Cytokine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Association between physical activity and the expression of mediators of inflammation in normal breast tissue among premenopausal and postmenopausal women

Mirette Hanna[a], Isabelle Dumas[b], Michèle Orain[b], Simon Jacob[c], Bernard Têtu[c], Caroline Diorio[d,*]

[a] Oncology Research Unit, CHU de Québec Research Center, Department of Social and Preventive Medicine, Cancer Research Center, Université Laval, 1050 Avenue de la Médecine, Québec, QC G1V 0A6, Canada
[b] Oncology Research Unit, CHU de Québec Research Center, 1050 Chemin Sainte-Foy, Québec, QC G1S 4L8, Canada
[c] Oncology Research Unit, CHU de Québec Research Center, Service of Molecular Biology, Medical Chemistry and Pathology, Hôpital Saint-Sacrement, CHU de Québec, Centre des Maladies du Sein Deschênes-Fabia, Hôpital du Saint-Sacrement, Department of Molecular Biology, Medical Chemistry and Pathology, Cancer Research Center, Université Laval, 1050 Avenue de la Médecine, Québec, QC G1V 0A6, Canada
[d] Oncology Research Unit, CHU de Québec Research Center, Centre des Maladies du Sein Deschênes-Fabia, Hôpital du Saint-Sacrement, Department of Social and Preventive Medicine, Cancer Research Center, Université Laval,1050 Avenue de la Médecine, Québec, QC G1V 0A6, Canada

ARTICLE INFO

Keywords:
Physical activity
Mediators of inflammation
Risk of breast cancer

ABSTRACT

Physical activity is associated with decreased breast cancer risk. The underlying biological mechanisms could include the reduction of the local inflammation in the breast tissue. We conducted a cross-sectional study to assess the association between the physical activity and the protein expression levels of eleven mediators of inflammation in normal breast tissue of 164 women having breast cancer. Information on total physical activity (household, occupational and recreational) performed during a one-year period was collected using a questionnaire. Normal breast tissue was obtained from mastectomy blocks distant from the tumor. The expression of the mediators of inflammation in normal breast tissue was visually evaluated by immunohistochemistry. Multivariate linear regression analyses were used to assess the prevalence ratios (PR) and 95% confidence intervals (CI) for higher protein expression levels of the mediators of inflammation in normal breast tissue across quartiles of physical activity. Higher total physical activity was associated with lower expression levels of the pro-inflammatory mediator TNF-α in normal breast epithelial tissue among all (PR = 0.64, 95% CI = 0.44–0.93 for the fourth quartile; P_{trend} = 0.013), premenopausal (PR = 0.61, 95% CI = 0.41–0.91 for the fourth quartile; P_{trend} = 0.014) and postmenopausal women (PR = 0.45, 95% CI = 0.21–0.96 for the fourth quartile; P_{trend} = 0.022). Conversely, higher total physical activity was associated with higher expression levels of the anti-inflammatory mediator IL-10 in normal breast epithelial tissue among all (PR = 1.66, 95% CI = 0.97–2.85 for the fourth quartile; P_{trend} = 0.071) and postmenopausal women (PR = 4.69, 95% CI = 1.26–17.43 for the fourth quartile; P_{trend} = 0.010). Our findings suggest a beneficial effect of physical activity on the local inflammatory profile in the breast tissue.

1. Introduction

Local inflammation is suggested to be an early event in the development of many cancers. Local inflammation is controlled by several mediators of inflammation and some are suspected to play a role in breast cancer (BC) development. Some mediators of inflammation are reported to directly affect mammary cell proliferation, survival and apoptosis. The pro-inflammatory mediators can promote a sustained cellular proliferation, DNA damage and angiogenesis, increase local estrogen synthesis and suppress the anti-tumor immune response providing thus an ideal environment for cancer development [1–8]. Conversely, the anti-inflammatory mediators exert an inhibitory activity on

