1. Biochem Biophys Res Commun. 2016 Apr 8;472(3):401-9.

**Current perspectives of molecular pathways involved in chronic inflammation-mediated breast cancer.**

Suman S, Sharma PK, Mishra

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Inflammation has multifaceted role in cancer progression including initiation, promotion and invasion by affecting the immune surveillance and associated signaling pathways. Inflammation facilitates the over-expression of cytokines, chemokines and growth factors involved in progression of different cancers

including breast cancer progression. Deregulation of biological processes such as oxidative stress, angiogenesis, and autophagy elicit favorable immune response towards chronic inflammation. Apart from the role in carcinogenesis, chronic inflammation also favors the emergence of drug resistance clones by inducing the

growth of breast cancer stem-like cells. Immunomodulation mediated by cytokines, chemokines and several other growth factors present in the tumor microenvironment regulate chronic inflammatory response and alter crosstalk among various signaling pathways such as NF-κB, Nrf-2, JAK-STAT, Akt and MAPKs involved in the progression of breast cancer. In this review, we focused on cellular and molecular processes involved in chronic inflammation, crosstalk among different signaling pathways and their association in breast cancer pathogenesis. PMID: 26522220

2. J Mammary Gland Biol Neoplasia. 2015 Dec;20(3-4):109-19.

**New Insights on COX-2 in Chronic Inflammation Driving Breast Cancer Growth and Metastasis.**

Hugo HJ, Saunders C, Ramsay RG, Thompson EW

Author information: VBCRC Invasion and Metastasis Unit, St Vincent's Institute, Fitzroy, VIC,

Australia.

The medicinal use of aspirin stretches back to ancient times, before it was manufactured in its pure form in the late 19th century. Its accepted mechanistic target, cyclooxygenase (COX), was discovered in the 1970s and since this landmark discovery, the therapeutic application of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has increased dramatically. The most significant benefits of NSAIDs are in conditions involving chronic inflammation (CI). Given the recognized role of CI in cancer development, the use of long-term NSAID treatment in the prevention of cancer is an enticing possibility. COX-2 is a key driver of CI, and here we review COX-2 expression as a predictor of survival in various cancer types, including breast. Obesity and post-partum involution are natural inflammatory states that are associated with increased breast cancer

risk. We outline the COX-2 mediated mechanisms contributing to the growth of cancers. We dissect the cellular mechanism of epithelial-mesenchymal transition (EMT) and how COX-2 may induce this to facilitate tumor progression. Finally we examine the potential regulation of COX-2 by c-Myb, and the possible interplay

between c-Myb/COX-2 in proliferation, and hypoxia inducible factor-1 alpha (HIF1α)/COX-2 in invasive pathways in breast cancer. PMID: 26193871

3. Cancer Epidemiol Biomarkers Prev. 2015 Oct;24(10):1439-49.

**Circulating C-Reactive Protein and Breast Cancer Risk-Systematic Literature Review and Meta-analysis of Prospective Cohort Studies.** Chan DS, Bandera EV, Greenwood DC, Norat T

Author information: Imperial College London

We conducted a systematic literature review to explore the association between circulating C-reactive protein (CRP), a low-grade inflammation biomarker, and breast cancer risk. Relevant prospective studies in women were identified in PubMed and Web of Science until February 2015. Random-effects dose-response

meta-analysis was conducted, overall and in postmenopausal women. Twelve out of 15 studies identified were included in the meta-analysis on any breast cancers (3,522 cases; 69,610 women) and nine on postmenopausal breast cancer (2,516 cases; 36,847 women). For each doubling of CRP concentration, a 7% [95%

confidence interval (CI), 2%-12%] and 6% (95% CI, 1%-11%) increased risk was observed (I(2) = 47% and 32%; Pheterogeneity = 0.04 and 0.17), respectively. The association was linear over most of the range of CRP concentrations. Positive associations remained in the studies that examined the exclusion of early years

of follow-up. Associations were attenuated in studies adjusted for lifestyle factors, which partly explained the significant heterogeneity between studies in the overall analysis. On average, the associations in studies adjusted or not adjusted for body mass index were similar. Low-grade inflammation may have a role

in breast cancer development. Additional prospective studies are needed to better understand confounding and effect modification from lifestyle factors. PMID: 26224798

