. In the Nordic countries, many of the required costs are readily available from the health care systems. In the US, with different healthcare organizations involved, costs vary, and many healthcare organizations either cannot, or are reluctant, to supply them. In one of the PLCO centers where the downstream costs of interventions after both positive and negative screens are being studied, preliminary estimates from one of the three healthcare organizations in that area have been derived. Additional estimates are needed from other PLCO centers with different healthcare organizations, especially those with a more minor participation.

FUTURE HRQL AND COST-EFFECTIVENESS STUDIES IN ERSPC AND PLCO

Specific aims

1. Collect serial HRQL data in intervention and UC subjects who remain free of prostate cancer, stratifying the intervention group according to whether the screening tests were negative or falsely positive.

2. Measure the immediate and short-term HRQL effects from among those with positive and negative screening tests.

3. Collect serial HRQL data in intervention and UC subjects who develop a prostate cancer, including information about cancer-related side-effects and complications arising from treatment.

4. Determine the HRQL decrements from those activities that contribute to the indirect costs of screening (e.g. travel to the screening centre, time spent on screening, diagnostic tests, etc.).

5. Determine the differential in HRQL effects from the terminal illnesses of subjects who die in the intervention and UC arms separately for prostate cancer and other causes of death, and evaluate whether there are differences according to the age at which death occurs.

6. Track utilization of health care associated with screening for prostate cancer for each country by centre and healthcare system.

7. Collect data on the cost of screen-related diagnostic and treatment procedures for suspected and confirmed prostate cancers. Compare these costs with corresponding costs in the UC group.

8. Collect data on the opportunity costs for attendance for screen-related diagnostic and treatment procedures.

9. Determine the differential between the costs of treatment and subsequent follow-up and terminal care for screen-detected and non-screen-detected cancers.

10. Determine a utility measure yearly in each arm for each trial within each country for the duration of the trials.

11. Develop methodology for adjusting comparisons in items 1–10 for underlying differences in the nonrandomized comparison groups, based on data collected at enrolment or data available from medical records. Methods may be adapted from those used to adjust for compliance in Randomized trials [27-30], or to adjust for lead-time and length-bias in observational studies of screening [31].

COMMENTS ON FUTURE STUDIES

A high priority is to decide on the instruments that should be used for the HRQL studies, as well as to determine the utility measure. There is a conflict between group (population) HRQL estimates which will be influenced by the *healthy screenee* effect, and individual (prostate cancer patient-based) estimates. In overall evaluations, the former could easily submerge the latter, yet it is the latter on which we wish to concentrate. The emerging ability to map generic HRQL measures such as the SF-36 to utilities, and the development of prostate-specific health status and utility measures such as the PORPUS [32], may facilitate collecting this full range of data while minimizing the respondent burden.

It clearly is not possible to make the assessments summarized above in relation to the framework on all study participants, nor is it necessary. However, there is a difficulty in sampling, as the chain of measurements desirable for a sequence of events, e.g. (2)–(4)–(6)–(8), would require different size samples to assess the state with precision, and provide the 'before' measurement for what could follow. The solution may be to combine a series of cross-sectional samples with repetitive re-sampling of a series of individuals. Cross-sectional samples may be optimal for (1), (2), (3), (5), (15), (16) and (22). The sampling fractions will require further consideration, but will need to be stratified by age, race, gender, study centre and calendar year, and could differ between sampling times. The ongoing pilot studies will provide guidance on the required sample sizes, instruments and the timing of their administration.

Another difficulty is that not all of the potential requirements are currently being subjected to study; therefore, empirical decisions may be necessary. Close to 100% samples might be desirable for cancer states, e.g. (7), (9), (10), (11), (12), (13), (14), (19) and (20). The remaining states could either require different cross-sectional sampling fractions for precision, e.g. for (4), (6), (8), (17), etc., or would be derived by following the same previously sampled individuals at their subsequent events, e.g. (18) would repetitively resample those sampled for (3), and (6) and (8) those sampled for (4) (less those in (7)).

In conclusion, assessment of quality of life and costs within a large screening trial is clearly not a simple exercise. There is potential for significant respondent burden which could adversely affect the main trial processes. At the same time, it is essential that feasible steps are taken to ensure that the best possible data are collected. Otherwise, we will be left with trying to assess quality of life and cost-effectiveness after the fact. Funding to enable the necessary studies to be completed is essential.

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CHAPTER 3

Quality of life in patients with screen-detected versus clinically diagnosed prostate cancer preceding primary treatment

Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH: Health-related quality of life in patients with screen-detected versus clinically diagnosed prostate cancer preceding primary treatment. Prostate 46:87-97, 2001

ABSTRACT

BACKGROUND: The purpose of this study was to evaluate baseline health-related quality of life (HRQOL) in patients with localized prostate cancer before primary treatment (radical prostatectomy or radiotherapy).

METHODS: Two hundred patients with newly diagnosed localized (screen-detected or clinically diagnosed) prostate cancer completed HRQOL questionnaires (generic and disease-specific measures). Clinical data were collected from patients' medical records in four Rotterdam hospitals.

RESULTS: Screen-detected tumors were of more favorable stages and grades than clinically diagnosed ones. The diagnostic groups did not differ significantly in bowel and sexual functioning. Differences were found in urinary functioning, favoring patients with screen-detected tumors of T2-T3 stage. Patients with screen-detected T2 cancer reported better generic HRQOL (physical aspects) than the clinical group, but HRQOL of the latter group was similar to the population norm. Radiotherapy patients were significantly older and had more comorbidity than subjects referred to prostatectomy. Urinary, bowel and sexual problems were uncommon. Older (> 65 years) radiotherapy patients appeared to be less sexually active. Radiotherapy patients also reported poorer levels of generic HRQOL.

CONCLUSIONS: Screen-detected prostate cancer patients presented with more favorable cancer stage and grade. HRQOL was related to both tumor stage and the detection method. Pre-treatment HRQOL differences between prostatectomy and radiotherapy patients were associated neither with tumor characteristics nor with the detection method. Baseline differences in HRQOL should be taken into account when evaluating posttreatment HRQOL.

INTRODUCTION

Prostate cancer is the second leading cause of cancer death in men in Western countries. In recent years, the prostate cancer incidence has increased substantially, particularly because of the improvement in screening techniques. Especially, the widespread use of a prostate specific antigen (PSA) blood test has contributed to early detection of the disease.

The public health value of population-based screening is currently being investigated in two large randomized trials: the European Randomized Study of Screening for Prostate Cancer [1,2] and the Screening Trial for Prostate, Lung, Colorectal and Ovarian Cancers of the U.S. National Cancer Institute [3]. Preliminary evidence from the study by Labrie et al. [4] suggests that prostate cancer mortality decreased as a result of screening, but the magnitude of this decrease is still controversial [5].

Provided that the ultimate goal of screening: a reduction of disease-specific mortality is achieved, the effects of the screening program on health-related quality of life (HRQOL) may play a crucial role in the overall evaluation of prostate cancer screening. Prevention of occurrence of advanced disease and therefore, of poor HRQOL associated with end-stage prostate cancer can be seen as a benefit from screening [6]. Nevertheless, unfavorable HRQOL effects are inevitable when regarding the screening procedure itself (e.g., pain, discomfort, psychological distress) and particularly, in the treatment phase (overtreatment, side effects of primary treatment). Especially older men may not benefit from an earlier diagnosis and treatment. As a consequence of screening, relatively large numbers of indolent prostate tumors could be detected and treated, whereas there may not be an effect in terms of improved survival, and negative side-effects following treatment may be experienced during the remaining life years [7,8].

Evidence has become available that the screening process itself does not induce important short-term HRQOL effects [2]. Therefore, the potentially disadvantageous effects of a prostate cancer screening program may be expected in the (primary) treatment phase. Standard treatments for localized prostate cancer include radical prostatectomy and external beam radiotherapy. Although these primary treatments are potentially curative, they may cause serious side effects, including urinary, bowel and sexual dysfunction and therefore, may adversely affect patients' HRQOL [9,10]. Several studies, e.g. [11-15] focused on treatment-related complications, but their findings are often inconsistent, especially with respect to incidence. Retrospective study designs and selected patient populations [9,11,14] may be responsible for these inconsistent findings. Few investigations used prospective designs, including pre-treatment levels of patient functioning [16].

The current study was undertaken to describe prospectively the HRQOL effects of prostate cancer and of primary treatments in a cohort of men with newly diagnosed prostate cancer. The results of the study are ultimately to be implemented in the evaluation of screening effects in the European Randomized Study of Screening for Prostate Cancer. The data include both medical records of patients' disease and treatment history, and self-administered HRQOL questionnaires. Special emphasis is placed on possible differences between patients with screen-detected and otherwise-detected prostate cancer. The purpose of the present paper is to describe baseline HRQOL outcomes in men with newly diagnosed (locally confined) prostate cancer who were to receive primary treatment. This paper addresses the following questions:

Do patients with screen-detected prostate cancer differ from those with the disease diagnosed outside the screening program, in their clinical characteristics, problems in urinary, bowel and sexual functions, and generic HRQOL, before undergoing primary treatment?

Are there any pre-treatment differences in clinical characteristics and problems in urinary, bowel and sexual functions, and generic HRQOL of patients referred subsequently either to radical prostatectomy or to external beam radiotherapy?

MATERIALS AND METHODS

The Rotterdam trial within the framework of the European Randomized Trial of Screening for Prostate Cancer (ERSPC)

Seven European centers have participated in the ERSPC. The trial will provide an empirical answer to the question whether screening in men in the 55- to 69-year-old age group reduces prostate cancer mortality. The ongoing trial of the Rotterdam center started in 1994. Cost-effectiveness studies, including empirical HRQOL studies of the screening procedure itself and of the phases of primary treatment and advanced disease were conducted alongside. The current study was approved by the Medical Ethical Committees of four Rotterdam hospitals: the Academic Hospital Rotterdam, St. Franciscus Gasthuis, St. Clara Hospital and the Zuiderziekenhuis. In accordance with regulations, written informed consent was obtained from every participant enrolled in the study. Approval for the prostate screening program and the screening trial was obtained from the Minister of Health and the Health Council, as required by the Population Screening Act (The Netherlands, 1992).

Study group

In the period between June 1996 and October 1997, patients with newly diagnosed prostate cancer and younger than 76 years of age from the urology departments of the four Rotterdam hospitals were approached for participation in our

study. Prostate cancer was either screen-detected in the trial [2] or diagnosed in a regular clinical setting. All participants of the study were referred to one of the four hospital urology departments for diagnostic work-up and treatment for prostate cancer, most of them by their general practitioners. At baseline, the diagnosis 'prostate cancer' was known to the patient, but the stage of the disease was still to be determined and consequently, a treatment decision had not yet been made. During the six months following baseline, patients with localized prostate cancer were scheduled for radical prostatectomy, external beam radiotherapy or 'watchful waiting'. Because of the applied inclusion method, some patients enrolled for baseline assessments had already disseminated prostate cancer (M1 disease) and subsequently, received hormonal treatment for advanced disease. For the purpose of the present study, the statistical analyses of HRQOL measures were restricted to patients with localized prostate cancer (stages: T1–T3, N0 or NX, M0). Primary treatment groups were determined from hindsight, because at the moment of the baseline assessment the subsequent treatment was not yet known.

Data collection and instruments

Patient inclusion procedure

Patients were included into the study group according to the following protocol:

Every potential participant was approached for the study by his urologist. During the consultation, the patient received an information brochure about the study, and was asked to decide, within one week, on his possible participation. Simultaneously, urology departments of the four Rotterdam hospitals notified the Department of Public Health of the Erasmus University Rotterdam, where the study was performed, about patients eligible for the study by sending a weekly list containing patients' surnames and their telephone numbers. The patients were requested to contact the research office by telephone if they would participate. In case of no contact, the responsible researcher telephoned the patient to ask about the decision.

Every patient who agreed to participate received a mailing containing a cover letter, questionnaire, an informed consent form and a pre-paid envelope for returning the questionnaire.

If the questionnaire was not returned within 10 days, a reminder letter was sent.

Patients who refused to participate or cancelled their participation after receiving the questionnaire were registered separately in order to determine the non-response rate.

Assessments over time

Follow-up questionnaires were administered shortly after the diagnosis and preceding treatment decision (baseline), six months later, and one year after the baseline measurement. The analyses presented in this paper focus on baseline measurement of patients' HRQOL.

Health-related quality of life assessment

HRQOL was defined as the patient's functioning in physical, psychological and social domains. The patient self-administered questionnaire contained generic and disease-specific HRQOL measures.

The Medical Outcomes Study 36-Item Short Form (MOS SF-36) [17] is a generic HRQOL measure designed for use with both the general population and with a wide range of populations with chronic diseases. The items are organized into eight scales: Physical Functioning, Role-physical, Role-emotional, Bodily Pain, General Health, Vitality, Social Functioning, and Mental Health. After linear transformation, scores range from 0 to 100, with higher values indicating better levels of functioning [18]. The items can be reduced to two summary scale scores: Physical Component Summary and Mental Component Summary [19] with the mean norm score of 50 and a standard deviation of 10.

The UCLA Prostate Cancer Index was originally developed by Litwin et al. [20]. For the purpose of this study, two modules comprising urinary and bowel functions were adopted. The four scales assess the level of functioning (e.g. frequency of urinary leakage, number of pads worn to control urinary leakage, frequency of diarrhea or abdominal cramping) and the degree of urinary and bowel bother. Similar to the SF-36, all scores were linearly transformed and ranged from 0 to 100. A score of 100 described the best level of functioning or no bother.

To assess the patient's sexual functioning, a battery of items designed and applied previously in the Dutch situation by Slob et al. [21] was employed. We found that the sexual functioning module of the UCLA Prostate Cancer Index was not sufficiently detailed to meet the purpose of the study, especially regarding the level and causes of sexual dysfunction prior to the disease. Therefore, we decided to use the existing Dutch items in order to obtain more specific information on that topic. In the present study only a limited number of those items are presented.

Apart from generic and disease-specific HRQOL measures, the questionnaire contained items on background characteristics, such as sociodemographic variables (age, marital status and educational level) and comorbidity, assessed by the list of chronic conditions (Dutch Health Interview Survey, Statistics Netherlands).

Tumor stage (TNM clinical classification), histopathological tumor (biopsy) grade [22] and urologic treatment history were obtained from the Rotterdam Cancer Registry. For a small group of patients, information on clinical variables was collected from patients' medical records in the hospitals.

Statistical methods

The variables were examined with respect to their missing values. For SF-36 items, we used an imputation procedure according to the guidelines of the SF-36 Health Survey Manual [18]. Since the rest of the items had a rather low percentage (on average 2%) of missing values no imputation was applied.

All data analyses were performed using Statistical Package for the Social Sciences (SPSS 8.02 for Windows; SPSS Inc., Chicago, IL). Background variables, including sociodemographic data, comorbidity and clinical tumor characteristics, were analyzed by means of descriptive statistics, Student t-tests, chi-square tests and by non-parametric procedures (Mann-Whitney tests). To evaluate differences in generic HRQOL scores (SF-36 scales) and four scales of the UCLA Prostate Cancer Index, univariate analyses of variance and covariance (ANOVA and ANCOVA) were performed. Independent variables consisted of tumor stage, detection method, and the type of primary treatment. In all analyses, the variable 'age' was incorporated as a covariate to eliminate the possible confounding effect of age. Since the level of patients' sexual functioning was not described by a single scale, we applied stratification in two age categories: 65 years or younger and older than 65 years.

RESULTS

Characteristics of the study group

During the period from June 1996 to October 1997, 285 patients with newly diagnosed prostate cancer were eligible for participation in the study. Of these, 259 men (91%) returned filled-out questionnaires. Fifty six percent (n = 145) of the respondents had screen-detected prostate cancer. At the time that the questionnaires were completed, the majority of the patients had known the diagnosis for less than four weeks, which was similar for the subjects with screen-detected or clinically diagnosed cancer. Seventy seven percent of the respondents (n = 200) had early prostate cancer (stages: T1–T3, N0 or NX, M0) and underwent either radical prostatectomy or primary external beam radiotherapy within six months following baseline.

Background characteristics of the respondents are presented in Table 1. No significant differences were found between patients with screen-detected and clinically diagnosed prostate cancer in their mean age, educational level and the average number

of comorbid conditions. Tumor characteristics assessed according to the TNM (clinical) classification [22] showed significantly different distributions among screen-detected and clinically diagnosed respondents (all $p < .01$). The first group had smaller and locally confined tumors, whereas tumors of stage T3 and T4 were found more frequently in clinically diagnosed patients. Also, a significantly higher percentage of those patients had already metastatic spread, either regional (N+) or distant (M1). Clinically diagnosed cancers were characterized by poorer histopathological differentiation. Biopsy grade G3 was found in 21.7% of the clinically diagnosed, compared with 8.8% of the screen-detected ($p < .01$). Also, the mean value of PSA at the time of the diagnosis was significantly higher in this group, respectively 12.1 versus 7.9 ng/ml ($p < .01$). A significant difference ($p < .01$) was found in the distribution across various treatment modalities that were applied within half a year after baseline. More patients with clinically diagnosed prostate cancer received hormonal treatment and more men with screen-detected prostate cancer were scheduled for primary therapy or for 'watchful waiting' only, respectively.

Table 2 gives an overview of clinical stages and grades of the tumors that were treated by radical prostatectomy or external beam radiotherapy within six months following baseline. No significant differences were detected between both treatment groups regarding distributions across tumor stage and grade categories. However, a higher percentage of patients with T3 tumors underwent primary radiotherapy (29.3% versus 18.2%).

Regarding the background characteristics of the primary treatment groups, patients who subsequently received primary external beam radiotherapy were significantly older (67.9 versus 62.9 years, $p < .01$), and 38% of them had more than two comorbid conditions apart from prostate cancer, compared with 13% of subjects who were to receive prostatectomy ($p < .01$; data not shown in the tables).

Health-related quality of life

Mean score results from the SF-36 questionnaires completed by subjects with screen-detected and clinically diagnosed localized prostate cancer are shown in Table 3. To determine significant differences between the detection groups, two types of ANCOVA models were tested. Model 1 contained only one main effect: detection method (screen-detected and clinically diagnosed) and a covariate (age).

Table 1. Background characteristics of the entire sample of newly diagnosed patients with prostate cancer according to the method of cancer detection

Variable	Screen-detected (n = 145)	Clinically diagnosed (n = 114)	P	Total Sample (n = 259)
Age (years)			NS	
Mean (sd)	67.0 (5.3)	66.9 (6.6)		66.3
Median	66.0	68.0		67.0
Range	55 – 75	55 – 75		55 –75
Educational level (%):			NS	
Low	32.4	30.1		31.4
Intermediate	62.0	56.3		59.6
High	5.6	13.6		9.0
Comorbidity (%): *			NS	
0 conditions	38.6	43.9		40.9
1 condition	31.0	29.8		30.5
2 conditions	22.8	15.8		19.7
>2 conditions	7.6	10.5		8.9
Mean no. of conditions (sd)	1.0 (1.0)	1.0 (1.1)		1.0 (1.0)
PSA at diagnosis (ng/ml):				
Mean (sd)	7.9(10.2)	12.1(16.2)	<.01	10.0(13.7)
Median	5.7	6.8		6.0
Tumor stage (%):			<.01	
T1	15.9	7.8		12.4
T2	57.2	58.8		57.9
T3	26.2	24.6		25.5
T4	0.0	8.8		3.9
TX	0.7	0.0		0.4
N classification (%):			<.01	
N0	53.1	58.8		63.2
N1	2.1	13.2		7.9
N2	0.7	0.8		0.9
NX	44.1	27.2		28.0
M classification (%):			<.01	
M0	59.3	88.2		70.0
M1	0.0	10.6		3.9
MX	40.7	1.2		26.1
Biopsy grade (%):			<.01	
G1	57.4	37.8		48.6
G2	33.8	40.5		36.8
G3	8.8	21.7		14.6
Treatment: [a]			< .01	
External beam radiotherapy	51.7	42.1		47.5
Radical prostatectomy	33.8	24.6		29.7
Watchful Waiting	6.9	2.6		5.0
Treatment for advanced disease	7.6	30.8		17.8

* Conditions included: diabetes, pulmonary, cardiovascular and renal diseases. [a] Treatment applied within 6 months after baseline

Table 2. Tumor characteristics by subsequent primary treatment: radical prostatectomy vs primary radiotherapy*

	Prostatectomy (n = 77)	Radiotherapy (n = 123)	
Tumor stage (%):			NS
T1	14.3	12.2	
T2	67.5	58.5	
T3	18.2	29.3	
Tumor grade (%):			NS
G1	51.9	52.2	
G2	37.7	36.3	
G3	10.4	11.5	

* Treatment applied within 6 months after baseline

In Model 2 (Table 3), an additional main effect: tumor stage (T1, T2 and T3) and an interaction effect: detection x stage were incorporated. The analyses with Model 1 revealed significantly better functioning of the screening group regarding the following domains: Physical Functioning ($p < .05$), Role-Physical ($p < .01$), Bodily Pain ($p < .01$) and Role-Emotional ($p < .05$). In Model 2, no significant main effect of cancer detection method was found for any of the SF-36 scales. Scores for Physical Functioning, Role-Physical and Bodily Pain varied significantly with tumor stage. Patients with T1 versus T3 tumors had the following mean scores on these scales: 88.60 versus 77.62 ($p < .05$), 93.57 versus 72.37 ($p < .01$) and 82.78 versus 69.69 ($p < .05$). For the General Health Perceptions scale, there was a significant interaction between detection method and tumor stage. For tumors of T2 stage, subjects from screening had higher scores than those from a clinical setting (66.21 versus 59.00, $p < .05$).

HRQOL of the patients with clinically diagnosed cancer did not differ significantly from the Dutch population norm (SF-36 scores: men of 55-75 years of age) [23]. Conversely, patients from the screening tended to score higher (better functioning) than the general population, as for Physical Functioning, Role-Physical, Vitality and Bodily Pain (all $p < .05$). The SF-36 Summary Scale scores by tumor stage and detection method are reported in Table 4. The results indicated significantly better levels of physical functioning (SF-36 Physical Component Summary Scale) in patients with locally confined T1 carcinoma, compared with subjects diagnosed with T3 tumors ($p < .05$). Moreover, there was a significant interaction effect between tumor stage and detection method ($p < .05$). Within the T2 stage, men with screen-detected cancer reported better physical functioning. For mental health (SF-36 Mental Component Summary Scale), no significant differences were detected.

Table 3. Age-adjusted SF-36 mean scale scores according to the method of cancer detection*

HRQOL	Screen-detected (n = 124)	Clinically diagnosed (n = 76)	P Model 1 [a]	P values: Model 2 [b]	General Population [c] (n = 338)
SF-36 Scales:					
Physical Functioning (PF)	84.88	77.95	< .05	A) NS, B) < .05, C) NS	76.0 [d]
Role-Physical (RP)	86.18	70.33	< .01	A) NS, B) < .01, C) NS	71.0 [d]
Bodily Pain (BP)	80.25	69.99	< .05	A) NS, B) < .05, C) NS	72.1 [d]
General Health Perceptions (GP)	64.33	62.76	NS	A) NS, B) NS, C) < .05	64.1
Vitality (VT)	75.64	72.17	NS	A) NS, B) NS, C) NS	69.5 [d]
Social Functioning (SF)	85.89	80.43	NS	A) NS, B) NS, C) NS	82.2
Role-Emotional (RE)	87.05	74.67	< .05	A) NS, B) NS, C) NS	83.3
Mental Health (MH)	77.20	74.66	NS	A) NS, B) NS, C) NS	77.7

* Assessed in patients with localized prostate cancer shortly after diagnosis and preceding referral to primary treatment by radical prostatectomy or external beam radiotherapy.
[a] P values for the F tests in univariate ANCOVAs (detection method with 'age' as a covariate)
[b] P values for the F tests in 2 x 3 ANCOVAs (detection method x tumor stage with 'age' as a covariate):A) main effect of detection method, B) main effect of tumor stage, C) interaction effect: detection method x tumor stage.
[c] Population norm scores (men of 55-75 years of age). Scores were calculated for the sample previously published in [23]. Possible range for the SF-36 scores: 0 (poor functioning) to 100 (best functioning).
[d] Statistically significant (P < .05) differences between the screen-detected group and the general population (55-75 years of age). The clinically diagnosed group and the general population did not differ significantly.

Table 4. Age-adjusted SF-36 mean summary scale scores according to the method of cancer detection and tumor stage

Tumor Stage/ SF-36 Scales Summary Scales:	Screen-detected (n = 124)	Clinically diagnosed (n = 76)	P*	Total sample (n =200)	P†
Stage T1:					
Physical Component Summary (PCS)	51.71	55.88	a) NS	52.90	
Mental Component Summary (MCS)	51.21	49.81	a) NS	50.81	
Stage T2:					
PCS	51.47	48.34	a) <.01	50.10	
MCS	51.95	49.00	a) NS	50.66	
Stage T3:					
PCS	50.05	45.53	a) NS	48.45	
MCS	50.23	51.01	a) NS	50.50	
Stages T1 to T3					
PCS	51.18	48.56	a) NS b) <.05 c) <.05	50.14	A) <.05 B) NS C) <.05 D) NS
MCS	51.43	49.46	a) NS b) NS c) NS	50.65	A) NS B) NS C) NS D) NS

* P values for the F tests in 2 x 3 ANCOVAs with 'age' as a covariate: a) main effect of detection method, b) main effect of tumor stage, c) interaction effect: detection method x tumor stage; † P values for the F tests in univariate ANCOVAs (tumor stage with 'age' as a covariate): A) main effect of tumor stage B) T1 vs. T2, C) T1 vs. T3, D) T2 vs. T3.

Table 5. Mean scale scores for the SF-36 according to primary treatment modalities: radical prostatectomy versus external beam radiotherapy*

HRQOL	Prostatectomy* (n = 77)	Radiotherapy* (n = 123)	P values (a)	General Population (n = 338) (b)
SF-36 Scales:				
Physical Functioning (PF)	89.69	77.41	< .01	76.0 (c)
Role-Physical (RP)	87.66	75.41	< .05	71.0 (c)
Bodily Pain (BP)	81.23	73.30	NS	72.1 (d)
General Health Perception (GP)	68.99	60.44	< .01	64.1
Vitality (VT)	81.36	69.86	< .01	69.5 (c)
Social Functioning (SF)	88.80	80.69	< .05	82.2 (d)
Role-Emotional (RE)	85.71	80.11	NS	83.3
Mental Health (MH)	79.01	74.48	NS	77.7
SF-36 Summary Scales:				
Physical Component Summary	51.50	47.0	< .01	(e)
Mental Component Summary	53.65	51.78	NS	(e)

* Assessed shortly after diagnosis and preceding referral to primary treatment. Treatment groups were determined from hindsight. The type of treatment was unknown to the patient at the baseline assessment.
(a) P values for the F tests in univariate ANCOVAs (type of primary treatment with 'age' as a covariate).Population norm scores (men of 55-75 years of age). Scores were calculated for the sample previously published in [23].
(b) Possible range for the SF-36 scores: 0 (poor functioning) to 100 (best functioning).
(c) Statistically significant (p<.05) differences between prostatectomy patients and the general population (under 65 years of age).
(d) Statistically significant (p<.05) differences between prostatectomy patients and the general population (over 65 years of age). The radiotherapy group and the general population (55-75 years of age) did not differ significantly.
(e) Population mean scores were not available.

Table 5 presents the SF-36 baseline scores by subsequent treatment. After adjustment for age, five out of the eight SF-36 scales showed significantly lower levels of functioning of the radiotherapy group. Patients who were to undergo primary radiotherapy in the weeks following baseline reported poorer levels of physical ($p < .01$) and social functioning ($p < .05$), more limitations due to physical problems ($p < .05$), less vitality ($p < .01$) and they scored their general health profoundly lower than patients awaiting prostatectomy ($p < .01$). Consistently, the mean score on the SF-36 Physical Component Summary Scale was also significantly lower ($p < .01$).

