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Original article

Worry and risk perception of breast cancer in a prevention trial of low dose tamoxifen in midlife postmenopausal hormone users

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ABSTRACT

Objective: There is increasing interest in combining postmenopausal hormone therapy (HT) and SERMs in midlife women. We previously showed that refusal to participate in a prevention trial of low dose tamoxifen in HT users was associated with higher worry about breast cancer. Given this counterintuitive finding, we studied which factors influenced worry and risk perception of breast cancer.
Methods: We assessed the relationships of breast cancer worry and risk perception with age, age at menopause, Gail risk, education, adherence to mammographic screening, BMI, smoking, physical activity, alcohol use, anxiety and depression in 457 midlife HT users who were eligible to participate in the trial.
Results: Women with menopause <48 years were more worried about breast cancer than women with menopause >52 years (OR = 5.0, 95% CI, 1.2–21.1). Worry was also associated with high absolute risk perception and former smoking. Factors associated with higher risk perception were age>60 years, at-risk life style, worry about breast cancer and depression.
Conclusions: The inverse association between early menopause and worry about breast cancer is in contrast with the known protective effect of early menopause on breast cancer risk and seems to reflect a feeling of aging and disease vulnerability. Our findings indicate that worry about cancer has an affective construct which is independent of breast cancer biology but is engaged in health decision making. Increasing breast cancer risk awareness in subjects high in worry without a plan of emotional coping may therefore be counterproductive because of avoidant attitudes.

1. Introduction

Postmenopausal hormone therapy (HT) at the onset of menopause is an example of the paradigm shift towards a proactive behavior of health promotion inasmuch as users are required to possess a good sense of awareness and ability to carefully assess risks and benefits [1]. This is true also for the use of tamoxifen in primary prevention since the trade-off between risks and benefits is subject to continuous debate [2–4]. However, the decision-making process about participating in a breast cancer therapeutic prevention trial is poorly understood. Despite the highest evidence of efficacy ensuing from large trials, the uptake of selective estrogen receptor modulators such as tamoxifen and raloxifene [5] or aromatase inhibitors [6–8] has so far been very limited in clinical practice [9,10], mainly because of the risk of endometrial cancer and venous thromboembolism, partly attenuating the 50% reduction of breast cancer risk observed in the NSABP-P1 trial [11]. Likewise, the use of HT has dramatically dropped [12] after the initial publication of the WHI trial [13], notwithstanding the evidence of a timing effect with a mortality reduction in women aged 50 to 59 in subsequent analyses [1,14]. While initial reports linked a decrease in breast cancer incidence to the HT drop after the WHI trial results [15], most recent evidence on the association between breast cancer incidence and the rate of MHT use during the past years in Europe suggests in fact that breast cancer incidence in

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women aged 45–64 has not decreased in parallel with the HT drop, indicating the role of additional confounding factors [16]. While attention has mainly been focused on medical variables discouraging the use of tamoxifen for prevention, including concerns about adverse events [17] and lack of demonstrated mortality reduction [2,3], other studies have pointed to risk perception, worry about breast cancer and lived experiences as factors affecting the decision to participate in a preventive therapy trial for breast cancer [18–20]. This is not surprising given the notion that adherence to breast cancer screening programs is influenced by sociodemographic as well as emotional factors [21].

We pioneered the concept of combining postmenopausal HT and low dose tamoxifen to retain the benefits while reducing the risks of either agent in a phase III trial (HOT trial) in 1884 midlife women [22,23]. The results showed a non-significant 20% reduction of breast cancer in the tamoxifen arm compared with the placebo arm [23]. Importantly, tamoxifen showed favorable trends in women on HT for <5 years (adjusted RR = 0.35; 95% CI 0.15–0.85) and in estrogen-alone users (RR = 0.26, 95% CI 0.05–1.28), but no effect in the combined estro-progestin subgroup. Combining HT to tamoxifen was also associated with a lower incidence of menopausal symptoms relative to tamoxifen alone [24]. More recently, the combination of conjugated estrogen with the SERM bazedoxifene has proven to be beneficial on menopausal quality of life [25] without an increase in mammographic density [26].