4. Carcinogenesis. 2015 Oct;36(10):1121-8.

**Prediagnostic serum inflammatory markers in relation to breast cancer risk, severity at diagnosis and survival in breast cancer patients.** Wulaningsih W, Holmberg L, Garmo H, Malmstrom H

Author information: Division of Cancer Studies, King's College London, Cancer Epidemiology Group, Bermondsey Wing, Guy's Hospital, London UK,

Inflammation has been linked to cancer but its role in breast cancer is unclear. We investigated common serum markers of inflammation: C-reactive protein (CRP), albumin, haptoglobin and white blood cells (WBC) in relation to breast cancer incidence, severity and survival. A total of 155179 women aged 20 and older

without any history of cancer were selected from a large Swedish cohort. Hazard ratios (HRs) for breast cancer were estimated with Cox regression, adjusting for potential confounders. Ordered and binomial logistic regression models were used to assess the associations of serum inflammatory markers with breast cancer

severity and oestrogen receptor (ER) positivity at diagnosis, on the other. Cumulative incidence functions by levels of inflammatory markers were assessed for early death from breast cancer and all causes. During a mean follow-up of 18.3 years, 6606 women were diagnosed with breast cancer, of whom 1474 died. A

positive association with incident breast cancer was seen for haptoglobin ≥1.4g/l [HR 1.09; 95% confidence interval (CI): 1.00-1.18] compared to lower levels. No association was observed between inflammatory markers and breast cancer severity or ER positivity. Higher haptoglobin was linked to risk of early death from breast cancer (HR: 1.27, 95% CI: 1.02-1.59), whereas higher risk of early death from all causes was additionally found with CRP ≥ 10mg/l (HR: 1.19, 95% CI: 1.04-1.36) and WBC ≥ 10×10(9)/l (HR: 1.57, 1.14-2.16). Our findings

indicate that prediagnostic serum inflammatory markers were weakly linked to incident breast cancer but corresponded to worse survival after diagnosis. PMID: 26130675

5. Int J Oncol. 2015 Sep;47(3):797-805.

**The role of inflammation in progression of breast cancer: Friend or foe? (Review).**

Allen MD, Jones LJ.

Author information: Centre for Tumour Biology, Barts Cancer Institute, A Cancer Research UK Centre

of Excellence, Queen Mary University of London, John Vane Science Centre, London

There is a growing interest in the role of the microenvironment in cancer, however, it has been known for over one hundred years that the immune system plays a prominent role in cancer. Recent decades have revealed more and more data on how our own host response to cancer cells can help or hinder progression of the disease. Despite all this work it is surprising how little is known about the role of the immune system in human breast cancer development, as compared to other cancers. Recent successes of PD-1 blockade in treating multiple cancers, and new developments with other immune targets such as CTLA-4 and CSF-1 inhibitors, highlight that it is becoming ever more important that we understand the complexity of the immune and inflammatory systems in the development and progression of breast cancer. With this knowledge it may be possible to not only target therapy but also more accurately predict those patients that truly need it. This review summarises some of the most significant findings for the role of the immune system and inflammatory response in breast cancer progression. Focusing on how the inflammatory microenvironment may be involved in the progression of pre-invasive ductal carcinoma in situ to invasive breast cancer. It will also discuss the use of immune markers as diagnostic and prognostic tools and summarize the state of the art of immune-therapeutics in breast cancer treatment. PMID: 26165857

6. J Natl Cancer Inst. 2015 Aug 29;107(11).

**Cross Cancer Genomic Investigation of Inflammation Pathway for Five Common Cancers: Lung, Ovary, Prostate, Breast, and Colorectal Cancer.** Hung RJ, Ulrich CM, Goode EL, Brhane Y, Muir K

Author information: Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto,

Canada; National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany

BACKGROUND: Inflammation has been hypothesized to increase the risk of cancer

development as an initiator or promoter, yet no large-scale study of inherited

variation across cancer sites has been conducted.

