Prostaglandins, Leukotrienes and Essential Fatty Acids 113 (2016) 28–32

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

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

# Inflammatory $F_2$-isoprostane, prostaglandin $F_{2\alpha}$, pentraxin 3 levels and breast cancer risk: The Swedish Mammography Cohort

Samar Basu [a,b,*], Holly Harris [c,d,e], Alicja Wolk [c], Adrien Rossary [a], Florence Caldefie-Chézet [a], Marie-Paule Vasson [a,f,g], Anders Larsson [h]

[a] Chaire d'Excellence Program, Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, CRNH-Auvergne, INRA-UDA, Clermont-Ferrand, France
[b] Department of Public Health and Caring Sciences, Faculty of Medicine, Uppsala University, Uppsala, Sweden
[c] Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
[d] Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA
[e] Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[f] Centre Jean Perrin, Unicancer, Clermont-Ferrand, France
[g] CHU Clermont-Ferrand, Unité d'Exploration Nutritionnelle, Clermont-Ferrand, France
[h] Department of Medical Science, Faculty of Medicine, Uppsala University, Uppsala, Sweden

ARTICLE INFO

*Article history:*
Received 3 May 2016
Received in revised form
16 August 2016
Accepted 16 August 2016

*Keywords:*
$F_2$-isoprostane
Prostaglandin $F_{2\alpha}$
Pentraxin
Inflammation
Breast cancer
Cancer risk

ABSTRACT

*Introduction:* Breast cancer is a common cancer among women. Identifying cellular participation of $F_2$-isoprostane, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and pentraxin 3 (PTX3) in cancer we evaluated whether their prediagnostic systemic levels that originate from different inflammatory pathways were associated with breast cancer risk.
*Methods:* Seventy-eight breast cancer cases diagnosed after blood collection and 797 controls from the Swedish Mammography Cohort were analysed for urinary $F_2$-isoprostane, $PGF_{2\alpha}$ and plasma PTX3 levels.
*Results:* None of the biomarkers investigated were significantly associated with breast cancer risk. However, there was the suggestion of an inverse association with PTX3 with multivariable adjusted ORs (95% CI) of 0.56 (95% CI=0.29–1.06) and 0.67 (95% CI=0.35–1.28) for the second and third tertiles, respectively ($p_{trend}$=0.20). No associations were observed between $F_2$-isoprostane (OR=0.87; 95% CI=0.48–1.57; $p_{trend}$=0.67) and $PGF_{2\alpha}$ metabolite (OR=1.03; 95% CI=0.56–1.88; $p_{trend}$=0.91) comparing the top to bottom tertiles.
*Conclusions:* The systemic levels of $F_2$-isoprostane, $PGF_{2\alpha}$ and PTX3 witnessed in women who later developed breast cancer may not provide prognostic information regarding tumor development in spite of their known involvement *in situ* cellular context. These observations may indicate that other mechanisms exist in controlling cellular formation of $F_2$-isoprostane, $PGF_{2\alpha}$ and PTX3 and their systemic availability in breast cancer patients.



## 1. Introduction

Breast cancer is the most common cancer and one of the leading causes of cancer death among women [1–4]. Eicosanoids, especially prostaglandins and isoprostanes are related to the inflammatory and oxidative responses in various diseases including breast cancer [5–7]. $F_2$-isoprostanes are a family of prostaglandin derivatives generated *in vivo* by free radical-induced peroxidation of arachidonic acid, and a major $F_2$-isoprostane, bioactive 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) is increased in several syndromes and diseases associated with oxidative stress [6,8]. Currently, $F_2$-isoprostanes are regarded as the most reliable biomarker of oxidative stress. Cyclooxygenase (COX)-2 has been shown to be expressed in various cells including tumor cells after stimulation by pro-inflammatory compounds, such as growth factors and cytokines leading to the release of primary prostaglandins [9]. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a potent prostaglandin that regulates several female hormones is associated with breast

*Abbreviations:* ADME, absorption, distribution, metabolism and excretion; BBD, benign breast disease; BMI, body-mass index; CRP, C-reactive proteins; CV, coefficient of variation; CI, confidence interval; DNA, deoxyribonucleic acid; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$; OR, odds ratio; PGE-M, prostaglandin E metabolite; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PTX3, pentraxin 3; SMC, Swedish Mammography Cohort

* Corresponding author at: Chaire d'Excellence Program, Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, CRNH-Auvergne, INRA-UDA, Clermont-Ferrand, France.

http://dx.doi.org/10.1016/j.plefa.2016.08.005
0952-3278/

cancer [10] and is also involved in acute and chronic inflammation [5]. 15-Keto-dihydro-$PGF_{2\alpha}$, a major metabolite of $PGF_{2\alpha}$, is increased during inflammatory response and can be used as an indicator of *in vivo* lipid peroxidation through the COX pathway [5]. Experimental data suggest that both COXs and free radicals are involved in various cancers including breast cancer [7,10,11]. High urinary PGE-M levels were associated with elevated risk of breast cancer among normal weight and postmenopausal women but not among overweight postmenopausal women or premenopausal women [12]. However the role of circulating levels of $F_2$-isoprostane and $PGF_{2\alpha}$ in breast cancer remains uncertain although it is established that they are involved in cellular expression in the tumor and adjacent tissues to the tumor [10].