Abbreviations: BC, breast cancer; BMI, body mass index; CRP, C-reactive protein; COX-2, cyclooxygenase 2; DAB, diaminobenzidine; H & E, hematoxylin-eosin; HiER, heat induced epitope antigen retrieval; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; MET-h/week, metabolic equivalent of task-hours per week; PA, physical activity; PR, prevalence ratios; PYTPAQ, Past Year Total Physical Activity Questionnaire; SAA1, serum amyloid A1; STAT3, signal transducer and activator of transcription 3; TDLUs, terminal ductal lobular units; TGF-β, transforming growth factor-β; TMA, tissue microarray; TNF-α, tumor necrosis factor-α

* Corresponding author at: Oncology Research Unit, CHU de Québec Research Center – Université Laval, 1050 chemin Sainte-Foy, Quebec City, QC G1S 4L8, Canada.
E-mail address: Caroline.Diorio@crchudequebec.ulaval.ca (C. Diorio).

http://dx.doi.org/10.1016/j.cyto.2017.08.007
Received 27 February 2017; Received in revised form 24 July 2017; Accepted 10 August 2017

cellular proliferation [9,10]. The possible role of the mediators of inflammation in cancer development is further supported by the observed relative increased expression of the pro-inflammatory mediators [7,11–13] and reduced expression of the anti-inflammatory mediators [14,15] in malignant compared to normal breast tissue.

Physical activity (PA) is a modifiable lifestyle factor shown to be associated with reduced BC risk. A recent meta-analysis concluded that BC risk reduction ranged from 20% to 30% with increasing levels of PA [16]. This reduction followed a dose–response relationship. BC risk was further reduced by 2–5% for each additional 10–25 metabolic equivalent of task-hours per week (METs-h/week) performed [16]. The PA protective effect was consistent throughout the household, occupational, recreational or total PA among pre- and postmenopausal women of diverse race and ethnicities [16]. The current American PA guideline recommendations are to perform moderate PA for at least 30 min/day on most days of the week to achieve the greatest reduction in BC risk [17]. A recent study suggests that BC risk reduction is more significant for hormone receptor positive (HR+) and human epidermal growth factor receptor-2 positive (HER2+) tumors among pre- and postmenopausal women [18].

Several biological mechanisms could explain the protective effect of PA against BC. The anti-inflammatory effect of PA was proposed as one of the biological mechanisms mediating the protective effect of PA against BC but was not confirmed [19]. Yet, the effect of PA on the circulating levels of several mediators of inflammation was repeatedly addressed in randomized controlled trials and longitudinal studies [20]. Many of these studies reported a reduction in the pro-inflammatory mediators and an increase in the anti-inflammatory mediator levels with increasing levels of PA [20]. However, it is not known whether this beneficial effect of PA on the circulating levels of mediators of inflammation will be true when applied to the breast tissue. There is some evidence suggesting that the circulating levels of mediators of inflammation are not a mirror image of their protein expression levels in the breast tissue making it unclear whether the PA can exert the same effect in the breast tissue [21,22]. If PA could exert an anti-inflammatory effect in the breast tissue, this would provide a reasonable explanation of the PA anti-cancer effect, at least in part. To date, no data are available on the anti-inflammatory effect of PA in the breast tissue.

Therefore, we conducted a cross-sectional study to assess the association between PA performed during a one-year period and the expression of mediators of inflammation in normal breast tissue of 164 pre- and postmenopausal women diagnosed with BC. In the present study, we considered eight pro-inflammatory mediators [interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), cyclooxygenase 2 (COX-2), leptin, serum amyloid A1 (SAA1), interleukin 8 (IL-8) and signal transducer and activator of transcription 3 (STAT3)] and three anti-inflammatory mediators [transforming growth factor-β (TGF-β), interleukin 10 (IL-10) and lactoferrin]. We hypothesized that higher levels of PA would be associated with lower inflammation in the breast tissue. In other words, higher levels of PA would be associated with lower expression levels of the pro-inflammatory mediators and higher expression levels of the anti-inflammatory mediators in the breast tissue. Identifying lifestyle factors, such as PA, that may lower the expression of the pro-inflammatory mediators and increase the expression of the anti-inflammatory mediators in the breast tissue might be beneficial for future BC risk reduction.