METHODS: We conducted a cross-cancer genomic analysis for the inflammation

pathway based on 48 genome-wide association studies within the National Cancer

Institute GAME-ON Network across five common cancer sites, with a total of 64 591

cancer patients and 74 467 control patients. Subset-based meta-analysis was used

to account for possible disease heterogeneity, and hierarchical modeling was

employed to estimate the effect of the subcomponents within the inflammation

pathway. The network was visualized by enrichment map. All statistical tests were two-sided.

RESULTS: We identified three pleiotropic loci within the inflammation pathway,

including one novel locus in Ch12q24 encoding SH2B3 (rs3184504), which reached

GWAS significance with a P value of 1.78 x 10(-8), and it showed an association

with lung cancer (P = 2.01 x 10(-6)), colorectal cancer (GECCO P = 6.72x10(-6);

CORECT P = 3.32x10(-5)), and breast cancer (P = .009). We also identified five

key subpathway components with genetic variants that are relevant for the risk of

these five cancer sites: inflammatory response for colorectal cancer (P = .006),

inflammation related cell cycle gene for lung cancer (P = 1.35x10(-6)), and

activation of immune response for ovarian cancer (P = .009). In addition,

sequence variations in immune system development played a role in breast cancer

etiology (P = .001) and innate immune response was involved in the risk of both

colorectal (P = .022) and ovarian cancer (P = .003).

CONCLUSIONS: Genetic variations in inflammation and its related subpathway

components are keys to the development of lung, colorectal, ovary, and breast

cancer, including SH2B3, which is associated with lung, colorectal, and breast

cancer. PMID: 26319099

7. Breast. 2015 Aug;24(4):491-6.

**Dietary inflammation potential and postmenopausal breast cancer risk in a German case-control study.**

Ge I, Rudolph A, Shivappa N, Flesch-Janys D, Hébert JR

Author information: Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany

Unhealthy dietary habits can increase the risk for serious medical conditions, such as cancer, yet the association between diet and breast cancer remains unclear. We investigated whether individual diets based on their inflammatory potential are associated with postmenopausal breast cancer risk by employing an

energy-adjusted dietary inflammation index. In a German population-based case-control study, 2887 postmenopausal breast cancer patients (aged 50-74 years, first diagnosed between 2002 and 2005) and 5512 healthy age-matched controls provided information on dietary habits for the year prior to diagnosis (cases) or

recruitment (controls) using a 176-items food frequency questionnaire. Associations between the energy-adjusted dietary inflammation index (E-DII) score (both as continuous variable and in quintiles) and risk for breast cancer were assessed using conditional logistic regression adjusted for potential confounders. No significant associations between the E-DII score and postmenopausal breast cancer risk were observed (adjusted OR Q5 vs Q1: 1.01, 95% CI: 0.86-1.17). Associations did not differ by estrogen receptor/progesterone

receptor status (ER + PR+: adjusted OR Q5 vs Q1: 1.06, 95% CI: 0.88-1.27; ER + or PR+: OR Q5 vs Q1: 1,07, 95% CI: 0.79-1.45; ER-PR-: OR Q5 vs Q1: 0.87 95% CI: 0.63-1.20). Our results regarding E-DII are consistent with previous studies reporting a lack of association between C-reactive protein, a marker of systemic

inflammation, and postmenopausal breast cancer risk. The findings may reflect a real absence of association between dietary inflammatory potential and postmenopausal cancer risk or an underestimation of association due to recall bias. Further investigation is warranted in cohort studies. PMID: 25987487

8. J Natl Cancer Inst. 2015 Jul 16;107(9).

**Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk.**

Gunter MJ, Wang T, Cushman M, Xue X, Wassertheil-Smoller S

Author information: Imperial College, London, UK; Albert Einstein College of Medicine, Bronx, NY

BACKGROUND: Adipokines and inflammation may provide a mechanistic link between

obesity and postmenopausal breast cancer, yet epidemiologic data on their

associations with breast cancer risk are limited.