Comparison with the SF-36 population norm scores (Table 5) revealed significantly higher levels of generic HRQOL in prostatectomy patients. Younger men (< 65 years) reported significantly better levels of physical functioning, vitality and fewer limitations due to physical problems than the general population ($p < .05$). Older patients (> 65 years) who were to receive radical prostatectomy, had less bodily pain

and a higher level of social functioning, compared with men of similar age in the general population ($p < .05$). Generic HRQOL scores of the patients scheduled for radiotherapy were comparable with the population norm.

Table 6. Baseline disease-specific characteristics according to the method of cancer detection

Disease-specific measures	Screen-detected (n = 124)	Clinically diagnosed (n = 76)	P
Urinary Function*	81.74	80.49	a) NS, b) NS, c) < .05 †
Urinary Bother*	94.47	81.51	a) <.01 b) <.05, c) < .05
Bowel Function*	92.55	89.38	a) NS, b) NS, c) NS
Bowel Bother*	96.75	94.04	a) NS, b) NS, c) NS
Sexual Function			
Frequency of nocturnal erections (%):			NS
Never	37.4	49.3	
Once a week	25.2	14.7	
More than once a week	30.1	30.7	
Once a day	5.7	4.0	
More than once a day	1.6	1.3	
Sexually active prior to diagnosis (%):			NS
Yes	61.8	69.7	
No	38.2	30.3	
Sexually active during last 2 weeks (%):			NS
Yes	54.0	56.6	
No	46.0	43.4	
Erections with sexual stimulation:**			
Ability to achieve (%):			NS
(Almost) never	11.8	9.5	
Sometimes	20.6	21.4	
(Almost) always	64.7	66.7	
Unknown	2.9	2.4	
Ability to maintain (%)			NS
(Almost) never	11.8	9.3	
Sometimes	27.9	32.6	
(Almost) always	57.4	55.8	
Unknown	2.9	2.3	

* UCLA Prostate Cancer Index Scales; Possible score range: 0 (poor functioning) to 100 (best functioning);
** Sexually active patients
† P values for the F tests in 2 x 3 ANCOVAs with 'age' as a covariate: a) main effect of detection method, b) main effect of tumor stage, c) interaction effect: detection method x tumor stage

The results on urinary and bowel modules of the UCLA Prostate Cancer Index are presented in Tables 6 and 7. After adjustment for age, urinary functioning did not vary significantly with detection method or tumor stage. Though there was a significant interaction effect between detection method and tumor stage ($p < .05$); patients with screen-detected and clinically diagnosed tumors of T3 stage differed significantly in their level of functioning (83.17 versus 75.93, $p < .05$). The scores on the Urinary Bother scale varied significantly with both detection method and tumor stage. Patients from screening reported less bother than those from a clinical setting (94.65 versus

83.50, p < .01). Comparison of T1 and T3 tumors also revealed a significant difference in the mean scores on Urinary Bother (96.43 versus 87.50, p < .05).

Table 7. Baseline disease-specific characteristics according to primary treatment modalities*

Disease-specific measures	Prostatectomy (n = 77)	Radiotherapy (n = 123)	P
Urinary Function**	80.80	81.57	NS
Urinary Bother**	90.33	89.17	NS
Bowel Function**	90.52	91.86	NS
Bowel Bother**	95.45	95.90	NS
Sexual Function			
Frequency of nocturnal erections (%):			NS
Never	38.2	44.3	
Once a week	21.1	21.3	
More than once a week	32.9	28.7	
Once a day	6.6	4.1	
More than once a day	1.2	1.6	
Sexually active prior to diagnosis (%):			< .01
Yes	76.6	57.4	
No	23.4	42.6	
Sexually active during last 2 weeks (%):			< .05
Yes	66.2	48.0	
No	33.8	52.0	
Erections with sexual stimulation (sexually active patients)			
Ability to achieve (%):			NS
(Almost) never	5.8	15.5	
Sometimes	25.0	17.2	
(Almost) always	67.3	63.8	
Unknown	1.9	3.5	
Ability to maintain (%)			NS
(Almost) never	5.8	15.3	
Sometimes	30.8	28.8	
(Almost) always	61.5	52.5	
Unknown	1.9	3.4	

* Assessed before primary treatment. All analyses were controlled for age
** UCLA Prostate Cancer Index Scales; Possible score range: 0 (poor functioning) to 100 (best functioning)

Besides, a significant interaction effect of stage and detection method was found for the stages T2 and T3 (p < .05) where the patients from screening reported better functioning than the clinically diagnosed subjects (T2: 94.09 versus 84.80, p < .01 and T3: 95.12 versus 71.05, p < .01). Regarding the primary treatment groups, no significant differences in urinary and bowel functioning were found at baseline.

The data on sexual functioning (Table 6) showed no significant baseline differences among men who came from the screening trial and those who were otherwise diagnosed. Considering the treatment groups (Table 7), patients who subsequently underwent external beam radiotherapy were already less sexually active before treatment, and even prior to the diagnosis. Age-adjusted analyses (not presented in the tables) revealed that this finding applied only to the older patients (> 65 years) from the radiotherapy group. Younger (< 65 years) patients who were awaiting radical

prostatectomy or radiotherapy reported similar levels of sexual activity and erectile function.

DISCUSSION

This study focuses on baseline characteristics of a cohort of patients with newly diagnosed prostate cancer that was detected either in or outside the screening program. In accordance with previous expectations [7], the data showed marked clinical heterogeneity in prostate carcinoma detected by the screening or non-screening setting. Screen-detected tumors were of more favorable stages and grades, involving lower PSA values. Consequently, fewer cases of regionally or distantly disseminated cancer were found in this group.

The baseline data showed similar levels of bowel and sexual functioning for both diagnostic groups. Although the overall level of pretreatment urinary functioning was good, patients with screen-detected tumors of stages T2 and T3 reported much better functioning than the subjects from a clinical setting. Regarding generic HRQOL, differences were found only for patients with screen-detected and clinically diagnosed T2 tumors, where the first group indicated better (physical) health. Furthermore, prostate cancer patients from screening reported higher levels of generic HRQOL than the general population, whereas HRQOL scores of patients with clinically diagnosed cancer were not different from the population norm.

In this report, the term ‘patients with clinically-diagnosed prostate cancer’ was used when referring to the study participants who were diagnosed outside the screening trial. Although the term ‘clinically diagnosed’ may suggest the presence of clear symptoms or urinary complaints in these patients, since they were referred to the urologist, our data on urinary functioning did not provide much support for it. Despite the lower mean scores on urinary functioning of patients with clinically diagnosed T2 and T3 tumors as compared to the screening group, almost no urologic complaints were reported by these patients. On the other hand, the score difference for urinary functioning was also reflected by the difference in generic HRQOL.

There are a few possible explanations for these findings. First, the lack of clear urologic symptoms in the clinically diagnosed group can partly be caused by contamination due to opportunistic screening. We could not distinguish between the patients who visited the urology departments because of some urologic complaints and those who were referred to the urologist after PSA testing as part of a routine medical check-up or in relation to nonspecific symptoms (e.g. fatigue). Furthermore, early prostate cancer may involve, in general, very little or no symptoms at all [8]. Second, our data suggest that HRQOL is related to tumor stage, since T3 stage involved poorer levels of HRQOL than T1 stage. The observed discrepancy in generic HRQOL between

screen-detected and clinically diagnosed groups can only partly be explained by the difference in distributions across tumor stage categories in these groups. After adjustment for tumor stage, no distinction could be made between patients with screen-detected and clinically diagnosed cancer within each of the stages T1 and T3, however, within stage T2, patients from the screening trial had better HRQOL. In the light of these findings, it is conceivable that contamination due to opportunistic screening might not be equally represented in all tumor stage categories. As a consequence, patients with screen-detected and clinically diagnosed prostate cancer could be even more dissimilar.

Our findings also indicate that patients with screen-detected prostate cancer may be a selection of 'very healthy' men from the general population, who may have decided to attend the screening program in order to confirm their being 'healthy'. The results of a previous study [2] pointed out that participants to the screening program had better HRQOL than non-participants. This possible *healthy screenee* effect would be reflected in the patients with screen-detected cancer by high scores on generic HRQOL at baseline, compared to the population norm.

Regarding the baseline characteristics of the primary treatment groups, subjects who subsequently underwent surgery were younger and had on average fewer comorbid conditions. Consistent with previous findings [16], our results revealed that prior to treatment problems with urinary, bowel and sexual functioning were rather uncommon. After adjustment for age, radiotherapy patients had worse baseline generic HRQOL than patients awaiting radical prostatectomy, however, their HRQOL scores were in the range of the sex and age-adjusted Dutch population norm. Younger prostatectomy patients appeared to be a rather fit group that tended to score above the population norm.

The HRQOL diversity of the primary treatment groups, already at baseline, provides evidence for the fact that urologists apparently applied some selection criteria, when referring to the type of therapy. In line with other studies, e.g. [16], patients referred to radical prostatectomy seem to form a separate group characterized by good general health, while men scheduled for radiotherapy are generally older and suffer from several comorbid conditions, including cardiopulmonary disease(s).

In this study, screen-detected prostate cancer patients presented with more favorable tumor stage and grade. HRQOL was related to both stage at which cancer was detected and the detection method. Patients from screening had better pre-treatment HRQOL than subjects with clinically diagnosed cancer. Baseline differences in HRQOL should be incorporated into evaluation of HRQOL effects of primary treatment.

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CHAPTER 4

Quality of life effects of primary treatment for screen-detected or clinically diagnosed localized prostate cancer

Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH: Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. Journal of Clinical Oncology 19(6):1619-28, 2001

ABSTRACT

PURPOSE: The current study was undertaken within the framework of a screening trial to compare the health-related quality of life (HRQOL) outcomes of two primary treatment modalities for localized prostate cancer: radical prostatectomy and external beam radiotherapy.

PATIENTS AND METHODS: We conducted a prospective longitudinal cohort study among 278 patients with early, screen-detected (59%) or clinically diagnosed (41%) prostate cancer using both generic and disease-specific HRQOL measures (SF-36, UCLA Prostate Cancer Index (urinary and bowel modules and items relating to sexual functioning) at three points in time: t1 (baseline), t2 (6 months later) and t3 (12 months after t1).

RESULTS: Questionnaires were completed by 88%-93% of all initially enrolled patients. Patients referred for primary radiotherapy were significantly older than prostatectomy patients (63 versus 68 yrs., $p<.01$). Analyses (adjusted for age and pretreatment level of functioning) revealed poorer levels of generic HRQOL after radiotherapy. Prostatectomy patients reported significantly higher ($p<.01$) posttreatment incidences of urinary incontinence (39%-49%) and erectile dysfunction (80%-91%) than radiotherapy patients (respectively, 6%-7% and 41%-55%). Bowel problems (urgency) affected 30%-35% of the radiotherapy group versus 6%-7% of the prostatectomy group ($p<.01$). Patients with screen-detected and clinically diagnosed cancer reported similar posttreatment HRQOL.

CONCLUSIONS: Prostatectomy and radiotherapy differed in the type of HRQOL impairment. Because the HRQOL effects may be valued differently at the individual level, patients should be made fully aware of the potential benefits and adverse consequences of therapies for early prostate cancer. Differences in posttreatment HRQOL were not related to the method of cancer detection.

INTRODUCTION

In 1995, 6367 cases of prostate cancer were diagnosed in the Netherlands [1,2]. The incidence has climbed in recent years, mainly because of improved diagnostic techniques [3]. Questions about the potential benefits of screening for prostate cancer have been raised in the United States and Europe [4,5]. Reduction in disease-specific mortality is the primary outcome measure when evaluating screening for prostate cancer. If the reduction in mortality should prove to be moderate to small, health-related quality of life (HRQOL, defined as patient functioning in physical, psychological and social domains) effects may play a crucial role in the overall balance between the benefits and drawbacks of prostate cancer screening. There is no evidence for HRQOL impairment after the screening (biopsy) procedure itself [6], but possible detriment to HRQOL may result from side effects of primary treatment additionally induced by screening [7]. However, if screening prevents death from prostate cancer, it will also prevent metastatic prostate cancer. Consequently, the decrease in life-years lived with poor HRQOL associated with advanced disease is a favorable effect of prostate cancer screening at the population level.

The standard treatment options for locally confined prostate cancer in the Netherlands include radical prostatectomy and external beam radiotherapy. Radical prostatectomy can result in urinary incontinence and impotence because of surgical damage to the urinary sphincter and penile nerves. Radiotherapy is associated with bladder irritation (urgency, pain and frequency), rectal irritation (diarrhea, urgency, tenesmus and bleeding) and impotence [8].

In recent years, several studies on the clinical and HRQOL outcomes of primary treatments for localized prostate cancer have been published, indicating substantial posttreatment decrement in functioning [9,10]. Some of these studies were restricted to cross-sectional designs, assessing only (posttreatment) HRQOL in long-term survivors. Other studies solely addressed disease-specific problems of one type of primary treatment (surgery or radiotherapy), not including generic HRQOL measures. So far, no studies on HRQOL have distinguished between screen-detected cases of prostate cancer and clinically diagnosed prostate cancer.

The current study was undertaken within the framework of a screening trial [4] to compare the HRQOL outcomes of two primary treatment modalities: radical prostatectomy and external beam radiotherapy. We conducted a prospective longitudinal cohort study, including pretreatment assessments of generic and disease-specific HRQOL in patients with early, locally confined prostate cancer. We also investigated whether the HRQOL effects of primary treatment were different in patients with screen-detected prostate cancer compared with those with clinically diagnosed prostate cancer.

PATIENTS AND METHODS

The Rotterdam trial within the framework of the European Randomized Trial of Screening for Prostate Cancer

The European Randomized Trial of Screening for Prostate Cancer, with seven participating European centers, will provide an empirical answer to the question of whether screening in men between 55 and 69 years of age reduces prostate cancer mortality. The ongoing trial at the Rotterdam center started in 1994. Cost-effectiveness studies, including empirical HRQOL studies of the screening procedure itself and of the phases of primary treatment and advanced disease were conducted alongside. The current study was approved by the Medical Ethical Committees of four Rotterdam hospitals: the Academic Hospital Rotterdam, St. Franciscus Gasthuis, St. Clara Hospital and the Zuiderziekenhuis. In accordance with regulations, written informed consent was obtained from every participant who enrolled in the study. Approval for the prostate screening program and the screening trial was obtained from the Minister of Health and the Health Council, as required by the Population Screening Act (The Netherlands, 1992).

Study group and patient inclusion procedure

In the period between June 1996 and May 1998, patients with newly diagnosed prostate cancer who were younger than 76 years were approached for participation in our study. All participants in the study were culled from the urology departments of four Rotterdam hospitals, where they underwent a diagnostic work-up for prostate cancer. Prostate cancer was either screen-detected in the trial [6] or diagnosed in a regular clinical setting. In the current paper, only the subjects with localized prostate cancer are included.

Patients were admitted into the study group according to the following protocol: Every potential participant was approached for the study by his urologist. During the consultation, the patient received an information brochure about the study, and was asked to decide, within 1 week, on his possible participation. Simultaneously, the urology departments at the four Rotterdam hospitals notified the Department of Public Health at Erasmus University Rotterdam, where the study was performed, of patients eligible for the study by sending the department a weekly list of patients' surnames and their telephone numbers. The patients were requested to contact the research office by telephone if willing to participate. Patients failing to contact the office were telephoned by the responsible researcher and asked about their decision. Every patient who agreed to participate received a mailing containing a cover letter, questionnaire, an informed consent form and a pre-paid envelope for returning the questionnaire. If the questionnaire was not returned within 10 days, a reminder letter was sent. Patients who

refused to participate or cancelled their participation after receiving the questionnaire were registered separately to determine the non-response rate.

Because of the method of patient inclusion, i.e., before the stage of the disease was known, it was inevitable that patients with non-localized prostate cancer also were included in the study. However, the data on these patients were left out of the present report. Whether or not cancer was screen-detected was unknown at the moment of patient inclusion. The method of cancer detection (screening versus non-screening) was determined from hindsight on the basis of medical records. Details on characteristics of the screened population can be found in Essink-Bot et al.[6].

Assessments as a function of time

Questionnaires were administered three times in total. A baseline measurement (t1) was performed shortly after the diagnosis and preceding the decision on the type of primary treatment (radical prostatectomy or primary radiotherapy). Posttreatment assessments took place at 6 (t2) and 12 months (t3) after baseline. Primary treatment was performed between t1 and t2. At t2, patients had undergone a radical prostatectomy on average 5 months previously or had completed primary radiotherapy 3 months before. The t3 assessment corresponded to 11 months after prostatectomy or 9 months after radiotherapy.

Health-related quality of life measures

Health-related quality of life (HRQOL) was defined as the patient's functioning in physical, psychological and social domains. The patient self-administered HRQOL questionnaire contained generic and disease-specific measures.

The Medical Outcomes Study 36-Item Short Form (SF-36) [11] is a generic HRQOL measure designed for use with both the general population and a wide range of populations with chronic diseases. The items are organized into eight scales: Physical Functioning, Role-Physical, Role-Emotional, Bodily Pain, General Health, Vitality, Social Functioning, and Mental Health. After linear transformation, scores range from 0 to 100, with higher values indicating better levels of functioning [12]. The items can be reduced to two summary scale scores: the Physical Component Summary and Mental Component Summary [13] with the mean norm score of 50 and an SD of 10.

The UCLA Prostate Cancer Index was originally developed by Litwin et al. [14]. For the purpose of this study, two modules comprising urinary and bowel functions were adopted. The four scales assess the level of urinary and bowel functioning (e.g. frequency of urinary leakage, number of pads worn to control urinary leakage, frequency of diarrhea or abdominal cramps) and the degree of urinary and bowel bother. Like the SF-36, all scores were linearly transformed and ranged from 0 to 100. A score of 100 described the best level of functioning or no bother.

To assess the patient's sexual functioning, use was made of a battery of items designed for and previously applied to the Dutch situation by Slob et al. [15]. We found the sexual functioning module of the UCLA Prostate Cancer Index insufficiently detailed for the purpose of the study, especially as regards the level and causes of sexual dysfunction prior to the disease. We consequently decided to use the existing Dutch items to obtain more specific information on this topic.

Apart from generic and disease-specific HRQOL measures, the questionnaire contained items on background characteristics, such as sociodemographic variables (age, marital status and educational level) and comorbidity, assessed by the list of chronic conditions (Dutch Health Interview Survey, Statistics Netherlands).

Tumor stage (tumor-node-metastasis clinical classification [16]), histopathologic tumor (biopsy) grade and urologic treatment history were obtained from the Rotterdam Cancer Registry. For a small group of patients, information on clinical variables was collected from patients' medical records in the hospitals. Possible post-operative adjustments to staging in the prostatectomy group were not included to maintain comparability with the radiotherapy group.

Statistical methods

All variables were examined with respect to their missing values. For SF-36 items, we used an imputation procedure according to the guidelines of the SF-36 Health Survey Manual [12]. Inasmuch as the rest of the items had a rather low percentage (on average 2%) of missing values no imputation was applied.

Differences in distributions of the background variables (sociodemographic data, selected comorbidity conditions, prostate-specific antigen levels and clinical tumor characteristics) were evaluated by non-parametric procedures (chi-squared or Mann-Whitney tests). Mean values are presented as the measure of central tendency in the scores for the SF-36, UCLA Prostate Cancer Index. The observed dispersion of these scores is presented as the interval bounded by the 25th and 75th percentile scores.

To evaluate posttreatment differences in generic (SF-36) and disease-specific HRQOL (UCLA Prostate Cancer Index) between the treatment groups, two by two analyses of covariance were applied for t2 and t3 assessments separately (main effects, the therapy type and the method of cancer detection). The covariates included in the analysis were: patient's age and pretreatment level of functioning or bother (the scale included as a covariate was identical to the one used as a dependent variable). All statistical tests were conducted with a significance level of .01. Chi-squared tests were used to test the difference in incidence of specific problems in urinary, bowel and sexual functioning. Inasmuch as the level of patients' sexual functioning was not described by a single scale, a stratification was made into two age categories, 65 years or younger and older than 65 years, to eliminate a possible confounding effect of age.

All P values resulted from the use of two-sided statistical tests. The data analyses were performed using SPSS (SPSS 8.02 for Windows; SPSS Inc., Chicago, IL) or SAS (SAS 6.12 for Windows; SAS Institute Inc., Cary, NC).

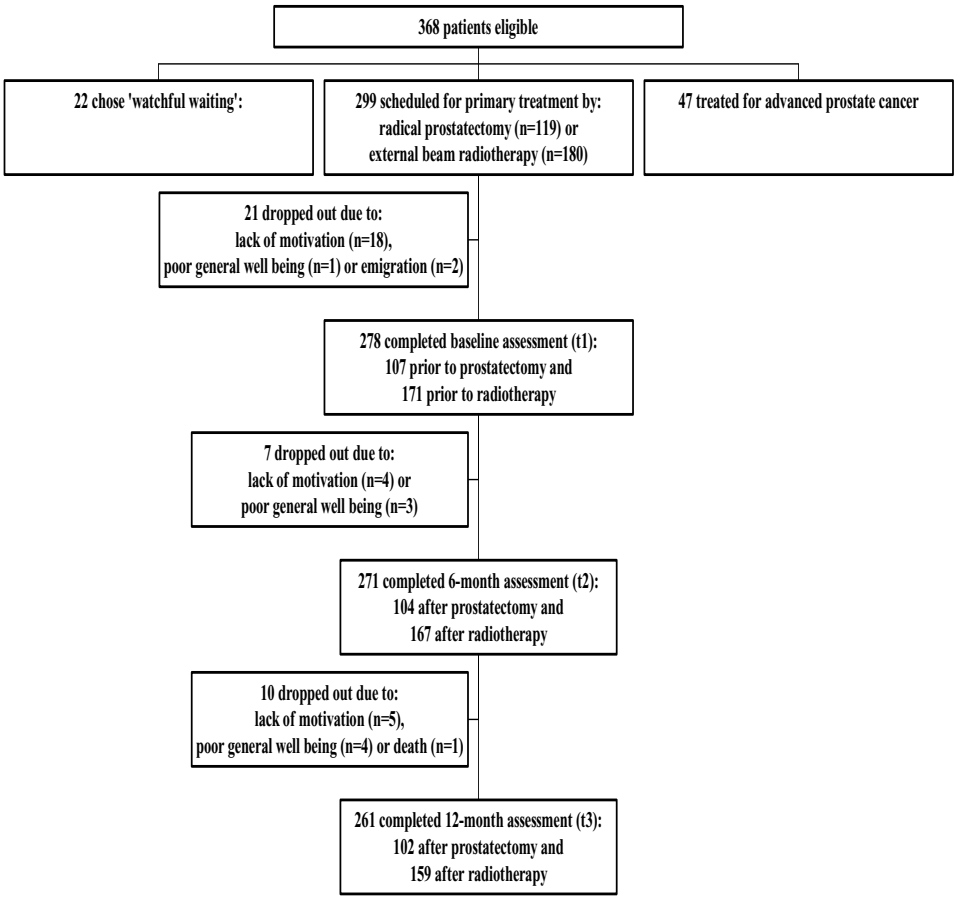
RESULTS

Background characteristics of the study group

Figure 1 shows the study profile. In the period from June 1996 till May 1998, 368 consecutive patients with newly diagnosed prostate cancer from four Rotterdam hospitals were approached for participation in the study. Of 368 men, 299 men underwent primary treatment by surgery (n = 119) or external-beam radiotherapy (n =180), 22 patients chose watchful waiting, and 47 patients received treatments for advanced prostate cancer. The current study includes results from the prostatectomy and radiotherapy groups. The questionnaire submission rates among these patients were 93% (n = 278) at baseline, 91% (n = 271) six months later, and 87% (n = 261) one year after baseline. Prior to baseline, a total of 21 patients dropped out for various reasons: 13 patients had no interest in the study, five found the questions on sexual functioning too intimate and therefore refused to fill out the questionnaire, one patient reported feeling too ill to participate, and two patients moved abroad and were treated outside the Netherlands. Dropping out at t2 was caused either by lack of motivation (n = 4) or by poor psychological well-being (n = 3). At t3, reasons for dropping out were lack of motivation (n = 5), poor general well being (n = 4), and death from cardiovascular disease (n = 1).

Table 1 presents information on the background characteristics of patients with localized (screen-detected or clinically diagnosed) prostate cancer who subsequently underwent radical prostatectomy or primary radiotherapy (33 irradiation sessions, each of 66 to 68 Gy, during 7 weeks). Patients from the prostatectomy group were significantly younger than those from the radiotherapy group, i.e., 62 versus 68 years of age ($P < .01$), in both patients with screen-detected and with clinically diagnosed cancer. No significant differences were found in distributions across categories of marital status and education. Prostatectomy patients from screening had less comorbidity than did radiotherapy patients. Screen-detected and clinically diagnosed patients showed similar levels of comorbidity. Fewer patients diagnosed by screening had prostate-specific antigen values greater than10 ng/ml compared with those from a clinical setting (33% versus 55%).

Figure 1. Study population profile based on completion of health-related quality of life (HRQOL) questionnaires



Tumor characteristics differed significantly in their distributions among patients with clinically diagnosed or screen-detected cancer, with the latter group having significantly more well-differentiated tumors, and also more non-palpable tumors, which were subsequently treated by radical prostatectomy rather than primary radiotherapy. In clinically diagnosed patients, tumor stage distributions were similar regardless of the type of therapy they were referred to.

Table 1. Comparison of background characteristics of study respondents with screen-detected or clinically diagnosed prostate cancer treated by radical prostatectomy (PR) or external beam radiotherapy (RT)

Characteristics, No. (%)	Screen-detected (n = 163)			Clinically diagnosed (n = 115)			P values*
	PR (n=66)	RT (n=97)	Total (n=163)	PR (n=41)	RT (n=74)	Total (n=115)	
Age at diagnosis, mean (SD)	62.8(5.0)	68.1(5.0)	65.9(5.6)	62.5(6.1)	68.3(6.6)	66.2(6.9)	.00(a), .00(b), .76(c)
Marital Status							.58(a), .68 (b), .13 (c)
Married/cohabiting	55 (83)	8 (87)	139 (85)	38 (93)	67 (90)	105 (91)	
No partner	11 (17)	13 (14)	24 (15)	3 (7)	7 (10)	10 (9)	
Educational Level							.25(a), .56(b), .19(c)
Low	21 (32)	39 (40)	60 (37)	9 (22)	21 (29)	30 (27)	
Intermediate	37 (55)	53 (54)	90 (55)	25 (61)	43 (58)	68 (59)	
High	8 (12)	5 (5)	13 (8)	7 (17)	10 (13)	17 (14)	
Comorbidity, median	0	1	1	1	1	1	
Selected onditions							
Diabetes	3 (5)	5 (5)	8 (5)	2 (5)	2 (3)	4 (4)	.85(a), .57(b), .57(c)
Cardiovascular disease	8 (12)	33 (34)	41 (25)	12 (29)	23 (31)	35 (30)	.002(a), 84(b), .33 (c)
Respiratory disease	8 (12)	13 (14)	21 (13)	3 (7)	8 (11)	11 (10)	.79(a), .50(b), .43(c)
Renal disease	1 (2)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	.23(a), .45(b), .79(c)
PSA before treatment							.29(a), .21(b), .001(c)
0 - 4 ng/ml	19 (29)	26 (27)	45 (28)	8 (20)	9 (12)	17 (15)	
4 – 10 ng/ml	30 (46)	35 (36)	65 (40)	15 (37)	20 (27)	35 (30)	
> 10 ng/ml	17 (26)	36 (37)	53 (33)	18 (44)	45 (61)	63 (55)	
Tumor stage							.006(a), .71(b), .039(c)
T1	14 (22)	12 (12)	26 (16)	4 (10)	6 (9)	10 (9)	
T2	44 (66)	52 (54)	96 (59)	28 (69)	53 (72)	81 (71)	
T3	8 (12)	33 (34)	41 (25)	9 (21)	13 (17)	22 (18)	
T4	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	2 (2)	
Tumor grade							.28(a), .57(b), .004(c)
G1	42 (63)	51 (53)	93 (57)	14 (33)	32 (43)	46 (39)	
G2	21 (32)	36 (37)	57 (35)	18 (44)	30 (40)	48 (41)	
G3	3 (5)	10 (10)	13 (8)	9 (23)	12 (17)	21 (19)	

* P values for the chi-squared or Mann-Whitney U tests of the following differences: (a) PR versus RT within the screen-detected group, (b) PR versus RT within the clinically diagnosed group, (c) screen-detected versus clinically diagnosed

Generic health-related quality of life: prostatectomy versus radiotherapy

The mean scores on generic HRQOL (SF-36 scales) at 6 (t2) and 12 months (t3) after baseline are shown in Table 2. In the short term, at t2, none of the differences were statistically significant at a 1% level, although radiotherapy patients tended to score lower for bodily pain (i.e., more pain; mean scores, 83 versus 92; P = .034) and general health perceptions (mean scores, 63 versus 75; P = .02) than prostatectomy patients. In the longer run, at t3, significant differences were found on two of the eight SF-36 scales. Radiotherapy patients reported more limitations because of physical (mean scores, 72 versus 89; P = .005) and emotional problems (mean scores, 83 versus 93; P = .009). Regarding bodily pain and general health perceptions, the similar tendency was observed as at t2.