2. Materials and methods

2.1. Study population and data collection

Detailed description of the recruitment of the study participants and the eligibility criteria have been provided elsewhere [23]. Briefly, women diagnosed with unilateral BC at the Centre des Maladies du Sein Deschênes-Fabia from January 2011 through April 2012 and fulfilling the eligibility criteria were invited to participate in the study. Eligibility criteria: (a) aged less than 70 years old; (b) had mammography within the six months preceding the diagnosis; (c) not currently pregnant; (d) had never had previous breast surgeries; (e) had not received hormonal, chemotherapy or radiotherapy; (f) have no history of cancers other than non-melanoma skin cancer. Of 168 women who met the eligibility criteria and agreed to participate, four women were subsequently excluded either because they had a history of breast surgery, they could never be reached for the telephone interview, or their surgical specimens lacked sufficient normal breast tissue. The remaining 164 women provided signed informed consent and the study protocol was reviewed and approved by the Research Ethics Board of the Centre Hospitalier Universitaire de Québec, Québec (QC), Canada.

Information on the laterality and location of the BC were obtained by review of medical records of consenting women. For all participants, weight, height, waist and hip circumferences were measured by a trained nurse during a personal interview held in the week preceding their breast surgery. The body mass index (BMI) was calculated as weight (kg)/height (m^2). Information on known and suspected BC risk factors were obtained during a telephone interview held by a trained research assistant; age at menarche, age at first pregnancy and number of full-term pregnancies, past history of lactation, oral contraceptive and hormonal replacement therapy use, first-degree family history of BC, smoking status, alcohol consumption and the use of regular multivitamins and anti-inflammatory drugs. Menopausal status was determined as previously reported [23]. Briefly, a woman was classified as postmenopausal if she reported that her menstrual periods had naturally stopped for 12 months or more, had hysterectomy with bilateral oophorectomy regardless of her age, or had hysterectomy without bilateral oophorectomy but is older than 53 or 55 years for smoker and non-smoker, respectively. Otherwise, a woman was considered premenopausal. Eleven women had unknown menstrual cycle status. These women were combined with premenopausal women (n = 71) in further analyses as they had similar characteristics.

2.2. Physical activity assessment

Detailed assessment of PA was previously described [23]. Briefly, information on different PA domains (household, occupational and recreational) was collected using the self-administered validated Past Year Total Physical Activity Questionnaire (PYTPAQ) referring to the year preceding the diagnosis [24]. For the occupational domain, tasks performed at work and transportation related were recorded. Women were required to report, the frequency (months/year, days/week), duration (hours/episode) and intensity (as perceived by heart rate changes and sweating) spend while performing each activity. Next, the frequency and duration of each activity were multiplied to obtain the mean hours per week spent on that activity. The mean hours per week was then multiplied by an intensity code, specific for that activity, assigned by the Compendium of Physical Activities to obtain the MET-h/week [25,26]. The assigned intensity code was adjusted according to the self-reported intensity values. Finally, METs-h/week for all PAs were summed to obtain the total METs-h/week of all PAs performed during the year preceding the diagnosis.

2.3. Assessment of the expression of mediators of inflammation

2.3.1. Tissue microarray construction

For each participant, zones of morphologically normal terminal ductal lobular units (TDLUs) located at more than 1.0 cm from the tumor were identified on the hematoxylin-eosin (H & E) stained slides by the study pathologists (BT and SJ). Six cores were then extracted from the corresponding zones on the formalin-fixed paraffin-embedded mastectomy blocks and used to build the tissue microarray (TMA) blocks. In addition, each TMA block, contained two cores of each BC cell lines (MCF-7, MDA-231 and SKBR-3) to serve as internal positive