METHODS: In a case-cohort analysis nested within the Women's Health Initiative

Observational Study, a prospective cohort of postmenopausal women, baseline

plasma samples from 875 incident breast cancer case patients and 839 subcohort

participants were tested for levels of seven adipokines, namely leptin,

adiponectin, resistin, interleukin-6, tumor necrosis factor-α, hepatocyte growth

factor, and plasminogen activator inhibitor-1, and for C-reactive protein (CRP),

an inflammatory marker. Data were analyzed by multivariable Cox modeling that

included established breast cancer risk factors and previously measured estradiol

and insulin levels. All statistical tests were two-sided.

RESULTS: The association between plasma CRP levels and breast cancer risk was

dependent on hormone therapy (HT) use at baseline (P interaction = .003). In a

model that controlled for multiple breast cancer risk factors including body mass

index (BMI), estradiol, and insulin, CRP level was positively associated with

breast cancer risk among HT nonusers (hazard ratio for high vs low CRP levels =

1.67, 95% confidence interval = 1.04 to 2.68, P trend = .029). None of the other

adipokines were statistically significantly associated with breast cancer risk.

Following inclusion of CRP, insulin, and estradiol in a multivariable model, the

association of BMI with breast cancer was attenuated by 115%.

CONCLUSION: These data indicate that CRP is a risk factor for postmenopausal

breast cancer among HT nonusers. Inflammatory mediators, together with insulin

and estrogen, may play a role in the obesity-breast cancer relation. PMID: 26185195

9. Exerc Sport Sci Rev. 2015 Jul;43(3):134-42.

**Influence of Exercise on Inflammation in Cancer: Direct Effect or Innocent Bystander?**

Murphy EA, Enos RT, Velázquez KT.

Author information: Department of Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina

We propose the hypothesis that the benefits of exercise on inflammation in cancer

are a result of a direct effect on inflammatory cytokines, including

interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein 1,

that are critical for cancer growth as well as a bystander effect of the

established relationship between exercise and cancer. PMID: 25906430

10. Breast Cancer Res Treat. 2015 Jun;151(2):235-8.

**A framework for the role of acute inflammation in tumor progression.**

Szalayova G, James TA, Rincon M.

Author information: Department of Surgery, Western Connecticut Health Network, Danbury, CT

Breast cancer remains the second leading cancer-related death in women in the United States. Despite improvements in early detection, prevention, and treatment, the mortality rate in breast cancer remains high secondary to the potential for cancer recurrence and the development of metastasis. To minimize breast cancer-related morbidity and mortality, understanding the factors leading to an increased risk of metastasis and developing clinical interventions that reduce this risk is essential. While the association between chronic inflammation and cancer progression is well documented in the literature, the role of acute inflammation and its impact on tumor proliferation and metastasis is less well understood. Here, we will review recently published preclinical studies in mouse models indicating that acute inflammation caused by clinical interventions plays

an important role in the risk of peripheral metastases. In addition, we will address the potential impact that these findings may have on the clinical management of breast cancer. PMID: 25893593

11. Sci Rep. 2015 May 22;5:10508.

**C-reactive protein and risk of breast cancer: A systematic review and meta-analysis.**

Guo L, Liu S, Zhang S, Chen Q, Zhang M, Quan P

Author information: Department of Cancer Epidemiology, Affiliated Cancer Hospital of Zhengzhou

University, Henan Cancer Hospital, Henan Office for Cancer Control and Research, China.

Associations between elevated C-reactive protein (CRP) and breast cancer risk have been reported for many years, but the results remain controversial. To address this issue, a meta-analysis was therefore conducted. Eligible studies were identified by searching the PubMed and EMBASE up to December 2014. Study-specific risk estimates were combined using a random-effects model. Altogether fifteen cohort and case-control studies were included in this meta-analysis, involving a total of 5,286 breast cancer cases. The combined OR

per natural log unit change in CRP for breast cancer was 1.16 (95% CI:1.06-1.27). There was moderate heterogeneity among studies (I(2) = 45.9%). The association was stronger in Asian population (OR = 1.57, 95% CI: 1.25-1.96) compared to European (OR = 1.12, 95% CI: 1.02-1.23) and American (OR = 1.08, 95%

