

# Genetic variation and circulating levels of IGF-I and IGFBP-3 in relation to risk of proliferative benign breast disease

Xuefen Su<sup>1,2</sup>, Graham A. Colditz<sup>2,3</sup>, Walter C. Willett<sup>1,2,4</sup>, Laura C. Collins<sup>5</sup>, Stuart J. Schnitt<sup>5</sup>, James L. Connolly<sup>5</sup>, Michael N. Pollak<sup>6</sup>, Bernard Rosner<sup>1,7</sup>, Rulla M. Tamimi<sup>1,2</sup>

<sup>1</sup>Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

<sup>2</sup>Department of Epidemiology, Harvard School of Public Health, Boston, MA

<sup>3</sup>Alvin J. Siteman Cancer Center and Department of Surgery, Washington University School of Medicine, MO

<sup>4</sup>Department of Nutrition, Harvard School of Public Health, Boston, MA

<sup>5</sup>Department of Pathology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA

<sup>6</sup>Departments of Medicine and Oncology, McGill University and Jewish General Hospital, Montreal, QC, Canada

<sup>7</sup>Department of Biostatistics, Harvard School of Public Health, Boston, MA

Insulin-like growth factor-I (IGF-I) and its major binding protein IGFBP-3 have been implicated in breast carcinogenesis. We examined the associations between genetic variants and circulating levels of IGF-I and IGFBP-3 with proliferative benign breast disease (BBD), a marker of increased breast cancer risk, in the Nurses' Health Study II (NHSII). Participants were 359 pathology-confirmed proliferative BBD cases and 359 matched controls. Circulating IGF-I and IGFBP-3 levels were measured in blood samples collected between 1996 and 1999. Thirty single nucleotide polymorphisms (SNPs) in IGF-I, IGFBP-1, and IGFBP-3 genes were selected using a haplotype tagging approach and genotyped in cases and controls. Circulating IGF-I levels were not associated with proliferative BBD risk. Higher circulating IGFBP-3 levels were significantly associated with increased risk of proliferative BBD (highest vs. lowest quartile odds ratio (OR) [95% confidence interval (CI)], 1.70 (1.06–2.72); p-trend = 0.03). The minor alleles of 2 IGFBP-3 SNPs were associated with lower proliferative BBD risk (homozygous variant vs. homozygous wild-type OR (95% CI): rs3110697: 0.6 (0.4–0.9), p-trend = 0.02; rs2132570: 0.2 (0.1–0.6), p-trend = 0.02). Three other IGFBP-3 SNPs (rs2854744, rs2960436 and rs2854746) were significantly associated with circulating IGFBP-3 levels ( $p < 0.01$ ). Although these SNPs were not significantly associated with proliferative BBD risk, there was suggestive evidence that the alleles associated with higher circulating IGFBP-3 levels were also associated with higher risk of proliferative BBD. These results suggest that genetic variants and circulating levels of IGFBP-3 may play a role in the early stage of breast carcinogenesis.

**Key words:** IGF-I, IGFBP-3, circulating levels, genetic variation, proliferative BBD

**Abbreviations:** AH: atypical hyperplasia; BBD: benign breast disease; BMI: body mass index; BPC3: Breast and Prostate Cancer Cohort Consortium; CI: confidence interval; CV: coefficient of variation; htSNP: haplotype tagging SNP; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein 3; LD: linkage disequilibrium; MEC: Multiethnic Cohort; NHSII: Nurses' Health Study II; OCs: oral contraceptives; OR: odds ratio; SNPs: single nucleotide polymorphisms

Additional Supporting Information may be found in the online version of this article.

**Grant sponsor:** National Institutes of Health Public Health Service Grants; **Grant numbers:** CA046475, CA050385, CA089393

**DOI:** 10.1002/ijc.24674

**History:** Received 9 Mar 2009; Accepted 28 May 2009; Online 23 Jun 2009

**Correspondence to:** Rulla M. Tamimi, ScD Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Avenue, 3rd Floor, Boston, MA 02115, USA, Fax: +(617)-525-2008, E-mail: rulla.tamimi@channing.harvard.edu

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths among women in the United States.<sup>1</sup> Benign breast disease (BBD) comprises a multiplicity of component histologic subtypes among which proliferative BBD is a marker of increased breast cancer risk and may even be in the pathway for a subset of breast cancers.<sup>2</sup> Women whose biopsies show proliferative changes without atypia have a 1.3–1.9-fold greater risk of subsequent breast cancer than women with nonproliferative lesions, and women with atypical hyperplasia (AH) have a 3.9–13-fold greater risk.<sup>2</sup>

Insulin-like growth factor I (IGF-I) is a polypeptide growth hormone that promotes proliferation of normal breast epithelial cells.<sup>3–5</sup> The vast majority of circulating IGF-I is bound to IGF binding proteins, in particular IGFBP-3, in conjunction with an acid-labile subunit.<sup>6</sup> IGF-I modulates cellular transformation and mammary carcinogenesis in animal studies.<sup>7,8</sup> By sequestering IGF-I, higher circulating IGFBP-3 levels were originally hypothesized to be protective against breast cancer.<sup>9</sup> However, epidemiological evidence of higher IGFBP-3 levels associated with an increased breast