Comparisons of the SF-36 scale scores at the 12-month follow-up (t3) with the reference scores of the general Dutch population revealed no significant differences among radiotherapy patients. However, prostatectomy patients had significantly higher scores on all SF-36 scales than did the general population group (P < .01).

Generic health-related quality of life: screen-detected versus clinically diagnosed

At 6 and 12 months, patients from screening and non-screening settings reported comparable levels of generic HRQOL, as measured by the SF-36 scales (data not shown). The screening group tended to score higher on general health perceptions than the clinically diagnosed group (mean scores, 74 versus 61; P = .038). Comparisons with the sex- and age-adjusted population norm scores revealed that screen-detected patients had similar or significantly better scores on all SF-36 scales. Significantly higher scores were reported for physical functioning, role-physical, bodily pain and social functioning scales (P < .01). The SF-36 scores of clinically diagnosed patients remained at the level of the population norm.

Urinary symptoms

Pretreatment urinary complaints (Table 3) were not common, regardless of the origin of the diagnosis of prostate cancer' or the type of primary treatment administered subsequently. Mean scores for urinary function and urinary bother were greater than 81, indicating a good function, and there were no statistically significant differences between the treatment groups at baseline.

Regular (on a daily basis) or incidental (a few days a week) urinary leakage was indicated by 10% (n = 107) of prostatectomy patients versus 7% (n = 171) of radiotherapy patients at baseline. At t2 and t3 (5 and 11 months after prostatectomy, respectively), 31 (30%) of 104 patients and 34 (33%) of 102 patients reported total urinary control after prostatectomy. Regular or incidental urinary leakage was

Table 2. Pretreatment and posttreatment SF-36 scores (mean values and 25th-75th percentile score intervals) of patients who underwent radical prostatectomy (PR) or primary radiotherapy (RT)

	Baseline (n = 278)*		6 months (t2) (n = 271)†			12 months (t3) (n = 261)†		
	PR (n = 107)	RT (n = 171)	PR (n = 104)	RT (n = 167)	P values‡	PR (n = 102)	RT (n = 159)	P values‡
Physical Functioning (PF)	89 (90–100)	77 (70-95)	88 (85-100)	77 (65-95)	.63 (T), .90 (D) .03 (C1), .000(C2)	86 (80-100)	75 (65-95)	.38 (T), .69 (D) .03 (C1), .000 (C2)
Role-Physical (RP)	86 (100-100)	71 (50-100)	83 (75-100)	72 (25-100)	.09 (T), .38 (D) .76 (C1), .000 (C2)	89 (100-100)	72 (33-100)	.005 (T),.58 (D) .66 (C1), .000 (C2)
Bodily Pain (BP)	89 (84-100)	80 (62-100)	92 (96-100)	83 (72-100)	.034 (T),.15 (D) .16 (C1), .000 (C2)	91 (84-100)	80 (62-100)	.030 (T), .90 (D) .01 (C1), .000 (C2)
General Health Perception (GP)	68 (57-80)	58 (45-72)	75 (62-87)	63 (50-77)	.020 (T), .038 (D) .43 (C1), .000 (C2)	74 (67-87)	62 (47-72)	.025 (T), .28 (D) .02 (C1), .000 (C2)
Vitality (VT)	79 (70-95)	69 (55-85)	77 (65-90)	70 (60-85)	.72 (T), .12 (D) .60 (C1), .000 (C2)	78 (70-90)	67 (50-85)	.11 (T), .35 (D) .65 (C1), .000 (C2)
Social Functioning (SF)	88 (75-100)	80 (62-100)	90 (88-100)	85 (75-100)	.93 (T), .73 (D) .46 (C1), .000 (C2)	92 (88-100)	83 (75-100)	.069 (T), .90 (D) .49 (C1), .000 (C2)
Role-Emotional (RE)	86 (100-100)	78 (67-100)	89 (100-100)	85 (100-100)	.35 (T), .67 (D) .25 (C1), .000 (C2)	93 (100-100)	83 (83-100)	.009 (T), .80 (D) .25 (C1), .000 (C2)
Mental Health (MH)	74 (64-84)	69 (56-84)	83(72-96)	80 (68-94)	.92 (T), .52 (D) .80 (C1), .000 (C2)	83 (76-92)	78 (64-92)	.58 (T), .83 (D) .56 (C1), .000 (C2)
Physical Component Summary (PCS)	53 (50-57)	48 (44-55)	52 (50-57)	47 (42-55)	.09 (T), .28 (D) .05 (C1), .000 (C2)	52 (49-57)	47 (43-54)	.02 (T), .66 (D) .09 (C1), .000 (C2)
Mental Component Summary (MCS)	52 (47-57)	50 (45-57)	55 (55-61)	54 (50-60)	.65 (T), .78 (D) .28 (C1), .000 (C2)	55 (54-61)	53 (48-60)	.29 (T), .43 (D) .32 (C1), .000 (C2)

* Baseline (t1) SF-36 scores and patient's age were included as covariates in the analyses. † Mean time (in months) from (the end of) treatment at t2: PR [x(sd)]: 5.5 (1.0) and RT [x(sd)]: 3.2 (1.1); Mean time (in months) from (the end of) treatment at t3: PR [x(sd)]: 11.5 (0.9) and RT [x(sd)]: 9.2 (1.1). ‡ P value for F tests in 2 x 2 factorial ANCOVAs (treatment x cancer detection method; covariates: age and pretreatment level of generic HRQOL); main effects: treatment (T) and detection method (D); covariates: age (C1) and baseline score on the SF-36 (C2). Interaction effects (treatment x detection method) are not significant ($p > .10$). For clarity reasons, they are not shown in the table.

Table 3. Pretreatment and posttreatment urinary symptoms: radical prostatectomy (PR) versus primary radiotherapy (RT)

	Baseline(t1)* (n = 278)			6 months (t2)* (n = 271)			12 months (t3)* (n = 261)		
	PR (n = 107)	RT (n = 171)	P	PR (n =104)	RT (n =167)	P	PR (n = 102)	RT (n = 159)	P
UCLA Prostate Cancer Index :Mean(25^{th}-75^{th} percentiles)†									
Urinary Function	81 (80-87)	82 (80-87)	.22	66 (54-80)	81 (80-87)	.000	70 (61-80)	79 (80-86)	.000
Urinary Bother	92 (100-100)	89 (100-100)	.99	73 (50-90)	85 (75-100)	.000	81 (75-95)	88 (100-100)	.010
Selected symptoms:									
Urinary control			.30			.000			.000
No control at all	2 (2%)	3 (2%)		5 (5%)	2 (1%)		3 (3%)	2 (1%)	
Frequent dribbling	1 (1%)	9 (5%)		15 (14%)	8 (5%)		13 (13%)	10 (7%)	
Occasional dribbling	24 (22%)	32 (19%)		53 (51%)	43 (26%)		52 (51%)	39 (25%)	
Total control	80 (75%)	127 (74%)		31 (30%)	114 (68%)		34 (33%)	108 (68%)	
Frequency of urinary leakage			.20			.000			.000
Almost every day	8 (7%)	3 (2%)		38 (37%)	10 (6%)		24 (24%)	11 (7%)	
A few days a week	3 (3%)	9 (5%)		12 (12%)	10 (6%)		15 (15%)	10 (6%)	
Almost never	96 (90%)	159 (93%)		54 (52%)	147 (88%)		63 (62%)	138 (87%)	
Use of incontinence materials			.20			.000			.000
> 3 pads a day	2 (2%)	0 (0%)		18 (17%)	2 (1%)		10 (10%)	2 (1%)	
1 – 2 pads a day	3 (3%)	2 (1%)		35 (34%)	12 (7%)		26 (25%)	11 (7%)	
No pads at all	102 (95%)	169 (99%)		51 (49%)	153 (92%)		66 (65%)	146 (92%)	
Satisfaction with functioning						.020			.06
(Very) dissatisfied	--	--		33 (32%)	27 (16%)		17 (17%)	21 (13%)	
Reported change in urinary function (t3 vs t2)									
(Much) better	--	--		--	--		48 (47%)	52 (33%)	.03
Same	--	--		--	--		50 (49%)	97 (61%)	
(Much) worse	--	--		--	--		4 (4%)	10 (6%)	

* t1: baseline assessment (shortly after diagnosis); Mean time (in months) from (the end of) treatment at t2: PR [x(sd)]: 5.5 (1.0) and RT [x(sd)]: 3.2 (1.1); Mean time (in months) from (the end of) treatment at t3: PR [x(sd)]: 11.5 (0.9) and RT [x(sd)]: 9.2 (1.1). † Possible score range: 0 (worst functioning) to 100 (best functioning).

experienced by 49% (n = 104) of patients at t2, and by 39% (n=102) of patients at t3. Forty-seven percent (n = 102) of the prostatectomy group also reported much improvement in urinary function with time (t3 versus t2). After radiotherapy at both t2 and t3 (respectively, 3 and 9 months after the end of treatment), 68% (n = 167 and n = 159) of patients reported total urinary control. Regular or incidental urinary leakage was indicated by 12% (of 167 patients) and 13% (of 159 patients) of these patients at t2 and t3.

Mean scores for urinary function and urinary bother revealed statistically significant posttreatment differences (both follow-up assessments $P < .01$) between radical prostatectomy and primary radiotherapy patients, with the first group reporting poorer levels of urinary functioning. No significant differences ($P > .45$) were found between groups with screen-detected and with clinically diagnosed prostate cancer (data not shown).

Bowel symptoms

Table 4 displays information on patients' pretreatment and posttreatment bowel symptoms. No significant differences between the treatment groups ($P>.35$) were observed prior to primary therapy. The 6 month follow-up (t2) data showed significant differences between radiotherapy and prostatectomy patients, with the former group reporting more daily problems with abdominal pain or cramps (9% versus 1%, P=.004), liquid stools (16% versus 2%, P=.000), and bowel urgency (15% versus 1%, P=.000). Moreover, rectal bleeding (daily or a few times a week) was reported more often by the radiotherapy than the prostatectomy group at t3 (15% versus 2%, P=.003). Consequently, radiotherapy patients had significantly lower (worse) posttreatment scores for bowel function and bowel bother on the UCLA Prostate Cancer Index than did subjects treated by prostatectomy (for both follow-up assessments, $P<.01$). The data did not reveal any statistically significant differences among patients from screening and non-screening settings regarding posttreatment bowel complaints ($P>.50$; data not shown).

Sexual functioning

Patient characteristics on pretreatment and posttreatment sexual functioning are summarized in Table 5. At baseline (t1), no statistically significant differences in sexual activity and erectile function were found between men who were referred for a radical prostatectomy and those undergoing radiotherapy ($P > .13$ for both age groups). Posttreatment erectile dysfunction (problems with getting erections) was reported by 91% of younger (< 65yrs.) and 80% of older (> 65 yrs. of age) prostatectomy patients at t2 and t3.

Table 4. Pretreatment and posttreatment bowel symptoms: radical prostatectomy (PR) versus primary radiotherapy (RT)

	Baseline (t1)* (n = 278)			6 months (t2)* (n = 271)			12 months (t3)* (n = 261)		
	PR (n = 107)	RT (n = 171)	P	PR (n =104)	RT (n =167)	P	PR (n = 102)	RT (n = 159)	P
UCLA Prostate Cancer Index: Mean(25^{th}-75^{th} percentiles) †									
Bowel Function	91 (88-100)	91 (86-100)	.99	92 (94-100)	80 (67-95)	.000	92 (93-100)	80 (69-95)	.000
Bowel Bother	95(100-100)	94 (100-100)	.68	95 (100-100)	81 (75-100)	.000	94 (100-100)	78 (75-100)	.000
Selected symptoms:									
Rectal bleeding			.11			.52			.003
(Almost) every day	2 (2%)	0 (0%)		1 (1%)	2 (1%)		1 (1%)	6 (4%)	
A few days a week	0 (0%)	2 (1%)		0 (0%)	2 (1%)		1 (1%)	17 (11%)	
Abdominal pain/cramps			.91			.004			.01
Daily	1 (1%)	3 (2%)		1 (1%)	15 (9%)		2 (2%)	11 (7%)	
A few times a week	4 (4%)	7 (4%)		7 (7%)	20 (12%)		6 (6%)	21 (13%)	
Liquid or loose stools			.90			.000			.000
More than half of times	12 (11%)	19 (11%)		5 (5%)	30 (18%)		4 (4%)	32 (20%)	
(Almost) always	3 (3%)	7 (4%)		2 (2%)	27 (16%)		2 (2%)	16 (10%)	
Bowel urgency (>3 stools a day)			.41			.000			.000
Daily	2 (2%)	9 (5%)		1 (1%)	25 (15%)		1 (1%)	16 (10%)	
A few times a week	5 (5%)	10 (6%)		6 (6%)	33 (20%)		5 (5%)	32 (20%)	
Satisfaction with functioning						.000			
(Very) dissatisfied	--	--		7 (7%)	27 (16%)		3 (3%)	24 (15%)	.000
Reported change in bowel function (t3 vs t2)									.000
(Much) better	--	--		--	--		9 (9%)	40 (25%)	
Same	--	--		--			91 (90%)	94 (59%)	
(Much) worse	--	--		--			2 (2%)	25 (16%)	

* t1: baseline assessment (shortly after diagnosis); Mean time (in months) from (the end of) treatment at t2: PR [x(sd)]: 5.5 (1.0) and RT [x(sd)]: 3.2 (1.1); Mean time (in months) from (the end of) treatment at t3: PR [x(sd)]: 11.5 (0.9) and RT [x(sd)]: 9.2 (1.1). † Possible score range: 0 (worst functioning) to 100 (best functioning).

Table 5. Pretreatment and posttreatment sexual functioning: radical prostatectomy (PR) versus primary radiotherapy (RT)

	Baseline (t1)* (n = 278)			6 months (t2)* (n = 271)			12 months (t3)* (n = 261)		
	PR (n=107)	RT (n=171)	P	PR (n=104)	RT (n=167)	P	PR (n=102)	RT (n=159)	P
Men < 65 yrs: No. (%)	70 (65)	56 (33)		65 (63)	50 (30)		61 60)	45 (28)	
Men > 65 yrs: No. (%)	37 (35)	115 (67)		39 (37)	117 (70)		41 (40)	114 (72)	
Spontaneous erections:									
< 65 yrs.									
Never, No. (%)	22 (31)	12 (22)	.77	51 (80)	13 (26)	.000	48 (79)	19 (43)	.003
> 65 yrs									
Never, No. (%)	16 (42)	59 (51)	.68	35 (89)	69 (59)	.007	35 (86)	70 (61)	.055
Sexually active (past two weeks):									
< 65 yrs, No. (%)	49 (70)	35 (63)	.54	27 (42)	30 (60)	.084	30 (48)	25 (55)	.47
> 65 yrs, No. (%)	19 (52)	45 (39)	.16	6 (16)	42 (36)	.014	10 (24)	38 (33)	.29
Problems with getting erections: No. (%)†									
< 65 yrs									
(Almost) always,	6 (9)	10 (18)	.13	58 (91)	19 (41)	.000	53 (91)	23 (55)	.000
> 65 yrs									
(Almost) always	6 (17)	33 (30)	.14	31 (80)	53 (48)	.001	31 (80)	54 (51)	.002
Satisfaction with functioning: No. (%)									
< 65 yrs.	--	--							
(Very) dissatisfied				47 (72)	20 (40)	.001	39 (64)	18 (40)	.020
> 65 yrs.	--	--				.001			
(Very) dissatisfied				27 (68)	42 (36)	.001	22 (54)	34 (30)	.038
Reported change in erectile function (t3 vs t2): No. (%)									
< 65 yrs.	--	--		--	--				.056
(Much) better							6 (11)	4 (9)	
Same, No. (%)							45 (73)	25 (55)	
(Much) worse							10 (16)	16 (36)	
> 65 yrs.	--	--		--	--				.13
(Much) better							2 (5)	6 (5)	
Same							35 (86)	76 (67)	
(Much) worse							4 (10)	32 (29)	

* t1: baseline assessment (shortly after diagnosis); Mean time (in months) from (the end of) treatment at t2: PR [x(sd)]: 5.5 (1.0) and RT [x(sd)]: 3.2 (1.1); Mean time (in months) from (the end of) treatment at t3: PR[x(sd)]: 11.5 (0.9) and RT [x(sd)]: 9.2 (1.1).
† Numbers apply to men who were sexually active and had erectile problems, and men who reported NOT being sexually active because of erectile problems.

In the radiotherapy group, posttreatment erectile problems were indicated, respectively by 41% (t2) and 55% (t3) of patients younger than 65 years, and by 48% and 51% of patients older than 65 years of age. Chi-squared tests revealed significant differences ($P < .01$) between men treated by radical prostatectomy or by primary radiotherapy, with the former group having poorer sexual functioning after treatment than the latter. The method of cancer detection did not account for any statistically significant differences in erectile problems between the two primary treatment groups at t2 and t3 (data not shown).

DISCUSSION

The present study addressed HRQOL effects of primary treatment for early screen-detected or clinically diagnosed prostate cancer. By applying both generic and disease-specific HRQOL measures, we documented the impact of treatment-related side effects on the patient's HRQOL. Radical prostatectomy appeared to affect urinary and erectile functions, whereas external beam radiotherapy was predominantly associated with bowel problems. Patients with screen-detected or clinically diagnosed prostate cancer did not differ in their posttreatment level of functioning.

Although posttreatment incontinence, impotence and bowel symptoms were also reported by other, primarily retrospective studies, the incidences of these functional problems lacked consistency [17-21]. Some recent prospective studies reported 7% to 23% for incontinence and 69% to 91% for impotence at 12 months after radical prostatectomy [22,23]. At the same time, the rates for impotence and bowel problems in radiotherapy patients were 61% and 12% to19%, respectively. In line with these findings, our data show high posttreatment incidences of urinary leakage at least a few days a week (39% to 49%) and erectile dysfunction (80% to 91%) in patients who underwent radical prostatectomy, compared with the level of their pretreatment functioning, and compared with the patients who were treated by external beam radiotherapy. The most important postirradiation problem involved the bowel function (urgency: 30% to 35%), and to a lesser degree some changes in urinary and sexual functioning (posttreatment incontinence, 12% to 13%; posttreatment erectile dysfunction, 41% to 55%). However, for a proper evaluation of possible functional impairment or improvement, a longer follow-up time may be necessary. Postradiotherapy effects in particular may become manifest even after more than a year after treatment has ceased [24,25]. On the other hand, prostatectomy patients may experience further improvement in functioning [24]. Our posttreatment data (t2 and t3) did not allow for determination of such long-term effects, since the assessments comprised a time interval of 3 to 9 months after radiotherapy, and 5 and 11 months after surgery.

After adjustment for pretreatment levels of functioning, radiotherapy patients showed poorer posttreatment levels of generic HRQOL than did prostatectomy patients. However, neither group scored below the age- and sex-adjusted Dutch population norm [26]. Irrespective of the difference between radiotherapy and prostatectomy patients, decrements in generic HRQOL scores do not seem to correspond to decrements in patients' urinary, bowel and sexual functioning after treatment. Possible explanations for this discrepancy may include the response shift [27] or the lack of relevance of the SF-36 items to patients with prostate cancer.

Although our data indicate decreased levels of posttreatment HRQOL, selecting the optimal treatment for early prostate cancer in terms of HRQOL is considerably complicated for two reasons. First, radical prostatectomy and external beam radiotherapy involve different consequences, which may be valued differently by individual patients. Second, inasmuch as there was no random allocation to the treatment groups, it is conceivable that men referred for prostatectomy or radiotherapy may not come from similar populations of patients with prostate cancer. In the past, other studies [3] have found pelvic lymphadenectomy to be relatively rare in radiotherapy patients, which resulted in the understaging of the disease. More advanced stages of the disease may possibly affect the level of generic HRQOL. As long as there are no results available from well-designed randomized trials comparing HRQOL effects of radical prostatectomy and external-beam radiotherapy in similar groups of patients, comparisons from non-randomized studies will have to be used, but their validity remains limited.

Despite the fact that compared with men with clinically diagnosed prostate cancer, men with screen-detected prostate cancer had a better generic HRQOL before primary treatment [7], no statistically significant cross-sectional differences (in both generic and disease-specific HRQOL) after primary treatment emerged from our data. Because of the pretreatment and posttreatment levels of urinary, bowel and sexual functioning were similar in patients with screen-detected and clinically diagnosed prostate cancer, we assume that all decrements in HRQOL revealed in our follow-up data were related to (the type of) primary treatment.

Regarding the question of whether or not to screen, early detection of prostate cancer will imply earlier primary treatment. The decrements in HRQOL after treatment are justifiable only if screening results in a substantial improvement of the survival rates. Because the data on mortality in the ERSPC trial will not be available until 2008 [4], HRQOL and survival outcomes cannot be weighed at the present moment. At the public health level, the benefits and drawbacks throughout all stages of screening must be thoroughly considered before a population-based screening program for prostate cancer is implemented. On an individual level, patients should be made fully aware of the potential benefits and adverse consequences of the available therapies for early prostate cancer.

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PART II:

STUDIES ON OVARIAN CANCER PREVENTION

CHAPTER 5

Predictors of prophylactic salpingo-oophorectomy versus gynecologic screening use in BRCA1/2 mutation carriers

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ABSTRACT

PURPOSE: Women with BRCA1/2 gene mutations who have completed their childbearing are strong candidates for risk-reducing prophylactic bilateral salpingo-oophorectomy (PBSO). The aim of the current study was to identify baseline predictors of PBSO versus gynecologic screening uptake in this group of high-risk women.

PATIENTS AND METHODS: Baseline questionnaires were available from 160 BRCA1/2 carriers who participated in a nationwide, longitudinal, observational study of the psychosocial consequences of prophylactic surgery versus periodic screening. Topics addressed by the questionnaire included generic quality of life, cancer-specific distress, risk perception, knowledge of ovarian cancer, and perceived pros and cons of surgery versus screening. PBSO uptake during the 12-month period following the first gynecologic consultation was determined on the basis of medical record data.

RESULTS: During the 12 month follow-up, 74% percent of women had undergone PBSO and 26% opted for screening. Statistically significant multivariate predictors of PBSO uptake included education, general health perceptions, perceived incurability of ovarian cancer, and perceived benefits of surgery.

CONCLUSION: Women with lower educational levels, with poorer general health perceptions, those who view ovarian cancer as an incurable disease, and those who believe more strongly in the benefits of surgery are more likely to undergo PBSO. Clinicians should ensure that high-risk women are well-informed about the low predictive value of gynecologic screening techniques and about the lethal threat posed by ovarian cancer due to its limited curability.

INTRODUCTION

BRCA1 and BRCA2 gene mutation carriers have a lifetime risk of developing ovarian cancer of between 39% and 54% (BRCA1), and between 11% to 23% (BRCA2) [1-3]. Women from hereditary breast/ovarian cancer (HBOC) families may opt either for periodic gynecological screening (GS) or prophylactic bilateral salpingo-oophorectomy (PBSO) to manage their cancer risk. Ultimately, these preventive options are aimed at reduction of disease-specific mortality.

The available screening techniques, transvaginal ultrasonography and CA 125 serology, have low predictive value for early cancer detection [4,5]. In contrast, PBSO reduces substantially the risk of both ovarian (96%) and breast cancers (53%) [6,7]. The earlier PBSO is performed, the greater its beneficial effect [8], with the most risk-reducing effect being observed among premenopausal women [9]. PBSO is usually recommended as a treatment option for women who carry BRCA1/2 mutations, have completed their childbearing, and who are older than 35 years of age [10-12].

Among premenopausal women, PBSO results in infertility and immediate onset of menopause, including vasomotor and urogenital symptoms [13,14]. Compared to natural menopause, surgical menopause may cause more severe symptoms [15] which, in turn, may result in more compromised quality of life [16]. Although hormone replacement therapy (HRT) should, in principle, compensate for endocrine deficiencies, there is evidence that it may be less effective in alleviating PBSO-induced menopausal symptoms than it is often assumed [17]. A woman's choice between PBSO and periodic screening is likely to be influenced by a myriad of factors, including cancer risk perception, cancer-specific distress, and concerns about menopausal symptoms, sexuality and body image [18].

Few studies have investigated factors related to intentions to undergo PBSO or to actual PBSO uptake among high-risk women [19-25]. Two cross-sectional studies found that older age, greater perceived risk of developing ovarian cancer, strongly perceived benefits of PBSO [19] and increased cancer anxiety [20] were associated positively with interest in surgery. Prospective studies have found PBSO uptake to be associated with older age [21,22], parity [22], family history of ovarian cancer, high perceived risk of cancer [24] and early breast tumor stage [25]. However, these latter, prospective studies did not focus on BRCA1/2 carriers only, but rather included all women from HBOC families who were undergoing genetic counseling and/or testing [21,23-25]; they included relatively small numbers of women with known BRCA1/2 status [22,24]; they employed single-center designs [23-25]; or they did not include psychosocial measures [23,25].

To our knowledge, no population-based studies have yet been conducted to identify prospectively those factors associated significantly with PBSO uptake among women who are strong candidates for such preventive surgery. In this paper, we report the results of a prospective, observational, nationwide study of factors associated significantly with PBSO uptake among this specific group of women, i.e., women who are BRCA1/2 carriers, older than 35 years of age, and who have completed their childbearing.

PATIENTS AND METHODS

Sample and procedures

This study was part of a larger prospective investigation focusing on the impact of ovarian cancer prevention on psychosocial health and symptom experience. Study participants were recruited from the gynecology departments of seven hospitals in the Netherlands between 2002 and 2004. The inclusion criteria for the larger, parent study were: 1) age between 30 and 70 years; 2) HBOC in the family; and 3) referral to the gynecology clinic specifically for purposes of discussing the prevention of ovarian cancer. Exclusion criteria were: 1) prior oophorectomy performed as treatment for breast cancer or for any pathology in the ovaries, or 2) metastatic cancer or any other severe comorbidity. The current analysis was limited to BRCA1/2 carriers older than 35 years who had completed their childbearing.

All eligible women were invited to participate in the study by their gynecologist during the first consultation during which ovarian cancer prevention was discussed. This initial invitation was followed by a letter by mail, an informed consent form, and a baseline questionnaire. In case of non-response, systematic reminders by mail and telephone were used. For non-respondents, age and type of ovarian cancer prevention ultimately chosen were registered. Women who completed the baseline assessment received two follow-up questionnaires at 3 and 9 months post-surgery (PBSO group), or at 6 and 12 months after baseline (GS group). The study was approved by the institutional review boards of all participating hospitals.