CI: 1.01-1.16). Prediagnostic high-sensitivity CRP concentrations (OR = 1.22, 95% CI: 1.10-1.35) was superior to common CRP (OR = 1.08, 95% CI: 1.01-1.15) in predicting breast cancer risk. The meta-analysis indicated that elevated CRP levels was associated with increased risk of breast cancer. Further research effort should be performed to identify whether CRP, as a marker of inflammation, plays a direct role in breast carcinogenesis. PMID: 26001129

12. Semin Reprod Med. 2015 May;33(3):208-12.

**Estrogens, obesity, inflammation, and breast cancer-what is the link?** Brown KA, Simpson ER.

Author information: MIMR-PHI Centre for Medical Research, Monash Medical Centre, Victoria, Australia.

It gives me great pleasure to contribute to this special issue of Seminars which

honors the career of Bruce Carr. As it happens, Bruce was my first Fellow upon my

arrival at the Green Center for Reproductive Biology Sciences at UT Southwestern

Medical Center in 1977. At that time, the Center was filled with luminaries of

Reproductive Endocrinology, such as John Porter, Jack Johnston, Norman Gant, and

of course the Director, Paul MacDonald, so to be given the responsibility of

mentoring a new Fellow was a daunting responsibility. However, Bruce quickly

rolled up his sleeves and plunged straight in, and we forged a relationship which

led to some 36 manuscripts in 4 years. The first of these was entitled "The Role

of Serum Lipoproteins in Steroidogenesis by the Human Fetal Adrenal Cortex,"

published in the Journal of Clinical Endocrinology and Metabolism, volume 49,

pages 146-148, in 1979, and the authors were Simpson ER, Carr BR, Parker CR Jr,

Milewich L, Porter JC, and MacDonald PC. Bruce quickly moved up the ranks of the

Obstetrics/Gynecology Department to become full Professor and we went our

separate ways professionally, but we remain close friends to this day. This

special issue is indeed a worthy tribute to an outstanding career and especially

to Bruce's role as editor-in-chief of Seminars which he has guided through the

rapid evolution of the specialty, always maintaining a strong research focus and

thus carrying on the rich tradition of the Green Center and the

Obstetrics/Gynecology Department. PMID: 26036902

13. Mutat Res. 2014 Dec;770:19-28.

**Diet and lifestyle factors modify immune/inflammation response genes to alter breast cancer risk and prognosis: the Breast Cancer Health Disparities Study.** Slattery ML, Lundgreen A, Torres-Mejia G, Wolff

Tumor necrosis factor-α (TNF) and toll-like receptors (TLR) are important

mediators of inflammation. We examined 10 of these genes with respect to breast

cancer risk and mortality in a genetically admixed population of Hispanic/Native

American (NA) (2111 cases, 2597 controls) and non-Hispanic white (NHW) (1481

cases, 1585 controls) women. Additionally, we explored if diet and lifestyle

factors modified associations with these genes. Overall, these genes

(collectively) were associated with breast cancer risk among women with >70% NA

ancestry (P(ARTP) = 0.0008), with TLR1 rs7696175 being the primary risk

contributor (OR 1.77, 95% CI 1.25, 2.51). Overall, TLR1 rs7696175 (HR 1.40, 95%

CI 1.03, 1.91; P(adj) = 0.032), TLR4 rs5030728 (HR 1.96, 95% CI 1.30, 2.95;

P(adj) = 0.014), and TNFRSF1A rs4149578 (HR 2.71, 95% CI 1.28, 5.76; P(adj) =

0.029) were associated with increased breast cancer mortality. We observed

several statistically significant interactions after adjustment for multiple

comparisons, including interactions between our dietary oxidative balance score

and CD40LG and TNFSF1A; between cigarette smoking and TLR1, TLR4, and TNF;

between body mass index (BMI) among pre-menopausal women and TRAF2; and between

regular use of aspirin/non-steroidal anti-inflammatory drugs and TLR3 and TRA2.

