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Plasma levels of leptin and mammographic density among postmenopausal women: a cross-sectional studyAnne Stuedal¹, Giske Ursin^{1,2}, Marit B Veierød^{1,3}, Yngve Bremnes⁴, Janne E Reseland^{1,5}, Christian A Drevon¹ and Inger T Gram⁴¹Department of Nutrition, University of Oslo, Norway²Department of Preventive Medicine, University of Southern California, Los Angeles, California, USA³Department of Biostatistics, University of Oslo, Norway⁴Department of Preventive Medicine, Institute of Community Medicine, University of Tromsø, Norway⁵Department of Biomaterials, Faculty of Dentistry, University of Oslo, NorwayCorresponding author: Anne Stuedal, anne.stuedal@medisin.uio.no

Received: 23 May 2006 Revisions requested: 28 Jul 2006 Revisions received: 22 Sep 2006 Accepted: 29 Sep 2006 Published: 29 Sep 2006

Breast Cancer Research 2006, **8**:R55 (doi:10.1186/bcr1603)This article is online at: <http://breast-cancer-research.com/content/8/5/R55>

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This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Abstract**

Introduction Obesity has been linked to increased risk of breast cancer in postmenopausal women. Increased peripheral production of estrogens has been regarded as the main cause for this association, but other features of increased body fat mass may also play a part. Leptin is a protein produced mainly by adipose tissue and may represent a growth factor in cancer. We examined the association between leptin plasma levels and mammographic density, a biomarker for breast cancer risk.

Methods We included data from postmenopausal women aged 55 and older, who participated in a cross-sectional mammography study in Tromsø, Norway. Mammograms, plasma leptin measurements as well as information on anthropometric and hormonal/reproductive factors were available from 967 women. We assessed mammographic density using a previously validated computer-assisted method. Multiple linear regression analysis was applied to investigate the association between mammographic density and quartiles of plasma leptin concentration. Because we hypothesized that the effect of leptin on mammographic density could vary depending on the amount of nondense or fat tissue in the breast, we also performed analyses on plasma leptin levels and mammographic density within tertiles of mammographic nondense area.

Results After adjusting for age, postmenopausal hormone use, number of full-term pregnancies and age of first birth, there was an inverse association between leptin and absolute mammographic density ($P_{\text{trend}} = 0.001$). When we additionally adjusted for body mass index and mammographic nondense area, no statistically significant association between plasma leptin and mammographic density was found ($P_{\text{trend}} = 0.16$). Stratified analyses suggested that the association between plasma leptin and mammographic density could differ with the amount of nondense area of the mammogram, with the strongest association between leptin and mammographic absolute density in the stratum with the medium breast fat content ($P_{\text{trend}} = 0.003$, P for interaction = 0.05).

Conclusion We found no overall consistent association between the plasma concentration of leptin and absolute mammographic density. Although weak, there was some suggestion that the association between leptin and mammographic density could differ with the amount of fat tissue in the breast.

Introduction

Obesity has been associated with increased risk of postmenopausal breast cancer in epidemiological studies [1-3]. The increased conversion of androgens to estrogens by the aromatase enzyme in peripheral adipose tissues [4] along with reduced levels of serum sex hormone binding globulin have

been hypothesized to be the main link between obesity and increased risk of postmenopausal breast cancer [2].

Whether the influence of estrogens on the breast tissue is direct or is mediated via other factors, however, has not been established [5]. In addition to being the main site for

BMI = body mass index; r_{sp} = Spearman's rank correlation.