Measures

Sociodemographic and clinical data

The respondents' age, marital status, education, employment status, reproductive history, current menstrual status, and the type of ovarian cancer prevention discussed with the gynecologist were obtained from the self-report questionnaire. Information about family history of breast/ovarian cancer, personal

history of cancer and its treatments, mutation status, and the date of PBSO were abstracted from the medical records.

Psychosocial measures

Overall health perceptions, generic mental health and overall quality of life (QOL)

General health perceptions and generic mental health were assessed with the relevant scales from the SF-36 Health Survey [26,27]. Overall QOL was assessed with the single QOL item of the European Organization for Research and Treatment of Cancer QLQ-C30 [28]. All raw scale scores were linearly converted to a 0 to 100 scale, with higher scores indicating better perceived health, mental health and QOL [29,30]. The internal consistency reliability of the two SF-36 scales was high (Cronbach's alpha = 0.81 and 0.85).

Cancer-specific distress

Five items adapted from previous research [31] were used to assess the frequency of cancer-related worries (ovarian and breast cancer worries, the impact of worries on mood and daily functioning, and worries about cancer risk in family members). All items were summed to create a cancer worry scale (range: 5 to 20), with higher scores representing more frequent worries (Cronbach's alpha = 0.70). The 7-item intrusive thoughts subscale of the Impact of Event Scale (IES) was used to measure ovarian cancer-specific distress [32,33]. A higher sum score (range: 0 – 35) corresponds to more distress (Chronbach's alpha = 0.91). A cut-off score of 20 was used to identify individuals with clinically-relevant levels of distress [34].

Risk perception

Four items, adapted from previous studies [35,36] assessed current perceived breast/ovarian cancer risk. Women were asked to rate that risk on a continuous scale from 0% to 100%. Additionally, two questions were posed about the perceived curability of breast/ovarian cancer ('Do you think that breast/ovarian cancer can be cured?; response categories: 'never', 'seldom', 'sometimes', 'often' and 'always').

Knowledge about hereditary ovarian cancer and its prevention

Knowledge about hereditary issues in ovarian cancer was assessed by 11 statements about objective cancer risk, preventive options, and possible consequences of PBSO (e.g., premature menopause). Each statement could be rated as 'true' or 'false'. The total score reflected the number of correct answers (range: 0 to 11).

Perceived benefits and barriers of PBSO

Eleven items, adapted from previous research, were developed to evaluate women's perceptions of the potential benefits (pros: 5 statements) and barriers (cons: 6 statements) of PBSO [37,38]. Response categories varied from 'strongly disagree' to 'strongly agree'. Sum scores for the pro and con subscales were calculated (ranges: 5 to 25, and 6 to 30, respectively).

Statistical Analysis

Classification of women into the PBSO and GS groups was based on medical record data covering the 12-month period following study entry. Descriptive statistics were used to characterize the sample in terms of sociodemographic, medical and psychosocial variables at baseline. Bivariate predictors of PBSO versus screening uptake were tested using chi-square and t- tests. Significant bivariate predictors ($p < 0.05$) were entered in a forward, stepwise multivariate logistic regression model to identify the most parsimonious set of variables predicting subsequent uptake of PBSO versus screening. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 12.0.1; SPSS Inc., Chicago, IL, USA). All tests were two-sided, with p values lower than .05 considered statistically significant.

RESULTS

Sample characteristics

In total, 426 high-risk women were invited to participate in the study, of whom 359 (84 %) completed the baseline assessment. The causes for non-response were: no interest (n = 50), previous oophorectomy (n = 6), participation in other studies (n = 4); health or emotional problems (n = 4), insufficient knowledge of Dutch (n = 2), and emigration (n = 1). Non-respondents did not significantly differ from respondents regarding age or choice of preventive measure. Due to restrictions by the medical ethics committees of the participating centers, no other clinical data on the non-respondents were available (e.g., DNA status). Of the respondent group, 160 women (43%) were BRCA1/2 carriers, were over 35 years of age, and indicated no wish to have (more) children. These women met criteria for discussion of both PBSO and screening during the consultation with their gynecologist. Within 12 months following that initial consultation, 118 of these 160 women (74%) had undergone PBSO, and 42 women (26%) had opted for screening. PBSO was performed, on average, four months after the initial gynecologic consultation (median: 2.8 months).

Table 1. Baseline characteristics of high-risk women meeting clinical criteria for PBSO (BRCA1/2 carrier, age > 35 years, and no wish of bearing (more) children)

	PBSO (n=118)*	GS (n = 42)	P values
Age (M, SD)	48.3 (8.4)	45.3 (8.1)	.037
35 – 45 yrs.	41%	60%	.069
46- 55 yrs.	37%	27%	
> 55 yrs.	22%	13%	
Marital Status (%)			.025
Married/ cohabitating	84%	67%	
Unmarried/ without partner	16%	33%	
Educational level (%)			.037
Primary school/ lower level high school	26%	12%	
Middle level high school	54%	50%	
Advanced vocational/ university	20%	38%	
Employment status			.214
Full-time job	8%	13%	
Part-time job	53%	64%	
Housewife	30%	17%	
Other	9%	6%	
Parity			.359
Null parity	15%	21%	
At least 1 child	85%	79%	
Menopausal state			.027
Premenopausal	54%	74%	
Peri/ postmenopausal	46%	26%	
Mutation type			.056
BRCA1	58%	40%	
BRCA2	42%	60%	
History of breast cancer: yes	53%	38%	.108
Comorbidity:**			.100
No conditions	64%	77%	
1 condition	23%	21%	
2 or more conditions	13%	2%	
Number of first-degree relatives with ovarian cancer:			.165
No relatives	70%	81%	
At least 1 relative	30%	19%	
Number of first-degree relatives with breast cancer:			.117
No relatives	41%	27%	
At least 1 relative	59%	73%	
Duration of being aware of high-risk status in years:			.543
Mean (SD)	1.7 (3.6)	2.6 (3.9)	
Median	1.0	1.0	
Prophylactic bilateral mastectomy prior to baseline:	2%	4%	.356
Prophylactic bilateral mastectomy within 12 months after baseline:	12%	4%	.000
Time to PBSO in months:			
Mean (SD)	4.0 (3.5)	--	
Median	2.8	--	
Range	0 – 15.1	--	

Abbreviations: PBSO (prophylactic bilateral salpingo-oophorectomy; GS (gynecologic screening); M, mean; SD, standard deviation. * PBSO within 12 months after baseline; **Following conditions were included: asthma and other chronic respiratory diseases, cardiovascular, renal and rheumatic diseases, hypertension, diabetes, and malignancies other than breast cancer.

Sociodemographic and clinical predictors of PBSO use

Women who opted for PBSO were significantly older, were more likely to be married, had lower educational levels, and were more likely to be post-menopausal than those who chose periodic screening (all p values < 0.5; Table 1).

Psychosocial predictors of PBSO use

Quality of life, cancer-specific distress and perceived risk

As shown in Table 2, women who opted for PBSO perceived their health as significantly worse ($p < .01$), and reported significantly higher levels of worries ($p < .05$) and intrusive thoughts ($p < .001$) about ovarian cancer than did women in the GS group. A significantly higher proportion of women in the PBSO group than the GS group reported intrusive thoughts (sum score ≥ 20) severe enough to indicate the possible presence of post-traumatic stress syndrome (PTSD) (26% vs. 7%, $p < .01$).

The PBSO and GS groups also differed significantly in their perception of ovarian cancer risk ($p < .001$), with those in the surgery group having the highest risk estimates. Conversely, 64% of the GS group versus 19% of the PBSO group perceived ovarian cancer as a disease that could often or always be cured ($p < .001$). There were no statistically significant between-group differences in the levels of perceived breast cancer risk or in the perceived curability of breast cancer.

Basic knowledge about prevention, and perceived pros and cons of preventive strategies

The PBSO and GS groups had similar levels of knowledge about risk of hereditary ovarian cancer, available preventive options and their consequences (Table 2). Eighty-three percent of the PBSO group and 90% of the GS group reported that both surgery and screening had been discussed by their gynecologist. There was no statistically significant between-group difference in the proportions of women who reported receiving strong recommendation for PBSO from their gynecologist. Women who underwent PBSO had significantly higher overall scores for perceived benefits of surgery, and significantly lower scores for perceived benefits of screening than the GS group (both p values < .05). No significant differences were observed in perceived barriers to PBSO and GS.

Table 2. Psychosocial characteristics of high-risk women at baseline by type of subsequent ovarian cancer prevention

Psychosocial variables:	PBSO (n = 118) Mean (SD)	GS (n = 42) Mean (SD)	P Values
Generic QOL:*			
Global Health Status	76.0 (20.6)	79.8 (17.9)	.298
General Health Perceptions	70.9 (20.5)	82.0 (13.3)	.002
< general population norm*	44%	17%	.001
≥ general population norm*	56%	83%	
Mental Health	70.2 (16.6)	73.1 (14.5)	.307
< general population norm*	52%	43%	.325
≥ general population norm*	48%	57%	
Cancer-specific distress:			
Worries about cancer risk: sum score:**	9.9 (2.7)	8.9 (2.1)	.025
Worried about ovarian cancer (%)	31%	12%	.014
Worried about breast cancer (%)	40%	31%	.354
Worries affected mood (%)	20%	17%	.658
Worries affected functioning (%)	8%	2%	.228
Worried about other family members at risk (%)	33%	17%	.044
Intrusive Thoughts about ovarian cancer risk:			
Sum score:**	16.8 (6.2)	12.8 (4.9)	.000
Patients scoring ≥ 20:	26%	7%	.010
Cancer risk perception:			
Perceived risk of ovarian cancer (0 – 100):			
Total group	53.3 (23.8)	37.9 (24.1)	.000
BRCA1 carriers	61.0 (20.0)	50.3 (20.8)	.051
BRCA2 carriers	42.4 (24.6)	29.4 (22.8)	.029
Ovarian cancer perceived as curable disease:			
Never or seldom	36%	12%	.000
Sometimes	45%	24%	
Often or always	19%	64%	
Perceived risk of breast cancer (0 – 100):			
Total group	62.8 (26.5)	54.6 (26.5)	.206
BRCA1 carriers	66.8 (26.2)	48.1 (3310)	.071
BRCA2 carriers	57.0 (26.5)	59.0 (21.2)	.809
Breast cancer perceived as a curable disease:			.885
Never or seldom	3%	2%	
Sometimes	23%	19%	
Often or always	74%	79%	
Knowledge about ovarian cancer and its prevention			
Basic knowledge of ovarian cancer prevention¶	7.4 (1.9)	7.6 (1.3)	.374
Topics on preventive options discussed by gynecologist:			
Both options PBSO and GS†	83%	90%	.439
PBSO only	12%	5%	
GS only	3%	5%	
None	2%	0%	
Gynecologist strongly advised to undergo PBSO†	19%	7%	.078
Perceived pros of PBSO±	21.4 (2.8)	19.9 (2.8)	.007
Perceived cons of PBSO±	12.2 (3.2)	13.1 (3.4)	.166
Perceived pros of GS±	18.1 (4.1)	19.8 (3.2)	.021
Perceived cons of GS±	14.5 (3.7)	13.6 (3.9)	.220
Ever involved in cancer care of close relatives	53%	60%	.582

Abbreviations: QOL, quality of life; PBSO, prophylactic bilateral salpingo-oophorectomy; GS, gynecologic screening. Unadjusted means, percentages and p values for Student's t tests and χ^2 tests; * Higher scores correspond to better functioning. The general population normative data for the SF-36 scales (General Health Perceptions and Mental Health) were based on the sample reported earlier by Aaronson et al. [27]; ** Higher scores indicate more worries or intrusive thoughts. ¶ Possible score range 0 to 11. The mean value refers to the mean number of questions answered correctly. † Topics discussed during the first gynecological consultation on preventive options for ovarian cancer. (patient-reported data); Patient-reported data on perceived advice from a gynecologist during the first consultation on preventive options for ovarian cancer. ± Possible score ranges: 5 to 25 (pros scale) and 6 to 30 (cons scale); higher scores indicate more perceived pros or cons of PBSO.

At the individual item level (data not reported in the tables), significantly more women in the PBSO group perceived surgery as an effective method to prevent ovarian cancer (87% vs. 74%), and as a method that would give them a feeling of certainty (88% vs.74%), compared to women undergoing screening (both p values < .05). Women in the GS group were significantly more likely than those in the PBSO group to perceive GS as an effective method to detect ovarian cancer (81% vs. 62%; p < .05), and to report that GS had an anxiety-reducing effect (79% vs. 61%, p < .05).

Table 3. Hierarchical logistic regression predicting PBSO versus GS use during a 12-month follow-up.

	OR	95% CI	P values
Step 1: sociodemographic and medical variables			
Age	--	--	n.s.*
Marital status			n.s.*
Unmarried/ without partner	--	--	
Married/cohabitating			
Educational level			
Primary school/ lower level high school	18.25	2.10 – 48.53	.002
Middle level high school	3.42	1.10 - 9.22	.037
Advanced vocational/ university (reference)			
Menopausal state			n.s.*
Premenopausal	--	--	
Peri/postmenopausal			
Step 2: psychosocial variables			
General Health Perceptions			.004
< general population norm	6.25	1.79 – 21.80	
≥ general population norm (reference)			
Intrusive Thoughts about ovarian cancer risk			n.s.*
PTSD symptoms present (sum score ≥ 20)	--	--	
PTSD symptoms absent (sum score < 20)			
Worried about ovarian cancer risk			n.s.*
Yes	--	--	
No			
Perceived risk of ovarian cancer (scale: 0 – 100)	--	--	n.s.*
Ovarian cancer perceived as a curable disease			.000
No	12.42	4.18 – 36.90	
Yes (reference)			
Perceived pros of PBSO (scale: 5 – 25)	1.23	1.03 – 1.46	.020
Perceived pros of GS (scale: 5 – 25)	--	--	n.s.*

Abbreviations: OR, odd ratio; CI, confidence interval; PBSO, prophylactic bilateral salpingo-oophorectomy; GS, gynecologic screening; n.s. (non-significant predictors of PBSO uptake in the final model)

Multivariate predictors of PBSO use

Variables exhibiting statistically significant bivariate associations with the choice of preventive strategy were entered into a forward logistic regression model. Education, general health perceptions, perceived curability of ovarian cancer and perceived pros of surgery remained in the final multivariate model (Table 3). Women with lower (OR, 18.25; 95% CI, 2.10 to 48.53) or intermediate education (OR, 3.42; 95% CI, 1.10 to 9.22) were more likely to undergo PBSO, as were women with poorer general health perceptions (OR, 6.25; 95% CI, 1.79 to 21.80), those who viewed ovarian cancer as an incurable disease (OR, 12.42; 95% CI, 4.18 to 36.90), and those who believed more strongly in the benefits associated with surgery (OR, 1.23; 95% CI, 1.03 to 1.46).

Behavioral intentions

Seventeen percent of women who were undergoing GS indicated at 12 months post-baseline that they intended to continue screening (no intention of surgery), 52% intended to undergo PBSO in the future, and 31% of women had no clear plans about surgery.

DISCUSSION

Women with BRCA1/2 gene mutations have at least a ten-fold greater risk of developing ovarian cancer than women in the general population, often at a relatively early age [11]. Given the high probability of developing this potentially lethal disease, it is important to understand the factors that are associated significantly with risk reducing behavior and preventive health actions. In this prospective, observational study, we investigated sociodemographic, medical and psychosocial factors associated with the use of prophylactic salpingo-oophorectomy (PBSO) versus screening among BRCA1/2 mutation carriers in the Netherlands who met prevailing eligibility criteria for preventive surgery.

Within 12 months following the first gynecologic consultation about prevention of ovarian cancer, almost three-quarters of the sample had undergone PBSO. This percentage is higher than that reported in studies in the U.S., the U.K. and Australia (ranging from 23% to 60%) [6,21, 22, 23, 24]. Younger mean age of the study participants [21,22,24], a shorter follow-up [22,24] and greater variability in objective cancer risk [21,24] may explain, at least in part, these differences. Moreover, financial issues may also impact on PBSO uptake [39]. The costs of PBSO are fully covered by health insurance policies in the Netherlands, and all of the study participants were insured. Insurance coverage is more variable in other countries.

Consistent with previous reports [6,21-24], we found that women who underwent PBSO were significantly older and were more likely to be postmenopausal. Women who have reached menopause naturally may be more inclined to undergo PBSO, as the expected consequences of the surgery may be less severe than for women who are premenopausal at the time of surgery. This latter group of women is more likely to experience abrupt, relatively severe, surgically-induced menopausal symptoms.

Women who underwent PBSO had significantly lower educational levels than those who opted for screening. We observed a similar negative association between education and PBSO uptake in a previous retrospective study [40]. Two other studies [24,41] reported no significant differences in educational level between women who underwent PBSO versus surveillance. However, these latter studies had relatively small sample sizes consisting primarily of college-educated women recruited from a single hospital.

Consistent with previous reports [19,24,42], higher levels of cancer-specific distress and perceived ovarian cancer risk were associated positively with PBSO uptake. More than one-quarter of the PBSO group versus 7% of the GS group exhibited symptoms suggesting the presence of PTSD, with ovarian cancer risk as the underlying stressor. Previous research has observed a 20% prevalence of PTSD among patients with genetic risk of developing serious disease [43].

During the period of observation, more than one-quarter of the women opted for gynecologic screening rather than PBSO. These women were significantly less convinced of the health benefits of surgery, and more convinced of the benefits of screening. Of particular importance is the finding that more than half of the women who opted for periodic screening believed that ovarian cancer could (almost) always be cured, as compared to 19% of women who opted for PBSO. This would suggest that a substantial percentage of women who choose screening may be uninformed about ovarian cancer and its high mortality rates due to advanced stage at diagnosis, and may overestimate the efficacy of screening in detecting ovarian cancer at an early stage. These issues merit further investigation.

A physician's recommendation may be a powerful determinant of PBSO uptake and, conversely, the failure to discuss this option (in any detail) may be perceived by women as an indirect recommendation against surgery [21]. Lobb et al. [44] found that prophylactic surgery was discussed in only half of consultations, which may reflect clinicians' reluctance to appear directive. Our data suggest that such reluctance is not an issue in the Dutch health care system, in that the large majority of women in our sample, irrespective of the type of subsequent prevention undertaken, indicated that both surgery and screening were discussed by their physician, and there was no

significant difference observed in the proportion of women from both groups who reported having received strong, directive advice to undergo surgery.

At the multivariate level, lower educational levels, poorer perceived general health, belief that ovarian cancer is an incurable disease, and higher levels of perceived benefits of surgery significantly predicted PBSO uptake. All of these associations were in the expected direction, with the exception of education, which emerged as the strongest negative predictor of PBSO uptake. We do not know why education emerged as the strongest predictor. Women with lower educational levels may be more inclined to promptly follow PBSO advice from their gynecologist, possibly without fully understanding the potential limitations and consequences of surgery. Conversely, women with higher educational levels may include a larger range of considerations in their decisions about prophylactic surgery (e.g., desire to delay onset of menopausal symptoms; realization that each year of delay brings with it a relatively small increase in risk). Qualitative investigations are needed to better understand the association between education and choice of preventive strategy.

We believe that the study sample was representative of BRCA1/2 mutation carriers in the Netherlands. The response rate was high, and the one hospital that declined to participate did so because of competing studies of BRCA1/2 carriers. In practice, all women in the Netherlands with proven BRCA1/2 gene mutation are referred to a gynecologist. Although we did not have access to appointment-keeping data, feedback from the participating clinicians indicated that very few women did not follow through with these referrals. PBSO uptake was ascertained by medical record audit for all women recruited into the study.

Several limitations of the study should be noted. PBSO versus screening use may be influenced by other factors not assessed in this study, including cultural or religious background, preferences of a partner or other family members, influence of the media or other health care professionals, or personal circumstances (e.g., new job, illness of a family member). Moreover, participation in the study and administration of the questionnaires may have raised women's awareness of certain health issues, which could have influenced to some unknown degree decisions regarding PBSO versus screening.

In conclusion, this study identified a number of significant predictors of PBSO uptake among BRCA1/2 carriers who are at high risk of developing ovarian cancer and who are eligible for risk-reducing surgery. Women's education, general health perceptions, perceived incurability of ovarian cancer, and perceived benefits of surgery predict uptake of PBSO. High-risk women should be provided with more information about the low predictive value of the current screening techniques for early cancer detection, and about the lethal threats posed by ovarian cancer due to its limited curability. Additionally, we would recommend that women who opt for PBSO be

screened for possible PTSD and other relevant psychological problems, as these problems may affect their post-treatment adjustment.

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CHAPTER 6

Quality of life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer

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ABSTRACT

PURPOSE: Recommendations for women at high risk of ovarian cancer include periodic gynecologic screening (GS) or prophylactic bilateral salpingo-oophorectomy (PBSO). The aim of the current study was to determine the quality of life (QOL) effects of PBSO versus GS.

PATIENTS AND METHODS: Questionnaire data were obtained from 846 high-risk women who had participated in this nationwide, cross-sectional, observational study. Forty-four percent of women had undergone PBSO and 56% had opted for GS. Topics addressed by the questionnaire included generic QOL, cancer specific distress, endocrine symptoms and sexual functioning.

RESULTS: No statistically significant between-group differences were observed in generic QOL (SF-36), with women in both PBSO and GS groups scoring similarly to the general population. Compared to GS, PBSO was associated with fewer breast/ovarian cancer worries ($P < .001$) and more favorable cancer risk perception ($P < .05$). However, the PBSO group reported significantly more endocrine symptoms ($P < .001$) and worse sexual functioning ($P < .05$) than did the GS group. Eighty-six percent of women would choose PBSO again, and 63% would recommend it to a friend with familial risk of ovarian cancer.

CONCLUSIONS: PBSO had no measurable adverse impact on generic QOL of high-risk women. The favorable effects of PBSO in terms of reduced cancer worries and low perceived cancer risk need to be weighed against increase in endocrine and sexual symptoms. Balanced information will help clinicians and high-risk women to make informed decisions about the optimal preventive health strategy.

INTRODUCTION

Ovarian cancer is one of the most common and lethal of gynecologic malignancies. In the Netherlands, the average age-adjusted incidence and mortality rates are 13.1 and 9.6 per 100,000 women, respectively, which are comparable to the rates observed in the U.S [1,2]. A family history of ovarian cancer is considered to be one of the strongest predictors of developing the disease, and it is estimated that 5 to 10% of all ovarian cancer cases have a hereditary basis [3,4]. Female carriers of a BRCA1 gene mutation have a lifetime ovarian cancer risk in the range of 39% to 54% [5,6]. Those with a BRCA2 mutation have a lower ovarian cancer risk (11% to 23%), but this is still approximately 10-fold greater than the risk of women in the general population [5,6].

Principal preventive health strategies for women at increased risk of ovarian cancer include periodic gynecologic screening (GS) and prophylactic bilateral salpingo-oophorectomy (PBSO) which are aimed at early cancer detection and cancer risk reduction, respectively. Although annual GS is offered as a basic surveillance strategy to high-risk women, its efficacy has yet to be established [7]. Current techniques, such as transvaginal sonography and CA 125 serology yield a significant number of false-positive or false-negative results, leading either to unnecessary medical investigations or to undetected early-stage malignancies. Since early ovarian cancer is asymptomatic and the available techniques have not been demonstrated to be effective for early diagnosis in the general population [8], the majority of diagnosed ovarian cancers are characterized by advanced stages and therefore by a poor prognosis [9].

In view of the uncertainty surrounding screening procedures, high-risk women may opt for surgical removal of their ovaries and fallopian tubes. PBSO reduces ovarian cancer risk in BRCA1/2 mutation carriers by 96%, and breast cancer risk by 53% [10,11]. However, PBSO does not eliminate the risk of ovarian cancer entirely, since 1% - 2% of women may develop peritoneal carcinoma [10-12]. Side effects associated with prophylactic surgery in premenopausal women are loss of fertility and immediate onset of menopause due to estrogen deprivation, including vasomotor symptoms and possible sexual dysfunction [13,14]. Estrogen deprivation may also lead to higher risk of developing osteoporosis [15]. To relieve climacteric symptoms, hormone replacement therapy (HRT) is often prescribed [16]. However, the effectiveness of HRT in combating symptoms associated with surgically-induced menopause has not yet been established.

Thus far, only four studies have explicitly focused on quality of life (QOL) effects associated with PBSO or PBSO versus screening [17-20]. Several studies [17-19] have reported beneficial effects of PBSO on cancer-specific distress (e.g., cancer worries, anxiety) and perceived cancer risk, but adverse effects on sexual functioning

and vasomotor symptoms. In these studies, generic QOL was not affected by prophylactic surgery, with oophorectomized women reporting similar levels of QOL as women in the general population [17,18]. The only study that has compared the QOL effects of PBSO and GS yielded somewhat conflicting results [20]. Oophorectomized women reported significantly worse generic QOL than did women in the GS group; however no comparisons with the general population were provided. Additionally, PBSO was not found to relieve cancer-specific distress or to worsen sexual functioning. Although this latter study was the first to provide a comparison of psychosocial effects of PBSO and GS, its results may not be generalizable to the entire population of high-risk women. It was a single-center study with a small sample size (PBSO = 29; GS = 28), and not all statistical analyses controlled for possible confounding medical variables (e.g., DNA status, history of breast cancer).

In this report we present the results of a nationwide, multi-center, cross-sectional, observational study that was conducted to determine possible differences in the generic and condition-specific QOL effects of PBSO versus GS.

PATIENTS AND METHODS

Sample and procedures

Study participants were recruited from the gynecology departments of eight hospitals in the Netherlands. Women were eligible for enrollment if they: 1) were between 30 and 75 years of age; 2) came from a hereditary (breast-) ovarian cancer (HBOC) family; and 3) had sought advice from a gynecologist on preventive measures at one of the eight participating gynecology clinics between 1996 and 2001. Patients were excluded from participation if: 1) they had undergone oophorectomy because of any suspicious changes in the ovaries as detected by medical examination, including both benign and malignant conditions; 2) oophorectomy was performed as adjuvant treatment for breast cancer; or 3) they had terminal cancer or any other severe medical comorbidity.

Eligible women received an invitation letter by mail, an informed consent form, a questionnaire and a postage-paid return envelope. In case of non-response within two weeks, systematic reminders by mail and telephone were used. Patients were classified as non-respondents if they actively declined to participate by mail or telephone, or if they could not be reached after multiple attempts. Age and the type of ovarian cancer prevention strategy used (PBSO versus GS) were the only available data that could be registered for non-respondents. The study was approved by the institutional review boards of all participating hospitals.

Measures

Generic quality of life

To assess generic QOL, four of the eight subscales of the SF-36 Health Survey [21,22] (general health perceptions, vitality, role limitations due to emotional problems, and general mental health), and the global QOL item of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [23] were employed. All raw scale scores were linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of QOL [24,25]. Cronbach's alpha coefficients in the present sample for the four SF-36 scales ranged from 0.80 to 0.86.

Condition-specific QOL

Condition-specific QOL included measures of cancer-specific distress (intrusive thoughts, cancer worries and anxiety), cancer risk perception, endocrine symptoms, and sexual functioning.

Cancer-specific distress: intrusive thoughts, cancer worries and postoperative anxiety

The seven-item Intrusion subscale of the Impact of Events Scale [26,27] measures the frequency of intrusive thoughts experienced because of a specific stressor, defined in the present study as an increased risk of developing breast/ovarian cancer. A higher sum score (range: 0 – 35) corresponds to more distress (Cronbach's alpha = 0.90). The recommended cut-off sum score for identifying persons likely to meet criteria for Post Traumatic Stress Syndrome (PTSD) is 20 [28].

Five Likert-type items, adapted from Lerman [29], were used to assess worries about breast/ovarian cancer. These included the frequency of ovarian and breast cancer worries (2 items), the impact of cancer worries on mood and daily functioning (2 items) and the frequency of worries about the possible cancer risk in family members (1 = rarely or never, 2 = sometimes, 3 = often, 4 = all the time). These five items were summed to create a cancer worry scale (possible range: 5 to 20), with higher scores representing more frequent worries in the past four weeks (Cronbach's alpha = 0.70).