Participation in the HOT trial was higher in women at younger age and in those satisfied with health care providers, whereas it was lower in women with breast cancer worry, suggesting a condition of psychological well-being as a promoting factor for the trial participation [27]. Given the counterintuitive finding and the discrepancy with some prior studies on the role of breast cancer worry in adopting prevention strategies, here we searched in depth which factors explained the worry about breast cancer and the risk perception of breast cancer. These factors may be important to better explain health promotion attitudes and therefore enhance compliance to therapeutic prevention in midlife postmenopausal women.

2. Materials and methods

2.1. Participants

Participants in the psychosocial study were postmenopausal healthy women currently on or about to start HT for the treatment of menopausal symptoms or health promotion who were eligible for a double-blind, placebo-controlled, phase III trial to assess the efficacy of low dose tamoxifen (5 mg/day) administered for 5 years in women undergoing different types of HT. A randomized phase II trial established the optimal dose of tamoxifen in HT users [28]. The main results of the phase III trial (the HOT study, HT Opposed by Low-Dose Tamoxifen, Clinical Trials.gov NCT01579734) have previously been published [23]. The current psychosocial study was conducted in two centers, the European Institute of Oncology, Milan, and the Galliera Hospital, Genoa, Italy. The institutional review board of each site approved the protocol, and all women gave their written informed consent.

2.2. Study procedures

Study procedures were previously described [27]. Briefly, participants were aware of the trial's launch through different means, including a mass media campaign (television, press, and web site announcements) or through direct contact with the study personnel during clinical consultations. A toll-free number was available to address initial questions and to fix an appointment with the study personnel, mostly physicians. Counseling about the trial included an evaluation of benefits and risks of HT and tamoxifen given alone, and description of the study procedures. Participant-physician communication was based on a scripted protocol. After counseling and subsequent decision making about the trial, all women received by mail a preprinted, self-report questionnaire based on previous research on medical decision making in the area of breast cancer prevention [29].

2.3. Psychological factors

Worry about developing breast cancer was the study's main outcome measure and was assessed by the following question: “How worried are you about getting breast cancer in the next 5 years?” Responses were graded using a Likert scale: “not at all worried”, “slightly worried”, “somewhat worried”, “worried” and “very worried.”

Risk perception of breast cancer were assessed as previously described [19]. Perception of absolute breast cancer risk was assessed using standard verbal and numerical measures within the span of 5 years. For the verbal measures, women were asked, “How likely are you to get breast cancer in the next 5 years?”.Responses were “very unlikely”,“unlikely”,“50/50 chance”, “likely” and “very likely.” For the numerical measures, women were asked, “On a scale from 0 to 100, with 0 indicating certain not to happen and 100 indicating certain to happen, how likely are you to get breast cancer in the next 5 years?”.

Perceptions of comparative breast cancer risk were assessed through the following question: “Compared with other women of your age, what are the odds that you will get breast cancer in the next 5 years?”. Responses were “much below average”, “below average”, “same average risk as other women my age”, “above average”, and “much above average”. Although the level of breast cancer risk knowledge was not formally measured, the results of the Gail model and the risk associated with HT use were illustrated to the screened women at face to face or telephone counseling.

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale [30].

2.4. Sociodemographic, health-related and lifestyle variables

We assessed age, education, marital status, and employment, whereas race was not included because all but three women were Caucasian. In addition, we included age at menopause, 5-year Gail risk of breast cancer (%), using 1.3% as cut off point for higher risk based on the Italian incidence data [31], body mass index (kg/m2), current use, type and duration of HT, frequency of mammographic screening (never, one to two times, or every 1–2 years), smoking habit (never, former, or current), physical activity (<3, 3 to 6,>6 h/week), use of any medication (sometimes vs regular), and alcohol use (<five, five to 10, 11 to 20, or>20 glasses a week).

2.5. Sample size and statistical analyses

In our initial decision making study [27], we had assumed the hypothesis (which turned out to be wrong) of a prevalence of breast cancer worry (worried + very worried) of 5% in trial decliners and 15% in trial participants. With 450 women, including 250 trial participants and 200 decliners, we would be able to detect such a difference with 90% power at 5% two-sided statistical significance.

Descriptive statistics used for continuous factors were mean and standard deviation (SD) or median and interquartile range (IQR); for categorical factors, absolute and relative (%) frequencies were adopted. Boxplots were used to visualize the associations between