The role of inflammatory PTX3 is well known in cardiovascular diseases and in some types of cancer [13]. The long PTX3 is a member of the pentraxin family, that includes C-reactive proteins (CRP) and whose related members have vital roles in inflammation. PTX3 is an acute phase protein consisting of 381 amino-acids and a molecular weight of 42 k Daltons and is synthesized at the site of infection or inflammation contrary to CRP which is mainly produced in the liver. Thus, PTX3 is extremely important in regard to local inflammation at the site of tumor [14]. Local inflammatory responses have crucial roles at various stages of tumor development, including initiation, progression, invasion, and metastasis. Overexpression of PTX3 has been described in prostate cancer [15] and lung cancer [16]. However, the role of PTX3 in breast cancer still remain uncertain.

Inflammation is believed to be one of the key promoters in the development and progression of breast cancer [7,11,17,18]. Breast cancer is generally regarded as a dynamic process and multifactorial heterogeneous disease among women that are predisposed by the local tumor microenvironment [19–21]. This microenvironment in breast cancer is enriched with various inflammatory factors including cyclooxygenases and free radicals that normally are unable to induce immune protective effects but rather are considered to have tumor-promoting actions by their downstream bioactive metabolites such as prostaglandins and isoprostanes. It has been shown that levels of COXs are elevated in several types of cancers, such as colorectal, pancreatic, breast, and prostate cancer or their experimental models [22–25]. In addition, some studies have indicated that acute phase proteins such as CRP may be critical long-term prognostic factors for breast cancer [26,27]. Experimental and clinical studies have demonstrated that chronic inflammation may promote and actively affect various types of tumor development and intracellular matrix modelling by PTXs possibly contribute to conditions related to tumor microenvironment. Such remodelling of matrix might influence cancer cell proliferation and migration, tumor angiogenesis, and metastasis.

Thus, we studied the association between prediagnostic urinary levels of $F_2$-isoprostane, $PGF_{2\alpha}$ metabolite, and plasma PTX3 and breast cancer risk in a case-control study nested within the Swedish Mammography Cohort (SMC).

## 2. Materials and methods

### 2.1. Study population

#### 2.1.1. Recruitment of study population and sample collection

This study included participants from a case-control study nested within the Swedish Mammography Cohort (SMC), which is a population-based prospective cohort study established from 1987 to 1990. Recruitment and characteristics of this cohort have been previously described [28]. In brief, all women born between 1914 and 1948 from Västmanland and Uppsala counties, Sweden received a questionnaire regarding diet and lifestyle factors (74% response rate). In 1997 a second questionnaire was sent to participants who were still alive and residing in the study area (70% response rate). Completion and return of the self-administered questionnaire was treated as informed consent of study participants. The study was approved by the ethics committee at the Karolinska Institutet, Stockholm.

The participants in the nested case-control study came from the SMC-Clinical, a subcohort of 5022 women under the age of 85 and living in the city of Uppsala, that was established between 2003 and 2009. Blood samples were collected at an in-person health examination and participants completed a questionnaire on diet and lifestyle factors. Venous blood samples were collected after a 12-hour overnight fast. Biological samples were immediately centrifuged and separated in a dark room, and stored at $-80\,^{\circ}C$. In addition, urine samples were also collected from these subjects and kept frozen at $-80\,^{\circ}C$ until analysis.

#### 2.1.2. Selection of cases and controls

From the SMC-Clinical, 78 cases and 797 controls were included in the study.

We defined our cases as participants who provided a blood and urine samples and had a histologically confirmed incident invasive breast cancer diagnosis after blood collection and before December 31, 2011. Cases were ascertained by linkage of the study cohort with Swedish Cancer Registers. These registers have been estimated to provide almost 100% complete case ascertainment (3). Controls were randomly selected from women without a breast cancer diagnosis who had provided a blood and urine sample.

### 2.2. Laboratory measurements

Urinary samples were analysed for 8-iso-$PGF_{2\alpha}$ as an index of oxidative injury by a validated radioimmunoassay [29]. Urinary samples were also analysed for 15-keto-dihydro $PGF_{2\alpha}$, major metabolite of $PGF_{2\alpha}$, as an index of inflammatory response by a validated radioimmunoassay [30].

Pentraxin 3/TSG-14 (PTX3) was determined by a sandwich ELISA kit (DY1826 from R&D Systems (Minneapolis, MN, USA)). The immunoassays were calibrated against highly purified recombinant PTX3 and had a total coefficient of variation of approximately 6%.

### 2.3. Statistical analysis

Tertiles of 8-iso-$PGF_{2\alpha}$, $PGF_{2\alpha}$ metabolite, and PTX3 were determined by the distribution among the controls. Logistic regression was used to estimate OR and 95% confidence intervals (95% CI) for the association between tertiles of each biomarker and breast cancer. In the covariate-adjusted model we adjusted for the following *a priori* potential confounders: age at blood sampling (continuous), date at blood sampling (continuous), oral contraceptive use (ever, never), hormone replacement therapy use (ever, never), age at menarche ($<13$, 13, $\geq 13$ years), age at menopause ($<51$, $\geq 51$ years), parity/age at first birth (nulliparous, age at first birth $<26$/1–2 children, age at first birth 26–30 years/1–2 children, age at first birth $\geq 31$/1–2 children, age at first birth $<26$/$\geq 3$ children, age at first birth $\geq 26$ years/$\geq 3$ children), family history of breast cancer (yes/no), history of benign breast disease (yes/no), body-mass index (BMI) at blood sampling (continuous), height (continuous), highest education level (elementary, high school, college or greater), physical activity ($<38.8$, 38.8-$<42.3$, 42.3-$<45.9$, $\geq 45.9$ MET-hours/day), and alcohol intake (continuous). Tests for trend were performed using tertile medians. We also conducted analyses excluding cases diagnosed within one