Additionally, women in the PBSO group were asked to rate the extent to which PBSO reduced their anxiety about developing ovarian and breast cancer, with response choices varying on a 4-point scale from 'not at all' to 'very much'.

Self-perceived cancer risk

Two items adapted from previous studies [30,31] assessed patients' current perceptions of their breast cancer risk. Women were asked to rate their self-perceived risk on a scale 0 – 100%, where '0' corresponded to no risk at all and '100' with being

certain about developing cancer in the future. Women in the PBSO group were also requested to estimate (retrospectively) their pre-surgery risk of developing breast cancer.

Endocrine symptoms and sexual functioning

The FACT-ES, an 18-item endocrine symptom scale, was used to assess menopausal symptoms [32]. Occurrence of each symptom in the past four weeks is scored on a 5-point Likert-type scale, ranging from 'not at all' to 'very much'. Item scores can be summed to obtain a scale score (range: 0 – 72), with lower values indicating more menopausal symptoms. The Cronbach's alpha in the present study was 0.81.

The Sexual Activity Questionnaire (SAQ) [33] was used to measure sexual functioning. The SAQ consists of three scales: pleasure (6 items on desire, enjoyment, satisfaction and current frequency of activities); discomfort (2 items on vaginal dryness, pain and discomfort during penetration); and habit (frequency of sexual activity as compared to the usual level). Lower scores represent poorer sexual functioning. In the present sample, Cronbach's alpha coefficients for the pleasure and discomfort scales were 0.82 and 0.77, respectively. The SAQ was introduced during the course of the study and thus was administered to only a subset of women (n = 513) from five study centers.

Satisfaction with preventive health strategies

A series of single items was employed to assess the level of satisfaction with or regrets about the decision to undergo PBSO or GS. On a five-point scale, varying from 'completely disagree' to 'completely agree', women were asked to indicate their level of (dis)agreement with the following statements: 'I am satisfied with the decision I have made' and 'I have regrets about the decision I have made'. Women who had chosen 'agree' or 'completely agree' were considered as being satisfied with their decision on the preventive health option or as having regrets about it. Additionally, women were asked two questions about whether or not they would choose to undergo the same preventive health strategy again, and about which preventive option they would recommend to a friend in a similar situation.

Medical and sociodemographic data

Medical data were obtained from two sources, the questionnaire and hospital medical records. In the case of discrepancies between self-reported and medical record data, the latter were considered as the primary information source. The questionnaire contained a series of questions on reproductive history, personal history of cancer and recent treatment for cancer, prevalence of ovarian and breast cancer among relatives,

prophylactic ovarian and breast surgery and use of HRT. Menopausal status was determined through a series of questions on menstrual history and symptoms during the 6 months preceding PBSO, or at the present moment for women who had opted for GS. Premenopause was defined as regular menstrual periods, perimenopause as irregular periods, and postmenopause as complete cessation of menstrual periods for at least one year. Women who had had PBSO were classified as postmenopausal. Additionally, clinical variables such as DNA status, type of prophylactic ovarian/breast surgery, possible use of HRT, history of (breast) cancer, its stage at diagnosis, and cancer treatment were retrieved from the medical records. Sociodemographic variables (age, marital status, education and employment) were obtained from the questionnaire.

Statistical analysis

Descriptive statistics (frequencies, means and standard deviations) were generated to characterize the sample in terms of sociodemographics and medical variables. Student's t tests and chi-square tests were used to explore potential differences in the background characteristics of women who had undergone PBSO and those who had opted for GS.

To test for the statistical significance of group differences in generic and condition-specific QOL, we employed one-way analysis of covariance (ANCOVA), controlling for possible confounders (age, BRCA1/2 status, parity, history of breast cancer and prophylactic mastectomy). To examine the magnitude of differences between the PBSO and GS groups, effect sizes based on differences between mean scores divided by the pooled standard deviation were calculated. Following Cohen [34], effect sizes of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively. Using ANCOVA, we also investigated possible differences in the SF-36 mean scale scores between the participating high-risk women and women of similar age from the general Dutch population. The SF-36 general population normative data were based on the sample reported earlier by Aaronson et al. [22].

A multivariate logistic regression analysis was conducted to investigate the effects of the type of ovarian cancer prevention (GS versus PBSO) on the odds of the presence of cancer worries, when controlling for the potential confounders. Separate items of the cancer worry scale were dichotomized (e.g., worried versus not worried), with the original categories ('sometimes', 'often' and 'all the time') describing the frequency of worries and their impact on mood and functioning collapsed into one category, 'worried'. The purpose of this analysis was to determine which specific aspects of distress contributed the most to a PBSO-GS difference.

Within the PBSO group, we also examined whether menopausal status (pre- versus postmenopausal) at the time of ovarian surgery had a significant impact on the current levels of QOL. Additionally, in an ANCOVA model, we controlled for the time since surgery and current HRT use.

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 11.5.0; SPSS Inc., Chicago, IL, USA). Because of multiple testing, the significance level was set at $p < .01$. P values between .01 and .05 were considered to be marginally significant. All statistical tests were two-sided.

RESULTS

Study sample

On the basis of the hospital census data (Figure 1), we identified 1,205 high-risk patients who were potentially eligible for participation in the study. After an additional medical record audit, 121 women were excluded because of oophorectomy carried out as treatment for benign or malignant conditions (n = 94), death (n = 23), terminal cancer (n = 3) or severe psychiatric problems (n = 1). In total, 858 of 1084 eligible women (79%) returned the questionnaires. The main reasons for non-participation were lack of motivation (n = 137), poor health (n = 8) and emotional problems (n = 8). The data of 12 women had to be excluded: 5 women reported that the questionnaire was not applicable to their present situation, since their cancer risk was found not to be increased according to DNA testing; 5 women had a high percentage (> 50%) of missing values; and 2 women reported having undergone an oophorectomy before 1996. There were no statistically significant differences between the respondents and non-respondents regarding the type of ovarian cancer prevention and mean age (data not shown). The final study sample (n = 846) consisted of 369 (44%) women who had undergone PBSO and 477 (56%) women who had opted for periodic GS (pelvic examination, transvaginal sonography and CA 125 serology). Among BRCA1/2 mutation carriers (n = 368), 265 women (72%) opted for PBSO and 103 (28%) for GS. The demographic and clinical characteristics of the sample are shown in Table1. Compared to the women in the GS group, the women in the PBSO group were significantly older and were significantly more likely to have been diagnosed with breast cancer, to be BRCA1/2 mutation carriers and to have undergone (uni- or bilateral) prophylactic mastectomy (all p values < 0.001).

Figure 1. Flow chart for recruitment of women at increased risk for ovarian cancer in a study to evaluate quality of life effects of prophylactic oophorectomy versus periodic gynecologic screening

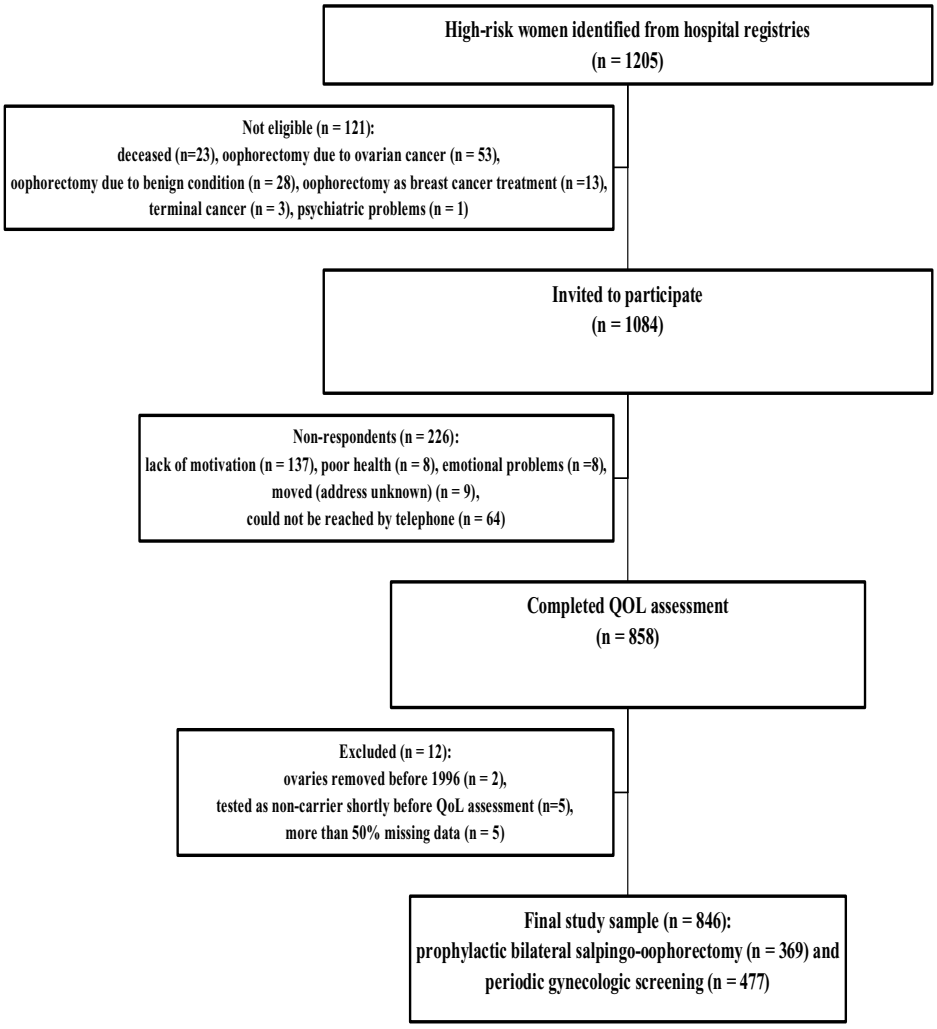

Table 1. Demographic and medical characteristics of the sample by preventive health strategies for ovarian cancer

	PBSO (n =369)	GS (n = 477)	P
Age (M, SD)	49 yrs. (SD 8 yrs.)	47 yrs. (SD 9 yrs.)	< 0.001
30 – 35 yrs.	1.6%	11.2%	< 0.001
36 – 45 yrs.	33.9%	37.9%	
46- 55 yrs.	45.5%	33.3%	
> 55 yrs.	19.0%	17.6%	
Marital Status (%)			0.520
Married/ cohabitating	83.6%	81.8%	
Unmarried/ without partner	16.4%	18.2%	
Educational level (%)			0.019
Primary school/ lower level high school	22.2%	18.3%	
Middle level high school	49.3%	44.1%	
Advanced vocational/ university	28.5%	37.6%	
Parity			0.003
Null parity	11.9%	19.5%	
At least 1 child	88.1%	80.5%	
Current menopausal state			
Premenopausal		62.1%	
Peri/ postmenopausal	100%*	37.9%	
Menopausal state prior to PBSO			
Premenopausal	38.2%	--	
Peri/ postmenopausal	61.8%	--	
(Ever) use of HRT: yes	36.9%**	5.9%	< 0.001
DNA status			< 0.001
BRCA 1/2 carrier	71.8%	21.6%	
Non-conclusive	13.3%	24.9%	
Not-tested/ other	14.9%	53.5%	
History of breast cancer: yes	49.3%	34.0%	< 0.001
Current use of tamoxifen: yes	5.1%	3.4%	0.194
Prophylactic mastectomy: yes	45.5%	13.2%	< 0.001
Self-reported time since first visit to gynecologist due to high-risk status:			0.202
Mean (SD)	4.1 yrs. (2.4)	4.3 yrs (3.2)	
Median	4.0 yrs.	4.0 yrs.	
Type of prophylactic oophorectomy:			
Laparoscopy	80.1%	--	
Laparotomy	19.9%	--	
Time since PBSO			
Mean (SD)	2.8 yrs (1.9)	--	
Median	2.0 yrs.	--	

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; GS, gynecologic screening; SD, standard deviation; HRT, hormone replacement therapy. * Including women with surgically induced menopause due to PBSO
**Use of HRT following PBSO

Women with less education and those having at least one child were also more likely to undergo PBSO, although these associations only reached marginal levels of statistical significance (all p values < 0.05). Following PBSO, slightly more than one-third of women had used HRT.

Generic and condition-specific QOL

Table 2 presents mean scores and standard deviations of the QOL measures for the PBSO and GS groups. Overall, the study respondents exhibited high levels of generic QOL as assessed by the SF-36, and no significant differences were found between the PBSO and GS groups. The SF-36 scores of both the PBSO and GS groups were, on average, not significantly different from those of similarly aged women from the general population.

There were no significant group differences in mean levels of intrusive thoughts about cancer and similar percentages of the PBSO and GS groups (9% - 10%) reported intrusive thoughts (sum score ≥ 20) severe enough to indicate the possible presence of post-traumatic stress syndrome (Table 2). However, women who had undergone PBSO reported significantly fewer cancer worries (scale mean = 7.0; range = 5 - 14) than did women in the GS group (scale mean = 7.9, range = 5 - 20) ($p < 0.001$; effect size = 0.44). The effect of prophylactic mastectomy and the interaction effect of prophylactic oophorectomy (yes/no) and prophylactic mastectomy (yes/no) were (marginally) significant, with p values lower than 0.05 and 0.01, respectively. Women who had undergone both prophylactic oophorectomy and mastectomy (PBSO+PM+) reported significantly lower levels of cancer worries (mean = 6.6; range = 5 - 13), as compared to mastectomized women undergoing GS (mean= 8.1; range = 5 – 20). Regarding specific aspects of cancer worries (Table 3), significantly fewer women in the PBSO group indicated being worried about their ovarian cancer risk ($p < 0.001$), being worried about cancer risk among their family members ($p < 0.05$), and that cancer worries had affected their mood ($p < 0.001$) and functioning ($p < 0.01$). Respectively, 82% and 45% of oophorectomized women reported that their anxiety about developing ovarian and breast cancer had decreased substantially since their surgery (Table 2). For the PBSO+PM+ group, these percentages were 90% and 57%, respectively. Comparable data were not available for the GS group.

Table 2: QOL Assessments by preventive health strategies for ovarian cancer: PBSO versus GS

QOL Mean (SD)*	PBSO (n = 369)	GS (n = 477)	P	Effect Size	Population Norm (n = 487)**
Generic QOL:¶					
Global Health Status	74.9 (19.0)	76.1 (19.4)	0.51		
General Health Perceptions	70.3 (22.4)	70.9 (19.7)	0.73		70.0 (20.0)
Vitality	62.7 (18.7)	64.0 (17.2)	0.55		65.1 (19.5)
Mental Health	73.7 (15.9)	72.9 (15.7)	0.29		74.1 (18.2)
Role-Emotional	75.4 (37.2)	79.2 (33.8)	0.95		79.8 (35.1)
Condition-specific QOL:					
Intrusive Thoughts:†					
Sum score:	6.8 (7.8)	7.0 (7.7)	0.37		
Patients scoring ≥ 20:	8.9%	9.6%	0.73		
Cancer Worries†	7.0 (1.9)	7.9 (2.2)	< 0.001	0.44	
Women reporting a large decrease in anxiety about ovarian cancer after PBSO:	82.1%	--	--		
Women reporting a large decrease in anxiety about breast cancer after PBSO:	44.9%	--	--		
Perceived breast cancer risk before PBSO (0 – 100)	58.6 (29.5)	--	--		
Currently perceived breast cancer risk (0 – 100):	29.5 (28.0)	39.0 (28.2)	< 0.05	0.34	
Endocrine Symptoms§	56.0 (9.5)	59.7 (9.6)	< 0.001	0.34	
Percentage of sexually active:‡	75%	81%	0.11		
Sexual Functioning:**	9.6 (3.5)	10.7 (3.2)	< 0.05	0.33	
Pleasure	4.4 (1.7)	5.1 (1.4)	< 0.05	0.45	
Discomfort	0 .9 (0.5)	0.9 (0.5)	0.73		
Habit					

Abbreviations: QOL, quality of life; PBSO, prophylactic bilateral salpingo-oophorectomy; GS, gynecologic screening; SD, standard deviation; ANCOVA, analysis of covariance.

* Unadjusted means, p values and effect sizes for the main effect: prophylactic oophorectomy versus gynecologic screening in ANCOVA. All analyses were controlled for age, DNA status, parity, history of breast cancer and prophylactic mastectomy. Effect sizes were calculated according to the following formula: Cohen's $d = M_{PBSO} - M_{GS} / \sigma_{pooled}$, where ($M_{PBSO} - M_{GS}$), σ_{PBSO}^2, σ_{GS}^2 , indicate, respectively, a difference in mean QOL scores, score variances of the PBSO and GS groups and where $\sigma_{pooled} = \sqrt{[(\sigma_{PBSO}^2 + \sigma_{GS}^2) / 2}$. Effect sizes are indicated only for p values < .05.

** Population norm scores were available only for the SF-36 scales (General Health Perceptions, Vitality, Mental Health and Role-Emotional). None of the comparisons between the general population scores and those of high-risk women (PBSO and GS groups) were statistically significant (all p values > 0.3). All analyses were adjusted for age.

¶ Higher scores correspond to better functioning or less symptoms. † Higher scores indicate more intrusive thoughts or worries.

§ Lower scores indicate higher levels of endocrine symptoms. ‡ The Sexual Activity Questionnaire was administered to a smaller sample of women (prophylactic oophorectomy: n = 248; gynecologic screening: n = 265). Scores for sexual functioning apply only to women who reported that they had been sexually active in the past four weeks. Higher scores represent higher levels of sexual functioning.

Table 3. Multivariate OR and 95% CIs for women who had opted for GS compared with women who had undergone PBSO by cancer worries in the past 4 weeks ('worried' versus 'not worried')

Selected items	PBSO (n = 369)*	GS (n = 477)*	OR (95% CI)**	P **
Worried about ovarian cancer	15.2%	37.4%	3.2(2.2- 4.7)	< 0.001
Worried about breast cancer	43.0%	61.0%	1.3 (0.9-1.8)	0.14
Worries affected mood	27.9%	43.3%	1.7 (1.3 – 2.6)	< 0.001
Worries affected functioning	11.0%	17.0%	1.9 (1.2 – 2.9)	< 0.01
Worried about other family members at risk	60.8%	65.9%	1.4 (1.0 –1.9)	< 0.05

Abbreviations: OR, odd ratio; CI, confidence interval; PBSO, prophylactic bilateral salpingo-oophorectomy; GS, gynecologic screening.
* Unadjusted percentages **All analyses were controlled for age, DNA status, parity, history of breast cancer, and prophylactic mastectomy.

Adjusting for possible confounders, the perceived risk of developing breast cancer was marginally significantly lower among women who had undergone PBSO than among women in the GS group The effect of prophylactic mastectomy (PM) was statistically significant ($p < 0.001$; effect size = 0.58), with the lowest estimated risk being in the PBSO+PM+ group (mean (SD): 12.9 (11.2)), and the highest risk being in women undergoing GS only (mean (SD): 46.9 (26.0)). For the entire PBSO group, the perceived risk of breast cancer had also decreased, on average, by 29.1 points on a scale 0 to 100, as compared to before ovarian surgery (retrospective estimate). For women who had also undergone prophylactic mastectomy, the decrease was 51.3 points (data not presented in the tables).

No significant differences in the level of sexual activity were observed between the PBSO and GS groups (Table 2). However, women in the PBSO group reported marginally significantly more discomfort (vaginal dryness, dyspareunia) and less pleasure and satisfaction during sexual activities (both p values < 0.05), as well as significantly more endocrine symptoms ($p < 0.001$) than the GS group. No significant differences were observed between HRT users and nonusers after ovarian surgery in the levels of endocrine symptoms and sexual functioning (data not shown). Menopausal status at the time of PBSO (pre- versus postmenopausal) and the time since PBSO were not significantly related to the current levels of generic and condition specific QOL reported by oophorectomized women (data not presented in the tables).

Satisfaction with preventive health strategies

Ninety-seven percent of women who had undergone PBSO reported being satisfied with the decision they had made versus 82% of women in the GS group ($p < 0.01$). Regrets about the decision on the preventive health strategy were expressed by 5% of the PBSO group and 6% of the GS group ($p > 0.05$). Eighty-six percent of women would choose PBSO again, and 63% would recommend it to a friend with familial risk of ovarian cancer. In the GS group, 14% of women intended to undergo PBSO within five years, 4% - within 10 years and 15% - at some unspecified time in the future. Dissatisfaction with GS was not related significantly to the intention to undergo PBSO in the future.

DISCUSSION

To our knowledge, this is the largest cross-sectional, observational study, to date, describing psychosocial issues of ovarian cancer prevention in high-risk women. The results provide a comprehensive assessment of the generic and condition-specific QOL in 846 women who had opted either for prophylactic bilateral salpingo-oophorectomy (PBSO) or periodic gynecologic screening (GS).

All study participants reported high levels of generic QOL that were not significantly different from those of women in the general Dutch population. Despite the fact that PBSO is an irreversible procedure with major consequences for the bodily hormonal balance, which in turn may affect the level of patients' general well-being, we found no adverse impact of PBSO on generic QOL. These results are consistent with earlier findings [17,18], but in contrast with one study [20] that suggested impairments in generic QOL due to PBSO. The discrepant results of the latter study may arise from methodological issues, such as a small sample size and the lack of statistical control for possible confounding medical factors.

Our results indicate that PBSO is associated with significantly lower levels of cancer worries, as compared to GS, with the fewest worries being expressed by women who had undergone both PBSO and prophylactic mastectomy (PM). Additionally, 45% and 82% of women also indicated that PBSO had led to a large decline in anxiety about breast and ovarian cancer, respectively. As expected, the anxiety reduction was even larger for women who had undergone both prophylactic ovarian and breast surgeries. Our findings are in line with other reports [17-19,35] that have found post-surgery reduction in cancer-specific distress, but contrast with those of Fry et al. [20] who found no beneficial effects of PBSO over GS on cancer worries. This discrepancy may be due to the fact that Fry and colleagues employed a different measure of cancer worries [36] than that employed in our and other studies. Also, their sample was small, and it may not have been representative of the larger population of high-risk women.

Their sample was recruited from a single center, and included fewer women with a history of breast cancer (31%), more women who were premenopausal at PBSO (50%) and no women who had undergone prophylactic mastectomy, as compared to our sample.

In addition to the cancer worry scale, we also administered the intrusion subscale of the IES to assess cancer-specific distress. No significant differences were observed in the level of intrusive thoughts about breast/ ovarian cancer between the PBSO and GS groups. The cancer worry scale can be viewed as a sub-clinical distress measure, while the intrusive thought subscale of the IES is intended to assess a more severe form of distress, capturing symptoms of post-traumatic stress syndrome (PTSD). In our study sample, approximately 10% of all women exhibited symptoms suggesting the presence of PTSD, with breast/ ovarian cancer risk as an underlying stressor. It is worth noting that although PBSO reduces objective cancer risk, it does not eliminate high levels of cancer-specific distress in some women.

After controlling for possible confounders, a significant difference was observed in breast cancer risk perception, with the PBSO group scoring significantly lower than the GS group. A comparison between the pre- and postoperative (retrospective) assessments of perceived breast cancer risk indicated a decrease, on average, of 29% following PBSO and 51% following both PBSO and PM. Our results suggest that high-risk women benefit both medically and psychologically from prophylactic surgery by the reduction of both their objective cancer risk and their perceived risk of developing cancer, and that this benefit is the greatest among women who undergo both ovarian and breast surgeries.

As expected, PBSO was associated with more endocrine symptoms and worse sexual functioning than GS. The use of HRT had relatively limited impact on the level of menopausal and sexual symptoms in the PBSO group (detailed data on this issue will be reported in a separate paper). Although the PBSO and GS groups included comparable numbers of sexually active women, prophylactic surgery was associated with more discomfort and less pleasure and satisfaction during sex. Post-surgery increase in levels of menopausal symptoms and declines in sexual functioning caused by estrogen deprivation symptoms (e.g. vaginal dryness, dyspareunia, vasomotor symptoms) have also been reported in other studies [17,18,35]. However, no significant PBSO-GS differences in sexual functioning were detected in the study by Fry et al., [20] using the same measure of sexual functioning. This may be due to their smaller sample size and lower rates of sexually active women (66.1%), as compared with our investigation.

Our findings suggest that the beneficial QOL effects of PBSO may outweigh the adverse effects, since almost all women who had undergone PBSO reported being highly satisfied with the procedure. These findings are in line with previous studies

[18,19,37-39]. The vast majority of women in the PBSO group would undergo surgery again, while less than two-thirds of women undergoing GS would choose for screening again. Almost one-third of women in the GS group expressed the intention to undergo PBSO in the future. These results suggest that high-risk women may perceive GS as only a temporary preventive health strategy.

Given its multi-center nature and the relatively high response rate, we believe that the study sample was representative of high-risk women in the Netherlands. However, some possible limitations of our study should be noted. First, we did not include measures of perceived anxiety reduction or a retrospective report of changes in self-perceived cancer risk in the GS group. Given the cross-sectional study design, and the longitudinal nature of screening itself, there was no clear reference point in time for the GS group that would be comparable to that for women who had undergone PBSO. Data from our on-going, longitudinal study will be able to inform this issue. Second, due to the cross-sectional design of the study, possible changes in QOL over time induced by prophylactic treatment or screening could not be assessed prospectively. A prospective, multicenter study is currently being conducted to obtain a more thorough picture of the QOL and symptom experience over time of high-risk women who opt for PBSO versus GS. Third, women who had undergone PBSO or GS may come from slightly different populations regarding their objective risk of developing ovarian cancer, since more than the half of the GS group did not have DNA testing. Although we controlled for known risk factors in our analyses, statistical adjustments for confounding factors may not have entirely ruled out possible selection bias resulting from non-randomized comparison groups. However, given the known benefits of PBSO for ovarian cancer risk reduction and the unknown efficacy of the current GS techniques in early ovarian cancer detection, a randomized trial is not feasible and would not be ethical.

In conclusion, this study has documented both beneficial and adverse QOL effects associated with the two major health strategies for ovarian cancer in high-risk women. Physicians should discuss both the pros and cons of PBSO and GS with high-risk women seeking medical advice about their risk management. Among the benefits, reduced cancer worries after PBSO should be emphasized. The likely increase of climacteric and sexual symptoms, which may not be alleviated by the post-surgical use of HRT, should be included in discussions of adverse effects of PBSO. Balanced information will help clinicians and high-risk women to make informed decisions about the optimal preventive health strategy. Finally, our results indicate that a minority of oophorectomized women may experience high levels of distress after prophylactic treatment. Such women should be identified in a timely manner, and they should be offered (additional) psychosocial care following PBSO.

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CHAPTER 7

The impact of hormone replacement therapy on menopausal symptoms following prophylactic salpingo-oophorectomy

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ABSTRACT

PURPOSE: Preventive health strategies for women at increased hereditary risk of ovarian cancer include gynecologic screening (GS) and/or prophylactic oophorectomy (PBSO). Hormone replacement therapy (HRT) is often prescribed to compensate for post-surgical endocrine deficiencies. This study examined the impact of HRT use on levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone PBSO. Comparisons were made with similar women undergoing GS.

PATIENTS AND METHODS: Questionnaire data on endocrine symptoms and sexual functioning were obtained from 450 premenopausal, high-risk women who had participated in this nationwide, cross-sectional, observational study.

RESULTS: Thirty-six percent of women had undergone PBSO and 64% had opted for GS. In the PBSO group, 47% of the women were current HRT users. They reported significantly fewer vasomotor symptoms than nonusers ($p < .05$). However, compared to premenopausal women undergoing GS, oophorectomized HRT users were more likely to report vasomotor symptoms ($p < .01$). HRT users and nonusers reported comparable levels of sexual functioning. Compared to women in the GS group, oophorectomized HRT users reported significantly more sexual discomfort due to vaginal dryness and dyspareunia ($p < .01$).

CONCLUSIONS: Although HRT has a positive impact on surgically-induced vasomotor symptoms, it may be less effective than is often assumed. Symptom levels remain well above those of premenopausal women undergoing screening, and sexual discomfort is not alleviated by HRT. Physicians need to provide younger high-risk women considering PBSO with realistic information about both benefits and drawbacks of this preventive strategy, including information about premature menopause and HRT.

INTRODUCTION

Preventive health care recommendations for women at increased hereditary risk of ovarian cancer include periodic gynecologic screening (GS) and/or prophylactic bilateral salpingo-oophorectomy (PBSO). In the face of uncertain efficacy of the currently available screening techniques, including transvaginal ultrasonography and CA 125 serology [1], and the established risk-reducing benefit of PBSO for ovarian and breast cancers [2,3], carriers of BRCA1/BRCA2 gene mutations are usually advised to undergo PBSO after the age of 35 years or following the completion of childbearing [4].

Side effects associated with PBSO in premenopausal women include loss of fertility, immediate onset of menopause with vasomotor and urogenital symptoms [5,6], and a decline in sexual interest and activity [7]. The management of surgically-induced menopause requires strategies for alleviating the climacteric symptoms, and improving women's functioning and quality of life. Hormone replacement therapy (HRT) is often prescribed at the time of surgery [8].

HRT has proven to be highly effective in alleviating vasomotor symptoms (e.g., hot flushes, sweats) and urogenital atrophy in women undergoing natural menopause [8,9]. Because of its androgenic properties, tibolone has shown to have additional beneficial effects on sexual functioning [10-12]. Recent studies [13-17], however, indicate that HRT use by healthy menopausal women is associated with increased risks of breast cancer and cardiovascular complications, and that these risks may overshadow the potentially beneficial effects on osteoporosis and colon cancer. Current recommendations call for short-duration HRT treatment for severe symptoms, and avoidance of long-term use for prevention of chronic health conditions [18,19].

Only two studies have investigated post-PBSO menopausal symptoms and sexual functioning as part of a larger investigation of the psychosocial impact of prophylactic surgery [20,21]. , In both studies, PBSO was found to be associated with the occurrence of menopausal symptoms. The results with regard to sexual functioning were inconsistent, with some evidence of sexual impairment in the study of Elit et al. [20], but not in the study of Fry et al. [21]. Neither of these studies explicitly investigated endocrine symptoms and sexual functioning in relation to post-PBSO HRT use.

The primary focus of this report is on the impact of HRT use on the levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone PBSO. Comparisons are made with premenopausal high-risk women undergoing GS.

METHODS

Participants and procedures

This investigation was part of a larger, cross-sectional, observational study of psychosocial issues surrounding ovarian cancer prevention among high-risk women in the Netherlands. Study participants were recruited from the gynecology departments of eight hospitals. Women were eligible for the larger study if they: 1) were between 30 and 75 years of age; 2) came from a hereditary breast/ovarian cancer family; and 3) had sought gynecologic advice on preventive measures at one of the clinics between 1996 and 2001. Patients were excluded from participation if they had: 1) undergone oophorectomy as treatment for a medical condition; or 2) metastatic cancer or any other severe comorbidity. The current analysis was restricted to data of women who were premenopausal at the time of PBSO or were currently premenopausal (GS group). Premenopause was defined as having regular menses during the past 6 months or prior to PBSO. Following surgery, women were prescribed standard doses of HRT (estrogen/progesterone or tibolone) administered either orally or transdermally.

Eligible women who had undergone PBSO or GS received an invitation letter by mail, an informed consent form, a questionnaire and a postage-paid return envelope. In case of non-response after two weeks, reminders by mail and telephone were used. Patients were classified as non-respondents if they actively declined to participate, or if they could not be reached after multiple attempts. The study was approved by the institutional review boards of all participating hospitals.

Measures

The 18-item FACT-ES was used to assess menopausal symptoms [22]. Occurrence of each symptom in the past four weeks is scored on a 5-point Likert-type scale, ranging from “not at all” to “very much”. Item scores can be summed to obtain a scale score (range: 0 – 72), with lower values indicating more symptoms.

The Sexual Activity Questionnaire (SAQ) [23] was used to measure sexual functioning. It consists of three scales: pleasure (6 items on desire, enjoyment, satisfaction and current frequency of activities); discomfort (2 items on vaginal dryness, pain and discomfort during penetration); and habit (frequency of sexual activity as compared to the usual level). Lower scores represent poorer sexual functioning.

Medical and sociodemographic data

HRT use was determined on the basis of patient’s self-report, confirmed by medical record audit. Sociodemographic and other medical data were obtained from the questionnaire and the medical records. These data included age, marital status, education, employment, menstrual and reproductive history, personal history of cancer

and its treatments, DNA status, prevalence of breast/ovarian cancer among relatives, and prophylactic surgery. In the case of discrepancies between self-reported and medical record data, the latter were considered as the primary information source.

Statistical analysis

Descriptive statistics were generated to characterize the sample in terms of sociodemographic and medical variables. Student's t tests and chi-square tests were used to examine potential differences in the background characteristics of women who had undergone PBSO versus GS.

The study sample was divided into 3 groups according to the type of prevention and the current hormonal status: oophorectomized, current users and nonusers of HRT (PBSO HRT users and PBSO HRT nonusers), and premenopausal women undergoing GS. One-way analysis of covariance (ANCOVA) was used to test for group differences in endocrine symptoms and sexual functioning, controlling for possible confounders (age, DNA status, history of breast cancer, tamoxifen use and prophylactic mastectomy). Among HRT users, the effect of the type of medication (estrogen/progesterone versus tibolone) was also investigated. Additionally, individual symptoms of the FACT-ES scale were dichotomized (symptom present = the two highest categories, 'very much' and 'quite a bit'). For each symptom, a multivariate logistic regression analysis was conducted to determine the significance of between-group differences, when controlling for potential confounders.

RESULTS

Study sample

Of 1,205 high-risk women in the hospitals' databases, 1,084 were eligible for study participation (Figure 1). The reasons for non-eligibility were: oophorectomy carried out as treatment for a medical condition (n = 94), death (n = 23), metastatic cancer (n = 3) and severe psychiatric problems (n = 1). In total, 858 (79%) women returned completed questionnaires. Lack of interest (n = 137), poor health (n =8) and emotional problems (n = 8) were the main reasons for non-participation. The data of 12 women had to be excluded: 5 women reported that the questionnaire was not applicable to their present situation, since their cancer risk was found not to be increased based on DNA testing; 5 women had a high percentage (> 50%) of missing values; and 2 women had undergone an oophorectomy before 1996. There were no statistically significant differences between the respondents and non-respondents in the type of ovarian cancer prevention and mean age (data not shown). Among the respondents, 450 premenopausal women were identified, of whom 164 (36%) had undergone PBSO. Data on menopausal status of non-respondents were not available.

Figure 1. Study participant flow

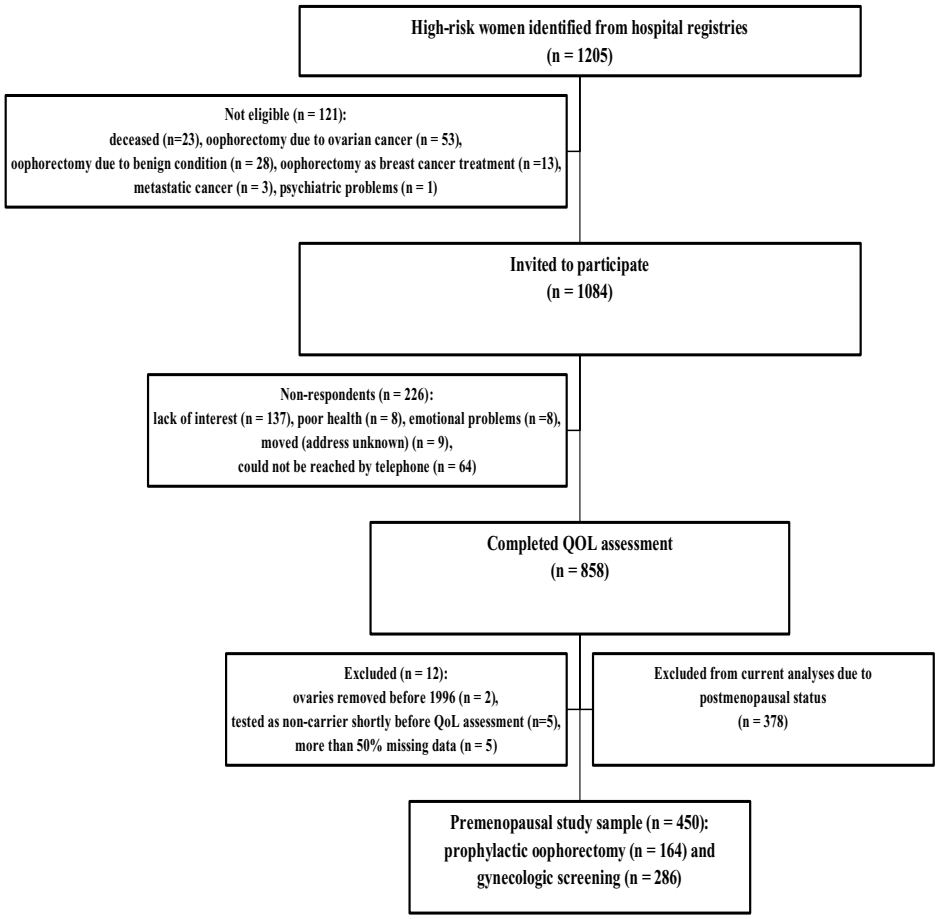

Table 1. Sample characteristics by type of ovarian cancer prevention

Characteristics	PBSO			GS (n = 286)	P values
	Total PBSO Group (n =164)	PBSO HRT User (n = 77)	PBSO HRT Nonuser (n = 87)		
Current age:					
Mean (SD)	46 yrs. (6 yrs.)	45 yrs (5 yrs.)	47 yrs. (7 yrs.)	41 yrs. (6 yrs.)	A: .000; B:.048; C: .000
Range:	34 - 59	34 – 51	34 – 59	30 -54	
Marital Status					A: .892; B: .315; C: .409
Married/ cohabitating	139 (85%)	68 (88%)	71 (83%)	243 (85%)	
Unmarried/ without partner	25 (15%)	9 (12%)	16 (17%)	43 (15%)	
Educational level					A: .087; B: .278; C: .719
Primary school/ lower level high school	30 (18%)	11 (13%)	19 (22%)	34 (12%)	
Middle level high school	85 (52%)	41 (53%)	44 (51%)	138 (48%)	
Advanced vocational/ university	49 (30%)	25 (34%)	24 (27%)	114 (40%)	
Parity					A: .006; B: .443; C: .110
Nulliparous	22 (13%)	12 (16%)	10 (11%)	69 (24%)	
Primi- or multiparous	142 (87%)	65 (84%)	77 (89%)	217 (76%)	
DNA status					A: .000; B: .135; C: .000
BRCA 1/2 carrier	128 (78%)	61 (79%)	67 (77%)	89 (31%)	
Non-conclusive	16 (10%)	4 (5%)	12 (14%)	51 (18%)	
Not-tested/ other	20 (12%)	12 (16%)	8 (9%)	146 (51%)	
History of breast cancer	54 (33%)	13 (17%)	41 (47%)	57 (20%)	A: .000; B: .000; C: .547
Current use of tamoxifen	3 (2 %)	0 (0%)	3 (3%)	3 (1%)	A: .359; B: .100; C: .462

Previous hysterectomy	7 (5%)	4 (5%)	3 (3%)	1 (0%)	A: .019; B: .360; C: .006
Prophylactic mastectomy	84 (51%)	48 (62%)	36 (41%)	49 (17%)	A: .000; B: .007; C: .000
Age at PBSO: Mean (SD)	43 yrs. (6.0)	41 yrs. (5.0)	44 yrs. (6.0)	--	B: .004
Time since PBSO: Mean (SD)	2.8 yrs (2.2)	3.1 yrs. (2.3)	2.5 yrs. (2.1)	--	B: .111
Ever use of HRT	99 (60%)	77 (100%)	22 (25%)	--	--
Current use of HRT	77 (47%)	77 (100%)	--	--	--
Type of HRT currently used:					--
Estrogen/ progesterone	--	54 (70%)	--	--	
Tibolone	--	23 (30%)	--	--	
Duration of HRT use in current users:*					
Mean (SD)	--	3.0 yrs. (2.3)	--	--	--
HRT prescribed at the time of PBSO**	--	63 (82%)	--	--	--
HRT use started directly after PBSO**	--	55 (72%)	--	--	--
HRT used as prescribed:**					--
Always	--	69 (90%)	--	--	
Most of the time	--	7 (9%)	--	--	

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone replacement therapy; GS, gynecologic screening; SD, standard deviation.
P values refer to the following comparisons:
A: total PBSO group versus GS group; B: PBSO HRT users group versus PBSO HRT nonusers group; C: PBSO HRT users group versus GS group
* Time interval between first post-surgical HRT use and current HRT use at the time of questionnaire assessment.
**Self-reported data.

The background characteristics of the sample are shown in Table 1. Compared to the GS group, the PBSO group was significantly older, more likely to have been diagnosed with breast cancer, to be BRCA1/2 mutation carriers, and to have undergone prophylactic mastectomy (all p values < 0.001). At the time of assessment, 47% of the PBSO group reported current use of HRT, with the largest percentage taking estrogen/progesterone medications. HRT users were younger (45 yrs. versus 47 yrs., $p < .05$) and had undergone PBSO at a younger age (41 yrs. versus 44 yrs., $p < .01$), were less likely to have a history of breast cancer (17% versus 47%; $p < .001$), and were more likely to have undergone prophylactic mastectomy (62% versus 41%; $p < .01$) than nonusers. A quarter of the latter group reported having used HRT at some time post-surgery. Data on the reasons for HRT discontinuation were not available. The majority of current HRT users (82%) received a prescription for HRT at the time of PBSO, reported having started HRT directly after surgery (72%), and being (highly) compliant with HRT use (99%) (Table 1).

Endocrine symptoms

Table 2 presents the mean FACT-ES scale scores and the individual symptom frequencies. As indicated by the mean scores, the PBSO HRT users group reported significantly fewer symptoms overall than the PBSO HRT nonusers group ($p < .05$). At the individual endocrine symptom level, significant between-group differences were found only for hot flushes, and cold and night sweats (all p values < .05).

The PBSO HRT users group reported significantly more endocrine symptoms overall (FACT-ES scale scores) than the GS group ($p < .05$). Significant group differences were found in the frequency of all vasomotor symptoms, vaginal dryness, pain/ discomfort during intercourse, and loss of interest in sex, with the PBSO HRT users group experiencing more problems (all p values < .01).

Sexual functioning

The majority of all study participants reported being sexually active (Table 3), and no significant differences between the groups were observed, after controlling for age, history of breast cancer, tamoxifen use and prophylactic mastectomy. “Lack of interest in sex” or “having a bodily problem” were the most common reasons reported by oophorectomized women for not being sexually active (44% - 78%). Thirty-three percent of premenopausal women in the GS group reported being too tired or their partner being too tired as the main reason for their sexual inactivity (data not shown in the table).

Table 2. Endocrine symptoms among HRT users and nonusers after prophylactic salpingo-oophorectomy, and premenopausal women undergoing screening

Endocrine symptoms	Premenopausal PBSO HRT User (n = 77)*	Premenopausal PBSO HRT Nonuser (n = 87)*	Premenopausal GS (n = 286)*	P-values**
FACT-ES: mean (SD)¶	58.0 (10.9)	54.6 (9.7)	61.7 (9.8)	B: .034; C: .026
Selected symptoms:				
Hot flushes	15 (20%)	36 (41%)	6 (2%)	B: .004; C: .000
Cold sweats	18 (23%)	33 (38%)	6 (2%)	B: .034; C: .000
Night sweats	19 (25%)	34 (39%)	20 (7%)	B: .037; C: .001
Vaginal discharge	4 (5%)	1 (1%)	26 (9%)	B: .176; C: .309
Vaginal itching/ irritation	4 (5%)	5 (6%)	11 (4%)	B: .865; C: .445
Vaginal bleeding	3 (4%)	1 (1%)	26 (9%)	B: .283; C: .107
Vaginal dryness	10 (13%)	21 (24%)	6 (2%)	B: .152; C: .002
Pain/discomfort with intercourse	9 (12%)	15 (17%)	9 (3%)	B: .133; C: .008
Lost interest in sex	12 (16%)	19 (22%)	11 (4%)	B: .350; C: .002
Gained weight	13 (17%)	16 (18%)	26 (9%)	B: .777; C: .106
Lightheaded/ dizzy	3 (4%)	5 (6%)	11 (4%)	B: .585; C: .610
Vomited	8 (1%)	1 (1%)	0 (0%)	B: .959; C: .994
Diarrhea	8 (1%)	1 (1%)	3 (1%)	B: .508; C: .516
Headaches	10 (13%)	9 (10%)	34 (12%)	B: .617; C: .826
Feel bloated	5 (6%)	7 (8%)	20 (7%)	B: .673; C: .480
Breast sensitivity/ tenderness	2 (2%)	4 (5%)	23 (8%)	B: .226; C: .080
Mood swings	9 (12%)	17 (20%)	31 (11%)	B: .174; C: .955
Irritable	6 (8%)	13 (15%)	23 (8%)	B: .160; C: .726

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone replacement therapy; GS, gynecologic screening; SD, standard deviation. * Unadjusted percentages; ** All analyses were adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy.
P values apply to the following comparisons: B: PBSO HRT users group versus PBSO HRT nonusers group; C: PBSO HRT users versus GS group; ¶ Possible score range: 0 – 72. Lower scores indicate more symptoms.

Table 3. Sexual functioning among HRT users and nonusers after prophylactic salpingo-oophorectomy, and premenopausal women undergoing screening

	Premenopausal PBSO HRT User (n = 77)	Premenopausal PBSO HRT Nonuser (n = 87)	Premenopausal GS (n = 286)	P-values*
Sexually active women (%):	83%	77%	86%	B: .713; C: .693
SAQ scale scores: mean (SD) **				
Pleasure	10.2 (3.2)	9.8 (3.6)	11.2 (2.8)	B: .700; C: .154
Discomfort	4.8 (1.5)	4.4 (1.7)	5.5 (1.0)	B: .166; C: .003
Habit	1.0 (0.5)	0.9 (0.6)	0.9 (0.5)	B: .451; C: .713

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone replacement therapy; GS, gynecologic screening; SD, standard deviation.
* All analyses were adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy.
P values apply to the following comparisons:
B: PBSO HRT users group versus PBSO HRT nonusers group; C: PBSO HRT users versus GS group
** Scores available only for sexually active women. Lower scores indicate poorer sexual functioning

The PBSO HRT users and PBSO HRT nonusers groups reported comparable levels of sexual functioning, as measured by the pleasure, discomfort and habit scales of the SAQ. Compared to the GS group, the PBSO HRT users group reported significantly more discomfort during sexual activities ($p < .01$).

Although the numbers were small (see Table 1), we examined whether the type of HRT used differentially affected levels of endocrine symptoms and sexual functioning. No statistically significant differences were found between those who used estrogen/ progesterone versus tibolone (data not shown in the table).

DISCUSSION

Many women from HBOC families consider PBSO or GS as a strategy for managing their increased risk of developing ovarian cancer. Although the risk reduction attributed to PBSO is largest in premenopausal women [2,3,24], the resulting post-operative endocrine imbalance may affect functioning in several health domains. In this report, we have presented the results of a study that investigated the impact of PBSO on endocrine symptoms and sexuality among premenopausal, high-risk women, and the effect of HRT in alleviating these symptoms.

In the Netherlands, HRT is recommended as a means of alleviating vasomotor and sexual symptoms only to high-risk women who are premenopausal at the time of

surgery. In clinical practice, it is generally recommended that HRT use begin immediately after PBSO, and be discontinued at the time of expected natural menopause (i.e., at approximately 52 years of age) [4]. There is currently no consensus as to whether post-oophorectomy HRT use contributes additionally to the already increased risk of breast cancer resulting from BRCA1 or BRCA2 mutation carriership [25]. Recent studies [4,26] have suggested that decisions regarding HRT use should be based on quality of life considerations, rather than on life expectancy. Moreover, short-term HRT use does not negate the protective effect of PBSO on subsequent breast cancer risk in BRCA1/2 mutation carriers [26].

When deciding to undergo PBSO, younger women may expect that post-surgical HRT use will minimize if not entirely prevent menopausal symptoms, and that their functioning will return to approximately the pre-surgery level. In our study, 47% of oophorectomized women were currently using HRT. The results indicated that current HRT use significantly reduced vasomotor symptoms, with prevalence rates being 14% to 21% lower among HRT users versus nonusers. Although these reductions are not trivial, previous studies of HRT use among women experiencing natural menopause have demonstrated larger reductions in vasomotor symptoms [9]. Also, contrary to expectations based on clinical experience, no significant differences in the frequency of other endocrine symptoms (e.g., vaginal dryness) were observed between HRT users and nonusers after controlling for possible confounders and type of medication. Surgical menopause may entail symptoms of higher severity for which commonly applied HRT may be less effective, as it was originally designed to compensate for gradual endocrine losses in naturally menopausal women. This issue, however, needs to be addressed empirically.

Although HRT use does have a salutary effect on vasomotor symptoms in women with surgically induced menopause, it does not alleviate these symptoms entirely, as evidenced by the comparison with premenopausal women undergoing GS. It is commonly assumed that HRT use will virtually eliminate hot flushes [27]. The current findings indicate that oophorectomized HRT users continue to report significantly more vasomotor and other endocrine symptoms than the group of premenopausal women undergoing screening. The only previous study [21], that has compared the physical and psychosocial functioning of women undergoing PBSO versus GS found an overall trend for the surgical group (n = 29) to report more menopausal symptoms than the non-surgical group (n = 28). However, it is unclear if that study adjusted statistically for current HRT use. Additionally, the observed group differences were with regard to aches and pains, weight gain and menstrual problems, but not vasomotor symptoms.

The majority of women in the current study reported being sexually active, and no significant differences were found in the level of activity between the oophorectomized HRT users, non-HRT users, and women undergoing screening. However, oophorectomized women who were not sexually active attributed their inactivity significantly more frequently to decreased libido and bodily problems than did women in the screening group. HRT users and nonusers reported similar levels of sexual functioning, and HRT users reported significantly more discomfort (e.g. vaginal dryness, dyspareunia) than women undergoing screening. These results are in line with other studies [6,20,28,29] that have reported impairments in sexual functioning due to surgically-induced menopause, and sustained problems with libido, lubrication and dyspareunia despite HRT use [6,28]. However, these studies included a more heterogeneous sample of women, including those who had undergone oophorectomy as a medical treatment. Two other studies of high-risk women who had undergone PBSO have reported that HRT may mitigate potential sexual problems [21,30]. However, these were single center studies whose results were based on (qualitative) data derived from small samples.

Decreased androgen concentrations after PBSO may underlie sexual problems [31]. Some studies have reported that use of transdermal testosterone [32] or tibolone improves sexual function [10,12,33]. In our sample, none of the women were treated by testosterone. We did not observe any significant differences in sexual functioning among women using tiblone versus estrogen/progesterone. However, the sample size for this specific comparison was limited, with small numbers of tibolone users.

The strength of our study lies in its multi-center study design, the large sample size and the high response rate. We believe that the study sample is representative of high-risk women in the Netherlands. The main limitation of the study is its cross-sectional design, which does not allow for interpretation of causal relationships or detection of changes in endocrine symptom levels or sexual functioning over time due to the absence of a baseline (i.e., pre-surgical) assessment. We are currently conducting a prospective, multi-center study with pre-surgical and follow-up assessment.

Additionally, although we controlled for possible confounders in our statistical analyses, statistical adjustments cannot entirely rule out the possibility of indication bias, since the study design was non-randomized. Indication bias would suggest that the severity of menopausal symptoms would be decisive in whether or not to use HRT following PBSO. In clinical practice, the gynecologists from the participating hospitals typically prescribe standard doses of HRT pre-operatively and recommend that women commence HRT use directly after PBSO, rather than waiting until menopausal symptoms occur. The majority of HRT users in our sample began using HRT directly after PBSO, and they were highly compliant with its use. Nevertheless, there are several reasons why one cannot entirely rule out the possibility of indication bias. First,

for those women who were current HRT users, no information was available on whether their use had been continuous or intermittent during the period following surgery. Second, no data were available about the reasons why some women had discontinued post-surgical use of HRT. We would emphasize, however, that although indication bias may play some role in the comparisons made between HRT users and nonusers, it does not when comparing symptoms of oophorectomized HRT users with those of women undergoing gynecologic screening. Ultimately, one would want to investigate these issues in a randomized clinical trial (RCT). However, the feasibility of such a RCT is questionable, as it is likely that many eligible women would not want to be randomized to HRT use or nonuse, or to a placebo group).

In conclusion, this study has documented relatively high levels of endocrine symptoms and impaired sexual functioning associated with PBSO. Although the efficacy of HRT in alleviating symptoms of natural menopause has been established in numerous randomized studies, our observational data suggest that HRT may be less effective in the case of surgically-induced symptoms. Randomized studies are needed to determine the efficacy of HRT and testosterone supplementation in alleviating menopausal symptoms following PBSO, including dose-response issues. Also the role of non-hormonal medical treatments and psychosocial interventions in alleviating climacteric complaints merits further study. Ganz et al. [34] have demonstrated that psychosocial interventions in combination with non-hormonal medications are a viable alternative to HRT among older breast cancer survivors suffering from menopausal symptoms. Possibly, younger oophorectomized women may also benefit from such interventions.

Physicians need to provide younger high-risk women considering PBSO with realistic and balanced information about both the benefits and possible drawbacks of this preventive strategy., including information about ovarian function, menopause, HRT, and psychosocial effects (e.g., reduced cancer worries and lower risk perceptions) [30,35,36]. Such balanced information will help women in making informed decisions about the optimal preventive health strategy.

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CHAPTER 8

General discussion

In the first section of this chapter, we present the most important findings from the current studies in the context of the research objectives listed in the general introduction. The second section contains a general discussion, including implications and recommendations for future research in this area.

8.1 STUDY FINDINGS

Objective 1: To evaluate pretreatment quality of life among patients with localized prostate cancer detected by a population-based screening or in a regular clinical setting

As expected, patients from screening were more likely to have localized prostate cancer, compared to men diagnosed in a clinical setting. Consequently, the vast majority of men with screen-detected prostate cancer were subsequently scheduled for primary therapy (radical prostatectomy or radiotherapy) or for 'watchful waiting', whereas one-third of the clinical group was to receive treatments for advanced disease due to disseminated prostate cancer at first diagnosis. Among men with localized disease, slightly more than a half received primary radiotherapy, and slightly more than one-third underwent radical prostatectomy.

Overall, patients with localized, screen-detected prostate cancer reported better levels of generic quality of life than did similar men with clinically diagnosed disease. In particular, men with screen-detected stage T2 tumors had significantly better general health perceptions than did those men diagnosed in a clinical setting. However, the scores for generic quality of life (SF-36) of both groups were not significantly different from those of the sex- and age-adjusted general population norm. Men with screen-detected and clinically diagnosed prostate cancer reported comparable levels of urinary, bowel and sexual problems before treatment. Considering the type of subsequent primary treatment, men who were to undergo primary radiotherapy were more likely to have lower levels of generic quality of life at baseline (shortly after diagnosis), as compared to men in the prostatectomy group. Overall, urinary, bowel and sexual problems were uncommon among men awaiting primary treatment, however, approximately one-third of men reported not-being sexually active prior to prostate cancer diagnosis. The baseline differences in quality of life between men who were to undergo surgery versus radiotherapy could not be explained by tumor characteristics or the type of cancer detection. However, these differences may be important when referring patients to radical prostatectomy versus radiotherapy. Our findings reflect the situation in clinical practice, where only those patients in reasonably good condition and who can withstand a relatively long period of general anesthesia are recommended to undergo a radical prostatectomy.

Objective 2: To determine the quality of life effects of primary treatment for localized prostate cancer detected by a population-based screening or in a regular clinical setting

In our prospective, observational study among men who received primary treatment for early prostate cancer, 59% had been diagnosed through the screening trial, and 41% in a regular clinical setting.. Men who underwent surgery were, on average, 5 years younger than men treated by irradiation and were less likely to have had comorbid conditions.

The types of quality of life problems reported during the first year after treatment differed as a function of treatment. Radical prostatectomy affected urinary and sexual functioning, while primary radiotherapy was mainly associated with bowel problems, and to a lesser degree with sexual dysfunction. Following surgery, between 39% and 49% of patients experienced urinary incontinence, and between 80% and 91% of patients reported having erectile problems. Among radiotherapy patients the rates of post-treatment bowel problems were between 30% and 35%, and for erectile problems between 41% and 55%. Our results also indicated poorer levels of generic quality of life after radiotherapy as compared to surgery, after controlling for age, pretreatment levels of quality of life and cancer detection method. Overall, patients from screening and non-screening settings reported comparable levels of generic quality of life. However, the screening group tended to have better perceptions of their general health after primary treatment. The posttreatment levels of quality of life in patients with clinically diagnosed or screen-detected prostate cancer were not below the general population norm, adjusted for sex and age. Decreased levels of urinary, bowel and sexual functioning after treatment were not related to the method of cancer detection.

Objective 3: To identify psychosocial and clinical factors predicting the uptake of prophylactic surgery versus gynecological screening among women with hereditary susceptibility for breast/ovarian cancer

Women who carry BRCA1/2 gene mutations and who have completed their childbearing are usually recommended to undergo risk-reducing prophylactic oophorectomy. In our prospective, observational study, we investigated which baseline factors were associated with use of prophylactic surgery during a 12-month follow-up. Seventy-four percent of women had undergone prophylactic oophorectomy and 26% opted for screening. Univariate statistical analyses revealed that BRCA1/2 carriers who opt for oophorectomy are more likely to be older, married, have lower educational levels, be postmenopausal, have poorer perceptions of their general health, be distressed about their ovarian cancer risk, have less favorable cancer risk perceptions, perceive ovarian cancer as a disease that seldom or never can be cured, and perceive more benefits of surgery, as compared to women who choose screening. At the

multivariate level, lower education, poorer general health perceptions, perceived incurability of ovarian cancer, and more perceived benefits of surgery were found to be independent predictors of short-term PBSO uptake. Women opting for screening may lack adequate information on the limited efficacy of screening in early detection of ovarian cancer, and they may not be fully aware of the lethal threat posed by ovarian cancer.

Objective 4: To determine the quality of life effects of prophylactic oophorectomy versus gynecological screening among high-risk women

In this nationwide, cross-sectional, observational study among women at increased hereditary risk of ovarian cancer who sought gynecologic advice for ovarian cancer prevention, 44% had undergone prophylactic oophorectomy and 56% had opted for gynecologic screening. At the time of the quality of life assessment, the oophorectomized group was, on average, 3 years post-surgery, and the screening group had, on average, been undergoing screening for 4 years. All study participants reported high levels of generic quality of life that were not significantly different from those of women in the general Dutch population. Compared to screening, prophylactic oophorectomy was associated with fewer breast/ovarian cancer worries and more favorable cancer risk perceptions, controlling for age, DNA status, parity, history of breast cancer, and prophylactic mastectomy. However, the oophorectomy group reported significantly more menopausal symptoms and worse sexual functioning than the screening group. When choosing the optimal preventive health strategy, the favorable effects of prophylactic surgery in terms of reduced cancer-specific distress and lower perceived cancer risk need to be weighed against an increase in endocrine and sexual symptoms.

Objective 5: To establish the impact of post-surgical hormone replacement therapy (HRT) use on the levels of menopausal symptoms and sexual functioning among younger high-risk women

Although the risk reduction attributed to prophylactic oophorectomy is largest in premenopausal women, the resulting post-operative hormonal imbalance may affect functioning in several health domains. HRT is often prescribed to compensate for post-surgical endocrine deficiencies. In this cross-sectional, observational study, we compared three groups of younger, high-risk women: oophorectomized HRT users and nonusers, and premenopausal women undergoing screening. The oophorectomized women were, on average, 3 years post-surgery, and 47% were using HRT at the time of the questionnaire assessment. HRT users reported significantly fewer vasomotor symptoms than nonusers, controlling for age, tamoxifen use and prophylactic mastectomy. However, oophorectomized HRT users were more likely to report

vasomotor symptoms compared to premenopausal women undergoing screening,. HRT users and nonusers reported comparable levels of sexual functioning. Compared to women in the screening group, oophorectomized HRT users reported significantly more sexual discomfort due to vaginal dryness and dyspareunia. These data suggest that climacteric symptoms after prophylactic oophorectomy may be more severe than those associated with natural menopause, and that HRT may be less effective in alleviating these abrupt symptoms than is often assumed. However, the efficacy of HRT in alleviating surgically-induced menopausal symptoms can only be established in a randomized control trial, Physicians need to provide younger high-risk women considering PBSO with realistic information about both benefits and drawbacks of this preventive strategy, including information about premature menopause and HRT.

8.2 GENERAL DISCUSSION

Assessment of quality of life is increasingly incorporated in clinical research as an important outcome of disease and treatment. Early cancer detection and detection of cancer susceptibility usually imply the necessity of targeted actions, including medical treatment or monitoring. Treatment and monitoring, in turn, are usually associated with both benefits and drawbacks in terms of possible disease outcomes or disease risk, and in terms of quality of life effects.

In this thesis, we have reported a number of studies of the impact of early cancer treatments, either with curative or prophylactic intent, on patients' physical and psychosocial functioning and well-being. The prostate cancer studies included in this thesis were conducted in the context of a large randomized screening trial investigating the efficacy of secondary prevention of prostate cancer. The results reported in this thesis primarily have implications for treatment of localized prostate cancer, and will possibly be used in the evaluations of the screening trial. Ovarian cancer prevention studies were conducted to gain insight into the quality of life effects of the currently available preventive health strategies for hereditary ovarian cancer, with a focus on prophylactic oophorectomy. Such information is needed in clinical practice to facilitate decision making about ovarian cancer prevention.

SCREENING ISSUES

Technological advances have resulted in a number of tests that can be used to detect cancer at an early stage. Many such tests have both screening and diagnostic uses. A screening test is carried out on asymptomatic individuals who are at risk of developing a specific type of cancer. A diagnostic test is carried out when there is clinical suspicion of disease. The rationale behind screening is to detect tumors at an early stage, when they are still curable.

Prostate cancer

Following the discovery of prostate-specific antigen (PSA) and recognition of its clinical utility as a serum marker for prostate cancer, the availability of PSA-testing has made prostate cancer screening a reality for many men. PSA screening followed by prostate biopsy leads to the detection of early prostate cancer in many cases. Through screening three basic groups of patients can be identified: men diagnosed with prostate cancer who would never have had clinically manifest disease during their lifetime (group 1), men diagnosed with curable prostate cancer who, in a regular clinical setting, would likely have been diagnosed with metastatic disease (group 2), and men whose cancer is diagnosed by screening at the same stage as it would have been diagnosed in a regular clinical setting (group 3) [1]. Ideally, screening should be targeted at the identification of the second group of patients only, as these patients are expected to obtain most benefit from early detection. In contrast, the first patient group may experience the potential harm of screening because of overdiagnosis and over-treatment. These men will be labeled as cancer patients, will receive treatment, and will have to live the remainder of their lives with the adverse consequences of the diagnosis and treatment, while experiencing no benefit in terms of extra life years. In the case of group 3, screening is not expected to be associated with any increased benefits or harms.

In the context of the studies presented in this thesis (Chapters 3 and 4), it is unknown to what extent patients from the screening trial were overdiagnosed and/or overtreated. A study by Etzioni et al. reported that, among men with prostate cancer that would be detected only at autopsy, the overdiagnosis rates resulting from screening would be between 15% and 37% [2]. Our study results indicate that patients with screen-detected localized prostate cancer were a fairly fit group, reporting high levels of generic quality of life at baseline and at the follow-up assessments. The levels of their generic quality of life were similar to or even above the sex- and age-adjusted Dutch population norm. They tended to have better perceptions of their own health one year posttreatment than men diagnosed clinically, despite the fact that they experienced comparable levels of treatment-related side effects. However, as a result of screening, some of these men (group 1) received diagnosis and treatment of prostate cancer that might never have become a clinically manifest disease. Urinary, bowel and sexual dysfunction could have been avoided if these men had not been screened or treated. Posttreatment morbidity may also interfere with patients' ability to work. A study by Bradley et al. found that previously employed patients diagnosed with prostate cancer were 10 percent less likely to be working 6 months after diagnosis than men in a non-cancer control group. Among patients who remained employed at 12 months after

diagnosis, up to 30% of patients indicated not being able to perform specific job tasks (usually physically demanding jobs) because of previous cancer treatment [3].

Given the trade-offs involved in the diagnosis and treatment of early prostate cancer via screening, better screening tools are needed to distinguish between aggressive, fast-growing tumors that, when left untreated, would lead to death, and tumors that are slow growing and may not become a significant health problem during the patient's life. At the population level, the ongoing randomized screening trials are likely to soon provide definitive answers to the question whether screening will reduce prostate cancer-specific mortality. Development of optimal screening techniques that minimize overdiagnosis is on-going [1,4].

Ovarian cancer

The currently available screening techniques for ovarian cancer, transvaginal ultrasound (TVU) and CA-125 serology, are also controversial. According to some studies, both techniques lack the sensitivity and specificity that are needed to screen large numbers of women, and currently, there is no evidence that either of these modalities would detect ovarian cancer at an early stage [5]. A recent study by Stirling et al. suggested that annual surveillance by TVU and CA-125 serology in high-risk women is ineffective in detecting tumors at a sufficiently early stage to influence prognosis [6]. Population-based screening for ovarian cancer is currently under evaluation in two large randomized trials in the U.K. and the U.S.. The results of these trials will help shape future policy regarding the value of screening for ovarian cancer in the general population [7].

In current clinical practice, both gynecological screening and prophylactic oophorectomy are offered as preventive management options to women at increased risk of developing the disease [8]. Women who opt for screening are usually younger, and they are less likely to have a history of breast cancer or to have undergone DNA testing for gene mutations than women who undergo prophylactic oophorectomy. For many women at increased risk, gynecologic screening is intended to be a temporary preventive health strategy until they have completed childbearing. Our study results (Chapter 5) indicate that, among BRCA1/2 mutation carriers potentially eligible for prophylactic surgery, use of screening is associated with higher levels of education, favorable general health perceptions, perceptions of ovarian cancer as a curable disease, and low levels of perceived benefits of surgery at the time of initial gynecological consultation. We also found (Chapter 6) that women who undergo screening tend to have higher levels of cancer-specific distress and heightened risk perception, as compared to women who have had prophylactic surgery. These findings are consistent with other studies focused on the quality of life impact of ovarian screening [9-11].

TREATMENT EFFECTS

Prostate cancer

In this thesis, the quality of life effects associated with radical prostatectomy and primary radiotherapy have also been investigated (Chapter 4). The results from our observational study have shown that primary treatment for prostate cancer affects patients' urinary, bowel and sexual functioning during the first year post-treatment. Additionally, patients treated by primary radiotherapy reported decreased levels of generic quality of life after treatment, as compared to patients treated by radical prostatectomy. A recent follow-up study conducted with the same cohort of patients has shown that improvements in urinary, bowel and sexual function are infrequent after the first year post-treatment, and that after that time functional impairments tend to become permanent [12].

Each of the main treatment modalities currently available for localized prostate cancer - radical prostatectomy, primary radiotherapy, brachytherapy, and monitoring – carries with it certain risks. Radical treatments offer the potential for cure, but they may have substantial side-effects, including pain, varying levels of incontinence, sexual dysfunction or bowel problems and, although rarely, death. With monitoring, men have to live with the knowledge that they have untreated cancer and with the risk of progression that in some cases may be fatal [13-15].

In the literature, there are no studies clearly indicating which therapy for localized prostate cancer is the best treatment in terms of oncologic outcomes and the impact on quality of life. Only randomized studies comparing all treatment options and including pretreatment assessments of patients' quality of life can provide a clear answer to that question. The recent results of a randomized study comparing radical prostatectomy with watchful waiting indicate reductions in disease-specific mortality, overall mortality and the risks of metastasis and local progression following surgery [16]. The prostatectomy arm of the study was associated with much higher rates of erectile dysfunction and urinary leakage than the watchful waiting arm, while no significant differences in psychosocial distress and subjective quality of life were observed between the arms [17]. Yet, there are no published data on similar randomized comparisons between radical prostatectomy and irradiation.

A study by Albertsen et al. reported that men with low-grade tumors had minimal risk of dying from prostate cancer during 20 years of follow-up [18]. An earlier observational study of the natural history of prostate cancer also found that many tumors may follow an indolent course for the first 10 to 15 years after diagnosis, but that beyond 15 years the prostate cancer-specific mortality increases rapidly [19]. These results would suggest that, in some cases, aggressive therapy (with its side-effects) might not be necessary in order to attain a favorable life expectancy. Recent

research efforts have been aimed at better understanding the factors underlying possible disease progression in order to develop better diagnostic tools, risk stratification models and effective treatments that would also involve fewer side-effects [4,20].

Prophylactic surgery for ovarian cancer

As there is no evidence that ovarian screening is effective in reducing mortality, it is currently widely accepted that prophylactic surgery is the best form of risk management among women at increased hereditary risk of breast/ovarian cancer [8]. Prophylactic oophorectomy reduces ovarian cancer risk in BRCA1/2 mutation carriers by 96%, and breast cancer risk by 53% [21,22]. The observational studies presented in this thesis (chapters 5 to 7) focus on the factors predicting the uptake of prophylactic oophorectomy among younger high-risk women, the quality of life effects associated with prophylactic surgery, and on the impact of post-surgical use of hormone replacement therapy and its effects on menopausal symptoms among younger high-risk women.

Women with BRCA1/2 gene mutations who have completed their childbearing are strong candidates for prophylactic oophorectomy, and they usually receive advice to undergo prophylactic surgery. During the 12-month follow-up period in our study, almost three-quarters of the sample had undergone prophylactic oophorectomy. Women with lower educational levels, with poorer general health perceptions, those who view ovarian cancer as an incurable disease, or those who believe more strongly in the benefits of surgery are more likely to undergo oophorectomy. All of these associations were in the expected direction, with the exception of education. We do not know why lower educational levels were predictive for use of surgery. This finding seems counterintuitive, since better educated women had higher levels of knowledge about hereditary issues. However, the knowledge scale that we used was not a standardized measure, and it did not focus explicitly on ovarian cancer as a disease. Furthermore, perceptions of the curability of ovarian cancer were not significantly associated with education and the knowledge of hereditary issues. This latter finding would suggest that emotional rather than cognitive factors may underlie beliefs about the curability of ovarian cancer. It may also be that women with lower educational levels are more inclined to adhere to their doctor's advice, without exploring the possible consequences of surgery in the short run. Conversely, more highly educated women may include a wider range of considerations (e.g., desire to delay onset of menopausal symptoms, realization that each year of delay brings with it a relatively small increase in cancer risk) when deciding on whether to undergo prophylactic surgery. We were unable to compare our results regarding the association between education and choice of preventive strategy with those of other studies, because earlier investigations were conducted primarily among college educated women, e.g., [23,24].

Future, qualitative (e.g., interview-based) investigations are needed to better understand the association between education and choice of preventive strategy.

Risk-reducing oophorectomy has both favorable and unfavorable quality of life effects. Surgery does not appear to have any significant impact on generic quality of life; it is associated with reduced cancer-specific distress and lower perceived risk of cancer. Unfavorable effects include a significant increase in endocrine and sexual symptoms. Although hormone replacement therapy (HRT) has a positive impact on surgically-induced vasomotor symptoms, it may be less effective than is often assumed. Symptom levels in oophorectomized HRT users remain well above those of premenopausal women undergoing screening, and sexual discomfort is not alleviated by HRT. Randomized studies are needed to determine the efficacy of HRT and testosterone supplementation in alleviating menopausal symptoms following prophylactic oophorectomy. Also, the role of non-hormonal medical treatments and psychosocial interventions to manage climacteric complaints should be further explored. Ganz et al. have demonstrated that psychosocial interventions in combination with non-hormonal medications are a viable alternative to HRT among older breast cancer survivors suffering from menopausal symptoms [25]. Possibly, younger oophorectomized women may also benefit from such interventions. A randomized intervention study will be soon initiated at the Netherlands Cancer Institute to evaluate the efficacy of a supportive intervention program in alleviating menopausal symptoms, improving sexual functioning and enhancing the quality of life of younger women with breast cancer who have become prematurely menopausal as a result of their treatment.

To our knowledge, our investigation of the psychosocial impact of screening versus preventive surgery among women at heightened risk of developing ovarian cancer is the largest cross-sectional study to date. We have also recently completed a prospective, observational study that will provide additional information about changes in quality of life and symptom experience over time.

In the case of both early prostate cancer detection and treatment, and hereditary ovarian prevention, medical decisions are complex because the evidence on outcomes is uncertain and each preventive health option carries with it different risks and benefits. Clinicians and other health care providers need to provide their patients with unbiased estimates of the risks, benefits and limitations associated with current screening and treatment options, so that they can make informed decisions that reflect both an understanding of the issues involved and the personal values that underlie such decisions.

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SUMMARY

Cancer prevention and control have become important challenges for public health, since cancer is a major cause of mortality and morbidity in the industrialized world. Screening for disease is increasingly being introduced as an integral part of medical practice. Population-based screening programs have already been introduced for some prevalent malignancies (e.g. breast cancer), or are still in the process of development (e.g., prostate cancer). Research efforts have also focused on understanding susceptibility to different types of cancers. The identification of risk factors facilitates defining groups of high-risk individuals who would benefit most from preventive programs. In the case of some cancers, e.g., breast and ovarian cancer, epidemiologic research has identified a positive family history as an important risk factor for developing the disease. By means of DNA tests, key gene mutations can be detected that are known to be responsible for increased risk of developing the disease. In the context of breast/ovarian cancer, women from hereditary breast/ovarian cancer families (HBOC) may undergo DNA testing, and they may opt for different preventive health measures targeted either at cancer risk reduction or early cancer detection.

Preventive health strategies, including screening and early medical treatments, either with prophylactic or curative intention, may substantially affect patients' quality of life (QOL; defined as patients' functioning in the physical, psychological and social domains of health). This thesis presents two large investigations focusing on the QOL issues in cancer prevention and control, using the examples of two gender-specific cancers -- prostate and ovarian cancer -- that are among the leading causes of death in Europe and in the United States.

Prostate cancer is the most common malignancy, and the second leading cause of cancer death in men in Western countries. Early-stage prostate cancer is usually a-symptomatic, and it can be detected by means of prostate-specific antigen (PSA) testing. Since the 1980's, PSA testing has been widely applied in medical practice, resulting in a higher prevalence of prostate cancer. PSA testing may lead to overdiagnosis, i.e., detection of indolent cases of prostate cancer that would never have been diagnosed in the absence of such a diagnostic technique. Overdiagnosis often carries with it the risk of the overtreatment of slow-growing tumors that might not ever become of clinical significance during the patient's life. Radical prostatectomy and primary radiotherapy are the most common treatment modalities for localized prostate cancer. Although primary treatment is potentially curative, it may result in side-effects and impairment of QOL.

Ovarian cancer is the fourth most frequent cause of cancer death and the most lethal of all gynecologic tumors in women in Northern and Western Europe. Ovarian cancer remains a fatal disease for most women, due to its advanced stages at diagnosis. Women who carry a BRCA 1/2 gene mutation have at least a 10-fold higher risk of developing ovarian cancer than women in the general population. In the Netherlands,

women from hereditary breast/ovarian (HBOC) cancer families have access to genetic counseling, including DNA testing, and they are offered gynecological health care services focused on ovarian cancer prevention. Principal preventive health strategies include periodic gynecological screening and prophylactic bilateral salpingo-oophorectomy. Preventive health strategies may affect women's physical and psychosocial functioning.

The focus of this thesis is on the psychosocial issues, including QOL, involved in the evaluation of early-detected and early-treated prostate cancer among men in the general population (Part I), and in the evaluation of preventive health strategies for ovarian cancer among women at increased hereditary risk of developing the disease (Part II). The main objectives of this thesis are:

1. To evaluate pretreatment quality of life among patients with localized prostate cancer detected by a population-based screening or in a regular clinical setting.
2. To determine the quality of life effects of primary treatment for localized prostate cancer detected by a population-based screening or in a regular clinical setting.
3. To identify psychosocial and clinical factors predicting use of prophylactic surgery versus gynecological screening among women with hereditary susceptibility for breast/ovarian cancer.
4. To determine the quality of life effects of prophylactic oophorectomy versus gynecological screening among high-risk women.
5. To establish the impact of post-surgical hormone replacement therapy (HRT) use on the levels of menopausal symptoms and sexual functioning among younger high-risk women.

Chapter 2 (Part I) describes the role of quality of life and cost-effectiveness studies within the framework of the two large population-based randomized screening trials in Europe and in the United States, respectively the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colon and Ovary (PLCO) trial. These randomized trials have been investigating if early detection of prostate cancer by screening and consequent earlier treatment lead to reduced disease-specific mortality. A population-based prostate cancer screening program can only be introduced if the findings from both trials indicate substantial reductions in disease-specific mortality as a result of early prostate cancer detection, followed by earlier treatment. Other important conditions for the introduction of such a program relate to costs and QOL effects. When the data on cancer-specific mortality reductions are available, cost per life year gained can be determined, using cost-effectiveness analyses. Both randomized trials have incorporated prospective studies of QOL and cost-effectiveness to provide relevant data for cost-effectiveness analyses.

Chapters 3 and 4 are based on a prospective cohort study conducted among men with localized prostate cancer, within the framework of the ERSPC trial. Pretreatment QOL (Chapter 3) is evaluated in relation to the type of prostate cancer diagnosis and of the subsequent primary treatment. Two hundred patients with newly diagnosed localized (screen-detected or clinically diagnosed) prostate cancer completed QOL questionnaires consisting of generic and disease-specific measures). As expected, patients from screening were more likely to have localized prostate cancer, compared to men diagnosed in a clinical setting. Among men with localized disease, 62% received primary radiotherapy, and 38% of the group underwent radical prostatectomy. Overall, patients with localized, screen-detected prostate cancer reported better levels of generic quality of life than did similar men with clinically diagnosed disease. However, the scores for generic quality of life (SF-36) of both groups were not significantly different from those of the sex- and age-adjusted general population norm. Men with screen-detected and clinically diagnosed prostate cancer reported comparable levels of urinary, bowel and sexual problems before treatment. Considering the type of subsequent primary treatment, men who were to undergo primary radiotherapy were more likely to have lower levels of generic quality of life at baseline, as compared to men in the prostatectomy group. Overall, urinary, bowel and sexual problems were rather uncommon among men awaiting primary treatment, however, approximately one-third of men reported not-being sexually active prior to prostate cancer diagnosis. The baseline differences in QOL between men who were to undergo surgery versus radiotherapy could not be explained by tumor characteristics or the type of cancer detection. The findings reflect the situation in clinical practice, where only those patients in reasonably good condition and who can withstand a relatively long period of general anesthesia are recommended to undergo a radical prostatectomy.

Chapter 4 investigates the QOL effects induced by radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed prostate cancer. We conducted a prospective longitudinal cohort study among 278 patients with early, screen-detected (59%) or clinically diagnosed (41%) prostate cancer, using both generic and disease-specific QOL measures at three points in time: t1 (baseline shortly after diagnosis), t2 (6 months later) and t3 (12 months after baseline). Men who underwent surgery were, on average, five years younger than men treated by irradiation. Analyses (adjusted for age and pretreatment level of functioning) revealed poorer levels of generic QOL after radiotherapy. Patients with screen-detected and clinically diagnosed cancer reported comparable levels of posttreatment QOL. However, the screening group tended to have better perceptions of their general health after primary treatment. The posttreatment levels of QOL in patients with clinically diagnosed or screen-detected prostate cancer were not below the general population norm, adjusted for sex and age. Regarding urinary, bowel and sexual functioning,

prostatectomy patients reported significantly higher posttreatment incidences of urinary incontinence (39%-49%), and erectile dysfunction (80%-91%) than radiotherapy patients (respectively, 6%-7% and 41%-55%). Bowel problems (urgency) affected 30%-35% of the radiotherapy group versus 6%-7% of the prostatectomy group. Decreased levels of urinary, bowel and sexual functioning after treatment were not related to the method of cancer detection. In line with other studies, we found that the types of QOL problems reported during the first year after treatment differed as a function of treatment. Radical prostatectomy affected urinary and sexual functioning, while primary radiotherapy was mainly associated with bowel problems, and to a lesser degree with sexual dysfunction. Because the QOL effects may be valued differently at the individual level, patients should be made fully aware of the potential benefits and adverse consequences of therapies for early prostate cancer.

Part II of the thesis (Chapters 5 to 7) comprises the studies investigating the impact of ovarian cancer prevention on psychosocial health and symptom experience, including quality of life, among women at hereditary risk of developing ovarian cancer. Women from hereditary breast/ovarian cancer families may opt either for periodic gynecological screening or prophylactic salpingo-oophorectomy to manage their cancer risk. Prophylactic surgery is usually recommended as a treatment option for women who carry BRCA1/2 mutations and have completed their childbearing. In our prospective, observational study among 160 BRCA1/2 carriers (Chapter 5), we investigated which baseline factors were associated with use of prophylactic surgery. Seventy-four percent of women had undergone prophylactic salpingo-oophorectomy and 26% opted for gynecologic screening during a 12-month follow-up. Univariate statistical analyses revealed that BRCA1/2 carriers who opt for prophylactic surgery are more likely to be older, married, have lower educational levels, be postmenopausal, have poorer perceptions of their general health, be distressed about their ovarian cancer risk, have less favorable cancer risk perceptions, perceive ovarian cancer as a disease that seldom or never can be cured, and perceive more benefits of surgery, as compared to women who choose screening. At the multivariate level, lower education, poorer general health perceptions, perceived incurability of ovarian cancer, and more perceived benefits of surgery were found to be independent predictors of short-term use of prophylactic salpingo-oophorectomy. Women opting for screening may lack adequate information on the limited efficacy of screening in early detection of ovarian cancer, and they may not be fully aware of the lethal threat posed by ovarian cancer.

Chapter 6 presents the quality of life effects associated with prophylactic bilateral salpingo-oophorectomy versus periodic gynecologic screening. We conducted a nationwide, cross-sectional, observational study among women at increased risk of developing ovarian cancer who sought gynecologic advice for ovarian cancer prevention. Questionnaire data were obtained from 846 high-risk women who had

participated in the study. Forty-four percent of women had undergone prophylactic salpingo-oophorectomy and 56% had opted for gynecologic screening. Topics addressed by the questionnaire included generic QOL, cancer specific distress, endocrine symptoms and sexual functioning. At the time of the QOL assessment, the oophorectomized group was, on average, three years post-surgery, and the screening group had, on average, been undergoing screening for four years. All study participants reported high levels of generic QOL that were not significantly different from those of women in the general Dutch population. Compared to screening, prophylactic salpingo-oophorectomy was associated with fewer breast/ovarian cancer worries and more favorable cancer risk perceptions, controlling for age, DNA status, parity, history of breast cancer, and prophylactic mastectomy. However, the oophorectomy group reported significantly more menopausal symptoms and worse sexual functioning than the screening group. Prophylactic salpingo-oophorectomy had no measurable adverse impact on generic QOL of high-risk women. The favorable effects of prophylactic surgery in terms of reduced cancer worries and low perceived cancer risk need to be weighed against increase in endocrine and sexual symptoms. Balanced information will help clinicians and high-risk women to make informed decisions about the optimal preventive health strategy.

Side-effects associated with prophylactic salpingo-oophorectomy in premenopausal women include loss of fertility, immediate onset of menopause with vasomotor and urogenital symptoms, and a decline in sexual interest and activity. Hormone replacement therapy (HRT) is often prescribed to compensate for post-surgical endocrine deficiencies. The study presented in Chapter 7 examined the impact of HRT use on levels of endocrine symptoms and sexual functioning among premenopausal women who had undergone prophylactic salpingo-oophorectomy. In this cross-sectional, observational study among 450 high-risk women, we compared three groups of women: oophorectomized HRT users and nonusers, and premenopausal women undergoing screening. The oophorectomized women were, on average, three years post-surgery, and 47% of them were using HRT at the time of the questionnaire assessment. HRT users reported significantly fewer vasomotor symptoms than nonusers, controlling for age, tamoxifen use and prophylactic mastectomy. However, oophorectomized HRT users were more likely to report vasomotor symptoms compared to premenopausal women undergoing screening. All oophorectomized women reported comparable levels of sexual functioning. Compared to women in the screening group, oophorectomized HRT users reported significantly more sexual discomfort due to vaginal dryness and dyspareunia. Although HRT has a positive impact on surgically-induced vasomotor symptoms, it may be less effective than is often assumed. Symptom levels remain well above those of premenopausal women undergoing screening, and sexual discomfort is not alleviated by HRT. The efficacy of

HRT in alleviating surgically-induced menopausal symptoms can only be established in a randomized control trial. Physicians need to provide younger high-risk women considering prophylactic salpingo-oophorectomy with realistic information about both benefits and drawbacks of this preventive strategy, including information about premature menopause and HRT.

Finally, Chapter 8 presents the most important findings from the current studies in the context of the research objectives listed in the general introduction. It also provides a general discussion of these findings. Early cancer detection and detection of cancer susceptibility usually imply the necessity of targeted actions, including medical treatment or monitoring. Treatment and monitoring, in turn, are usually associated with both benefits and drawbacks in terms of possible disease outcomes or disease risk, and in terms of QOL effects. The rationale behind screening is to detect tumors at an early stage, when they are still curable. Screening tests in prostate and ovarian cancers have a different status regarding early cancer detection. While screening by PSA testing has lead to a substantial increase in detection of early-stage prostate cancer, the efficacy of the currently available screening techniques for ovarian cancer is still uncertain. Screening may lead to overdiagnosis and overtreatment, on one hand. On the other hand, some clinically relevant cancers can be missed and remain untreated.

Each of the main treatment modalities currently available for localized prostate cancer - radical prostatectomy, primary radiotherapy, brachytherapy, and monitoring – carries with it certain risks. Radical treatments offer the potential for cure, but they may have substantial side-effects, including pain, varying levels of incontinence, sexual dysfunction or bowel problems. With monitoring, men have to live with the knowledge that they have untreated cancer and with the risk of progression that in some cases may be fatal. In the literature, there are no studies clearly indicating which therapy for localized prostate cancer is the best treatment in terms of oncologic outcomes and the impact on quality of life. Especially, a randomized comparison between radical prostatectomy and irradiation is needed. Recent research efforts have been aimed at better understanding the factors underlying possible disease progression in order to develop better diagnostic tools, risk stratification models and effective treatments that would also involve fewer side-effects.

Risk-reducing prophylactic salpingo-oophorectomy does not lead to any measurable impairment of generic QOL. Surgery is associated with reduced cancer-specific distress and lower perceived risk of cancer. Unfavorable effects include a significant increase in endocrine and sexual symptoms, and not all the symptoms are alleviated by use of HRT. Randomized studies are needed to determine the efficacy of HRT and testosterone supplementation in alleviating surgically-induced menopausal symptoms. Also, the role of non-hormonal medical treatments and psychosocial

interventions to manage climacteric complaints should be further explored, since they may be effective in symptom control.

In the case of both early prostate cancer detection and treatment, and hereditary ovarian prevention, medical decisions are complex, because each preventive health option carries with it different risks and benefits. Clinicians and other health care providers need to provide their patients with unbiased estimates of the risks, benefits and limitations associated with current screening and treatment options, so that they can make informed decisions that reflect understanding of the issues involved and the personal values that underlie such decisions.

SUMMARY IN DUTCH

(Samenvatting)

Kankerpreventie is een grote uitdaging geworden in het veld van de gezondheidszorg, omdat kanker een belangrijke oorzaak is van de mortaliteit en morbiditeit in de Westerse landen. Vroege opsporing van kanker maakt in een toenemende mate deel uit van de medische praktijk. Bevolkingsonderzoek is reeds ingevoerd om sommige prevalente maligniteiten vroegtijdig te kunnen opsporen en behandelen, bijv. borstkanker. Voor andere vaak voorkomende kankers, bijv. prostaat-kanker, wordt er gewerkt aan de ontwikkeling van bevolkingsonderzoek. Wetenschappelijk onderzoek heeft zich ook gericht op het doorgronden van een aanleg voor kanker en van risicofactoren die een belangrijke rol spelen bij het ontstaan van bepaalde tumoren. Op basis daarvan zouden groepen van individuen kunnen worden gedefinieerd die een verhoogd risico lopen om de ziekte te ontwikkelen. Epidemiologisch onderzoek heeft uitgewezen dat in het geval van sommige kankers, bijv. borst-/eierstokkanker, het vóórkomen van deze kanker in de familie een belangrijke risicofactor is. Door middel van een DNA-test kunnen mutaties worden opgespoord, waarvan het bekend is dat ze gepaard gaan met een verhoogd risico. Vrouwen afkomstig uit families, waarin vaak borst-/eierstokkanker voorkomt, kunnen voorspellend DNA-onderzoek ondergaan en eventueel voor preventieve maatregelen kiezen. Deze maatregelen zijn gericht op risicoreductie of op de vroege opsporing van een tumor.

De preventieve maatregelen, vroege opsporing van de tumor en vroege medische behandelingen, die een profylactisch of curatief doel hebben, kunnen van invloed zijn op de kwaliteit van leven (KvL) van patiënten (KvL wordt hier gedefinieerd als fysiek, psychologisch en sociaal functioneren van patiënten in relatie tot ziekte en/of behandeling). Dit proefschrift richt zicht op de KvL-effecten van curatieve en profylactische behandelingen, respectievelijk voor prostaat- en eierstokkanker. Deze geslachtsspecifieke kankers behoren tot de hoofdoorzaken van kankersterfte in Europa en in de Verenigde Staten.

Prostaatkanker is de meest prevalente kanker bij mannen en de tweede oorzaak van kankersterfte bij mannen in Westerse landen. Vroege prostaatkanker geeft meestal geen klachten en kan worden ontdekt door te testen op het prostaat-specifieke antigen (PSA). Sinds de jaren tachtig van de vorige eeuw, worden PSA-tests op grote schaal toegepast in de medische praktijk, hetgeen tot hogere prevalentiecijfers van prostaatkanker heeft geleid. Het testen op PSA kan mogelijkerwijs tot overdiagnose en overbehandeling leiden, d.w.z. tot opsporing en behandeling van langzaam groeiende tumoren die zonder deze techniek niet gediagnosticeerd zouden worden en die nooit als ziekte manifest tijdens het leven van de patiënt zouden worden. Gelokaliseerde prostaatkanker wordt vaak behandeld door radicale prostatectomie (operatieve verwijdering van de prostaat) of primaire radiotherapie. Deze behandelingen zijn in

principe curatief van aard. Ze gaan echter vaak gepaard met bijeffecten en kunnen ook van invloed zijn op de KvL van patiënten.

Eierstokkanker is de vierde oorzaak van kankersterfte in Noord en West Europa en is de meest dodelijke kanker onder alle gynaecologische maligniteiten. De meeste patiënten overlijden aan deze ziekte, omdat eierstokkanker vaak in een vrij laat stadium wordt ontdekt. Vrouwen die een BRCA1/2-mutatie dragen, hebben minstens een tienvoudig hoger risico om eierstokkanker te ontwikkelen dan vrouwen in de algemene populatie. Vrouwen met een familiare belasting op eierstokkanker hebben in Nederland toegang tot genetische counseling (inclusief DNA-onderzoek) en tot de gynaecologische zorg gericht op de preventie van erfelijke eierstokkanker.

Deel I van dit proefschrift richt zich op het bestuderen van KvL-effecten van vroege prostaatkanker en de behandelingen bij mannen die afkomstig zijn uit de algemene populatie. Deel II van het proefschrift heeft betrekking op de populatie van vrouwen met een verhoogd familiair risico op borst-/eierstokkanker, waarbij de psychosociale en KvL-effecten van de periodieke gynaecologische screening en profylactische eierstokverwijdering worden geëvalueerd. De belangrijkste doel-stellingen van het proefschrift zijn:

1. Het bestuderen van de KvL van patiënten met gelokaliseerde prostaatkanker, kort na de diagnose en voorafgaand aan de primaire behandeling, gedifferentieerd naar het type diagnose (gediagnosticeerd door de screening of in de reguliere medische zorg) en het type van de primaire behandeling.
2. Het vaststellen van de effecten van de primaire behandeling (radicale prostatectomie versus primaire radiotherapie) van gelokaliseerde prostaatkanker op de KvL van patiënten.
3. Het in kaart brengen van de psychosociale en klinische factoren die op korte termijn een rol spelen bij het ondergaan van profylactische eierstokverwijdering en de gynaecologische screening door vrouwen met een verhoogd erfelijk risico op borst-/eierstokkanker.
4. Het vaststellen van de effecten van profylactische eierstokverwijdering en de gynaecologische screening op de KvL van vrouwen met een verhoogd erfelijk risico op borst-/eierstokkanker.
5. Het bepalen van de invloed van postoperatieve hormoonsuppletie op overgangsklachten en het seksueel functioneren bij jongere vrouwen met een verhoogd erfelijk risico op borst-/eierstokkanker die een profylactische eierstokverwijdering hebben ondergaan.

Hoofdstuk 2 (Deel I) beschrijft de rol van KvL- en kosten-effectiviteitsstudies in twee grote gerandomiseerde prostaatkankerstudies in Europa en in de V.S., respectievelijk de ERSPC- en PLCO-studie. Deze studies onderzoeken of de vroege opsporing van prostaatkanker door de screening en het eerder behandelen van

prostaatkanker leiden tot een reductie in de ziekte-specifieke sterfte. Een aanzienlijke reductie van de ziekte-specifieke sterfte is de noodzakelijke voorwaarde voor de implementatie van bevolkingsonderzoek op prostaatkanker. De andere belangrijke voorwaarden hebben betrekking op de kosten en KvL. Gegeven dat een aanzienlijke reductie van sterfte is aangetoond, kunnen de kosten per gewonnen levensjaar, gecorrigeerd voor de KvL-effecten, worden berekend. Om de beschikking te hebben over de relevante data voor de kosten-effectiviteitsanalyses zijn in de ERSPC- en PLCO-studies aparte prospectieve zijstudies opgenomen die de KvL-effecten en de kosten hebben onderzocht.

Hoofdstukken 3 en 4 zijn gebaseerd op een prospectieve cohortstudie die uitgevoerd is bij mannen met gelokaliseerde prostaatkanker. Hoofdstuk 3 beschrijft de KvL van mannen voorafgaand aan de primaire behandeling voor gelokaliseerde prostaatkanker, afhankelijk van het type diagnose (kanker ontdekt door de screening of klinisch gediagnosticeerd) en het type behandeling (radicale prostatectomie of primaire radiotherapie). Tweehonderd patiënten met de recente diagnose prostaatkanker hebben een vragenlijst ingevuld, waarin de algemene en ziekte-specifieke KvL-maten zijn opgenomen. Zoals verwacht, was gelokaliseerde prostaatkanker in de screeningsgroep vaker vastgesteld dan in de klinische groep. In de totale groep van mannen met gelokaliseerde prostaatkanker, zijn 62% behandeld d.m.v. primaire radiotherapie en zijn 38% geopereerd. In het algemeen rapporteerden mannen afkomstig uit de screening betere algemene KvL dan mannen die in de reguliere medische zorg waren gediagnosticeerd. De scores van beide groepen waren echter niet-significant verschillend van de algemene populatienorm. De screenings- en klinische groepen verschilden niet in de mate van plas-, darm- en seksuele klachten vóór de behandeling. Met het oog op de latere primaire behandeling, bleken mannen die radiotherapie ondergingen, op ‘baseline’ lagere algemene KvL te hebben, dan mannen die later werden geopereerd. Plas-, darm- en seksuele klachten kwamen zelden voor, en beide groepen rapporteerden een vergelijkbaar niveau van deze klachten. Ongeveer een derde van alle mannen was niet-seksueel actief vóór de diagnose. De ‘baseline’ verschillen in de KvL tussen de latere primaire behandelingsgroepen kunnen niet worden verklaard door de tumorkenmerken of door de wijze waarop prostaatkanker is ontdekt. Onze bevindingen weerspiegelen de gang van zaken in de medische praktijk: alleen mannen die een goede algemene conditie hebben en die zonder problemen algehele anesthesie kunnen doorstaan, worden verwezen naar de radicale prostatectomie.

In hoofdstuk 4 zijn de resultaten beschreven van een studie naar de invloed van radicale prostatectomie en primaire radiotherapie op de algemene en ziekte-specifieke KvL van patiënten. Om deze gevolgen te meten is een prospectieve, longitudinale studie uitgevoerd onder 278 patiënten met recentelijk gediagnosticeerde gelokaliseerde prostaatkanker. Negenenvijftig procent van de mannen kwam uit de screening en 41%

was gediagnosticeerd in de reguliere medische praktijk. De KvL-metingen zijn op drie momenten verricht: kort na de diagnose (t1), 6 maanden later (t2) en 12 maanden na t1. De geopereerde mannen waren gemiddeld 5 jaar jonger dan mannen die met radiotherapie zijn behandeld. Statistische analyses, gecorrigeerd voor verschillen in leeftijd en het niveau van het functioneren vóór behandeling, lieten zien dat na de behandeling de bestraalde groep slechtere algemene KvL had dan de geopereerde groep. Wat algemene KvL betreft, zijn geen significante verschillen gevonden tussen mannen die uit de screening afkomstig waren, en die uit de reguliere medische zorg. Mannen uit de screening waren meer geneigd om na de behandeling hun eigen algemene gezondheid als beter waar te nemen, dan de tweede groep.

In het eerste jaar na behandeling, kwamen plas- en seksuele klachten vaker voor na radicale prostatectomie. Primaire radiotherapie ging voornamelijk gepaard met darmklachten en in mindere mate met een slechter seksueel functioneren. Incontinentie werd gerapporteerd door 39% - 49% van de geopereerde mannen en door 6%-7% van de bestraalde mannen. Tussen de 80% en 91% van de geopereerde mannen ondervonden erectieproblemen, tegenover 41% - 55% van de bestraalde mannen. De incidentie van darmklachten was na radiotherapie 30%-35%, en 6%-7% na radicale prostatectomie. Functionele klachten na behandeling waren niet gerelateerd aan het type prostaatkankerdiagnose. De bijeffecten van radicale prostatectomie en primaire radiotherapie en de last die deze bijeffecten kunnen veroorzaken, kunnen verschillend door iedere patiënt worden beoordeeld. Bij een afweging tussen prostatectomie en radiotherapie, moeten patiënten volledig op de hoogte zijn gesteld van deze bijeffecten van de behandelingen voor vroege prostaatkanker.

Deel II van het proefschrift (hoofdstukken 5 – 7) beschrijft de studies die gaan over psychosociale en KvL-effecten van de preventie van eierstokkanker bij vrouwen met een verhoogd erfelijk risico op deze ziekte. De preventieve maatregelen bestaan uit periodieke gynaecologische screening (gynaecologisch onderzoek, een echo van de eierstokken en CA-125 bloedonderzoek) en/of profylactische salpingo-ovariëctomie (operatieve verwijdering van beide eierstokken en eileiders). Profylactische chirurgie wordt meestal geadviseerd bij vrouwen met een BRCA1/2-mutatie, die geen kinderwens (meer) hebben. In een prospectieve, observationele studie onder 160 vrouwen met BRCA1/2 (hoofdstuk 5), is onderzocht welke ‘baseline’ factoren het gebruik van profylactische eierstokverwijdering kunnen voorspellen. Tijdens een follow-up van 12 maanden, waren er 74% vrouwen profylactisch geopereerd en 26% vrouwen ondergingen de screening. Univariate statistische analyses hebben laten zien dat, vergeleken met de screeningsgroep, vrouwen die een profylactische operatie ondergingen meer kans hadden om ouder, getrouwd, lager opgeleid en reeds in de overgang te zijn. Deze vrouwen hadden ook een slechtere perceptie van hun eigen algemene gezondheid, waren meer bezorgd over het risico op kanker, vonden dat

eierstokkanker zelden of nooit genezen kon worden en zagen meer voordelen van profylactische chirurgie. Op een multivariaat niveau bleken de volgende variabelen de beste onafhankelijke voorspellers te zijn van het gebruik van profylactische eierstokverwijdering op korte termijn: lagere opleiding, slechtere perceptie van eigen gezondheid, perceptie dat eierstokkanker zelden of nooit genezen kan worden en meer waargenomen voordelen van de profylactische chirurgie. BRCA1/2 mutatiedragers die voor de gynaecologische screening kiezen als een preventieve maatregel voor eierstokkanker, zijn zich mogelijkerwijs niet bewust van de beperkingen van de beschikbare screeningstechnieken in vroegtijdige opsporing van eierstokkanker, en van de aard van de ziekte die zelden genezen kan worden.

In hoofdstuk 6 worden de KvL-effecten van profylactische eierstok-verwijdering en de gynaecologische screening onderzocht. In deze landelijke, cross-sectionele en observationele studie participeerden 846 vrouwen met een verhoogd risico op borst-/eierstokkanker die in de afgelopen 5 jaar preventie voor eierstokkanker zochten. Vierenveertig procent van deze vrouwen onderging profylactische eierstokverwijdering en 56% koos voor de gynaecologische screening. Deze vrouwen vulden een vragenlijst in, waarin vragen waren opgenomen over algemene KvL, kanker-specifieke distress, endocriene symptomen en seksueel functioneren. Geopereerde vrouwen waren gemiddeld 3 jaar jonger dan gescreende vrouwen en ze waren gemiddeld 3 geleden geopereerd. De gescreende vrouwen ondergingen de screening gemiddeld gedurende 4 jaar. Alle respondenten rapporteerden een hoog niveau van algemene KvL, dat niet significant verschilde van de algemene Nederlandse populatienorm. Vergeleken met de screening, was profylactische eierstokverwijdering sterker gerelateerd aan minder zorgen over borst-/eierstokkanker en een betere perceptie van het risico op kanker. De bijeffecten van profylactische eierstokver-wijdering waren voornamelijk vervroegde overgangsklachten en een slechter seksueel functioneren. Er is geen nadelige invloed gemeten van de operatie op de algemene KvL. Bij het beoordelen van profylactische eierstokverwijdering moeten de gunstige psychosociale effecten, zoals zich minder zorgen maken over het krijgen van kanker en een betere risicoperceptie, worden afgewogen tegenover een toename aan endocriene en seksuele problemen. De informatie over de positieve en negatieve effecten van beide preventieve maatregelen is onmisbaar voor de betrokken artsen en vrouwen om de juiste afweging te maken bij het kiezen van de meest optimale preventieve maatregelen.

Een tekort aan vrouwelijke hormonen die als gevolg van profylactische eierstokverwijdering kan optreden, leidt tot het verlies van vruchtbaarheid en acute overgangsklachten, zoals opvliegers, overmatige transpiratie, plas- en seksuele klachten. Om deze klachten te verlichten wordt vaak na de operatie hormoonsuppletie voorgeschreven. Hoofdstuk 7 beschrijft een studie, waarin de overgangs- en seksuele problemen zijn geïnventariseerd van jongere vrouwen in relatie tot hun hormonale

status. In deze cross-sectionele en observationele studie onder 450 vrouwen hebben we drie groepen onderling vergeleken: 1) geopereerde vrouwen die premenopauzaal waren ten tijde van de operatie en hormoonsuppletie na de operatie gebruikten, 2) geopereerde, premenopauzale vrouwen die geen hormoonsuppletie na de operatie gebruikten en 3) premenopauzale vrouwen die de gynaecologische screening ondergingen. Geopereerde vrouwen hadden gemiddeld 3 jaar eerder een profylactische eierstokverwijdering ondergaan, en 47% van deze groep gebruikte hormoonsuppletie ten tijde van het invullen van de vragenlijst. Hoewel hormoongebruikers significant minder vasomotore klachten (bijv. opvliegers) dan niet-gebruikers rapporteerden (de analyses waren gecontroleerd voor verschillen in leeftijd, gebruik van tamoxifen en profylactische borstverwijdering in het verleden), waren deze klachten significant vaker aanwezig in de eerste groep dan bij premenopauzale vrouwen die de screening ondergingen. Gebruik van hormoonsuppletie was niet van invloed op het niveau van seksueel functioneren en geopereerde vrouwen rapporteerden vaker ongemak bij seksuele activiteiten (bijv. vaginale droogheid en pijnlijke geslachtsgemeenschap). Hormoonsuppletie heeft een positieve invloed op vasomotore klachten, maar deze is mogelijkerwijs minder effectief bij het bestrijden van andere klachten die als gevolg van chirurgische menopauze kunnen optreden. De prevalentie van overgangsklachten is ondanks hormoonsuppletie aanzienlijk hoger bij geopereerde vrouwen dan bij premenopauzale vrouwen in de screeningsgroep. De effectiviteit van hormoonsuppletie bij het bestrijden van klachten gerelateerd aan chirurgische menopauze kan alleen met zekerheid worden vastgesteld in een gerandomiseerd klinisch onderzoek.

In hoofdstuk 8 worden in het kort de belangrijkste bevindingen uit de eerder beschreven studies gepresenteerd in de context van de doelstellingen van het proefschrift. Vervolgens worden deze bevindingen besproken in het licht van recente literatuur. Vroege ontdekking van kanker of ontdekking van een aanleg voor kanker leidt meestal tot gericht medisch handelen, zoals het instellen van vroege medische behandelingen en/of regelmatige medische controle. Medische behandelingen en controle kunnen beide tot zowel positieve als negatieve effecten leiden in termen van de beheersing van het ziekteverloop en de invloed op de KvL. Screening heeft tot doel om tumoren in een vroeg stadium te ontdekken, omdat in een vroeg stadium nog curatieve behandeling mogelijk is. Screeningsmethoden voor prostaat- en eierstokkanker hebben geen gelijke status in termen van vroege opsporing van kanker. Terwijl het testen op PSA leidt tot een toegenomen incidentie van vroege prostaatkanker, is de effectiviteit van de huidige beschikbare screeningstechnieken voor eierstokkanker nog niet bewezen. Enerzijds kan screening leiden tot overdiagnose en overbehandeling met alle negatieve gevolgen van dien. Anderzijds kunnen klinisch relevante tumoren gemist worden en daardoor mogelijke curatieve behandelingen niet worden toegepast.

De momenteel beschikbare primaire behandelingen voor prostaatkanker (radicale prostatectomie, primaire radiotherapie en brachytherapie) hebben bijeffecten, zoals pijn, incontinentie, seksuele dysfunctie en darmproblemen. Patiënten met gelokaliseerde prostaatkanker die uitsluitend voor periodieke controle kiezen, kunnen ook nadelen van deze benadering ervaren. Ze leven immers met de wetenschap kanker te hebben die niet behandeld wordt en die zich nog verder kan ontwikkelen, in sommige gevallen zelfs met een dodelijke afloop. Er zijn geen studies gepubliceerd die duidelijk aangeven welke behandeling voor gelokaliseerde prostaatkanker het beste is, in termen van oncologische uitkomsten en KvL-effecten. In het bijzonder ontbreekt het aan een gerandomiseerde vergelijking tussen radicale prostatectomie en primaire radiotherapie. Recent onderzoek in het veld van prostaatkanker is gericht op het vaststellen van de factoren die bepalend zijn voor de ziekteprogressie om betere diagnostische tests te kunnen ontwikkelen, op het ontwikkelen van risico-stratificatiemodellen en op het ontwikkelen van behandelingen die met minder bijwerkingen gepaard zouden gaan.

Profylactische eierstokverwijdering die een aanzienlijke reductie van het borst- en eierstokkankerrisico biedt, leidt niet tot een meetbare verslechtering van de algemene KvL. Profylactische chirurgie is verbonden zowel met de positieve psychosociale effecten (minder kanker-specifieke distress en betere risicoperceptie), als met de ongunstige functionele klachten (endocriene en seksuele symptomen). Hormoonsuppletie lijkt niet altijd te helpen bij het bestrijden van deze klachten. Gerandomiseerd klinisch onderzoek is nodig om de effectiviteit van hormoonsuppletie (inclusief testosteronpreparaten) vast te stellen bij het bestrijden van acute overgangsklachten als gevolg van eierstokverwijdering. In deze context zou ook de rol van niet-hormonale medicaties en psychosociale interventies gericht op de beheersing van overgangsklachten verder onderzocht moeten worden. Recent onderzoek in het veld van eierstokkanker is ook gericht op het ontwikkelen van effectievere screeningsmethoden die zich beter zouden lenen voor vroege tumoropsporing en op het ontwikkelen van behandelingen voor eierstokkanker die tot langere overleving zouden kunnen leiden.

In het geval van vroege opsporing en behandeling van prostaatkanker en preventie van erfelijke eierstokkanker zijn medische beslissingen nogal complex. Iedere optie gaat gepaard met zowel positieve als negatieve effecten, waarbij het ziektevrij blijven als uitkomst vaak onzeker is. In de gezondheidszorg moeten patiënten grondig geïnformeerd worden over de mogelijke voor- en nadelen van screening en behandeling om samen met hun artsen een goede beslissing te kunnen nemen over de behandelstrategie die het beste past bij de individuele situatie van de patiënt.

LIST OF PUBLICATIONS:

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CURRICULUM VITAE

Joanna Barbara Madalinska werd geboren op 15 februari 1964 te Warschau, Polen. In 1983 behaalde zij het baccalaureaat (wiskundig en natuurkundig profiel) aan het 5-de Lyceum te Gdansk, Polen. In de jaren 1983 – 1986 studeerde zij fysische en sociale geografie aan de Universiteit van Gdansk, Polen. Na haar emigratie naar Nederland ging zij psychologie aan de Universiteit Leiden studeren, waar zij in 1994 haar doctoraal bul (afstudeerrichting Methoden en Technieken van Psychologisch Onderzoek) heeft behaald. Tijdens haar studie heeft ze gedurende een halfjaar een onderzoeksstage gelopen bij de vakgroep Sociale Psychologie van de Universiteit van Toronto (University of Toronto, Toronto, Canada). Na haar afstuderen was zij verbonden aan de vakgroep Klinische en Gezondheidspsychologie van de Universiteit Leiden, waar zij onderzoek deed naar de kwaliteit van leven van hartpatiënten en hun partners. In de jaren 1996 - 2001 werkte zij bij het Instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam (thans de afdeling Maatschappelijke Gezondheidszorg van het Erasmus Medisch Centrum Rotterdam), waar zij een longitudinaal onderzoek heeft verricht naar de kwaliteit van leven effecten van de primaire behandeling voor prostaatkanker. In 1998 rondde zij de postdoctorale (MSc) opleiding epidemiologie af aan het Netherlands Institute for Health Sciences van de Erasmus Universiteit Rotterdam. In de jaren 2001 – 2006 was zij werkzaam als wetenschappelijk medewerker bij de afdeling Psychosociaal Onderzoek en Epidemiologie van het Nederlands Kanker Instituut/ Antoni van Leeuwenhoek Ziekenhuis te Amsterdam, waar zij een onderzoek heeft verricht naar de gevolgen van een profylactische eierstokverwijdering bij vrouwen met een verhoogd erfelijk risico op borst-/eierstokkanker op psychosociaal welbevinden en lichamelijke klachten. Tevens was zij betrokken bij onderzoeksprojecten op het gebied van vervroegde overgangsklachten bij jongere vrouwen die voor borstkanker zijn behandeld. Per 1 oktober 2006 is zij als senior onderzoeker in dienst getreden bij het College Bescherming Persoonsgegevens te Den Haag.