In conclusion, our findings support a contributing role of certain TNF-α and TLR

genes in both breast cancer risk and survival, particularly among women with

higher NA ancestry. Diet and lifestyle factors appear to be important mediators

of the breast cancer risk associated with these genes. PMID: 25332681

14. Cell Signal. 2014 Nov;26(11):2350-7

**TLRs: linking inflammation and breast cancer.** Bhatelia K, Singh K, Singh R

Author information: Department of Bio-Chemistry, The M.S. University of Baroda, Gujarat, India.

Breast cancer is one of the leading causes of mortality in the females. Intensive

efforts have been made to understand the molecular mechanisms of pathogenesis of

breast cancer. The physiological conditions that lead to tumorigenesis including

breast cancer are not well understood. Toll like receptors (TLRs) are essential

components of innate immune system that protect the host against bacterial and

viral infection. The emerging evidences suggest that TLRs are activated through

pathogen associated molecular patterns (PAMPs) as well as endogenous molecules,

which lead to the activation of inflammatory pathways. This leads to increased

levels of several pro-inflammatory cytokines and chemokines mounting

inflammation. Several evidences support the view that chronic inflammation can

lead to cancerous condition. Inflammation aids in tumor progression and

metastasis. Association of inflammation with breast cancer is emerging. TLR

mediated activation of NF-κB and IRF is an essential link connecting inflammation

to cancer. The recent reports provide several evidences, which suggest the

important role of TLRs in breast cancer pathogenesis and recurrence. The current

review focuses on emerging studies suggesting the strong linkages of TLR mediated

regulation of inflammation during breast cancer and its metastasis emphasizing

the initiation of the systematic study. PMID: 25093807

15. Curr Opin Oncol. 2014 Nov;26(6):545-50.

**Obesity, proinflammatory mediators, adipose tissue progenitors, and breast cancer.**

Bertolini, Orecchioni S, Petit JY, Kolonin MG.

Author information: Laboratory of Hematology-Oncology, European Institute of Oncology, Milan, Italy

PURPOSE OF REVIEW: There is emerging evidence that obesity is associated with an

increase in the incidence, severity, and mortality from different types of

cancer, including postmenopausal breast cancer. Here, we discuss the role of

white adipose tissue (WAT) cells and of related soluble factors in the local and

metastatic growth of this neoplastic disease. Moreover, we discuss the recent

increase in the use of WAT-derived progenitor cells in breast cancer patients to

enhance the quality of breast reconstruction and the related risks.

RECENT FINDINGS: In several murine models, WAT cells and progenitors were found

to have cooperative roles in promoting local breast cancer. Moreover, they were

found to contribute to adipocytes and pericytes supporting the cancer

vasculature, and stimulated the metastatic progression of breast cancer. There

are some clinically retrospective data showing a significant increase in the

frequency of intraepithelial neoplasia in patients who received a lipofilling

procedure for breast reconstruction compared with controls.

SUMMARY: Preclinical models and clinical studies are urgently needed to

investigate how to inhibit the tumor-promoting activity of WAT cells and

progenitors. The risks associated with the use of WAT cells for breast

reconstructions should be better investigated retrospectively and prospectively. PMID: 25279961

16. Cancer Res. 2014 Jun 15;74(12):3248-58.

**Insulin, estrogen, inflammatory markers, and risk of benign proliferative breast disease.**

Catsburg C, Gunter MJ, Chen C, Cote ML, Kabat GC, Nassir R

Author information: Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx

Women with benign proliferative breast disease (BPBD) are at increased risk for

developing breast cancer. Evidence suggests that accumulation of adipose tissue

can influence breast cancer development via hyperinsulinemia, increased estrogen,

and/or inflammation. However, there are limited data investigating these pathways

with respect to risk of BPBD. We evaluated serologic markers from these pathways

in a case-control study of postmenopausal women nested within the Women's Health

Initiative Clinical Trial. Cases were the 667 women who developed BPBD during

follow-up, and they were matched to 1,321 controls. Levels of insulin, estradiol,

C-reactive protein (CRP), and adiponectin were measured in fasting serum

collected at baseline. Conditional logistic regression models were used to

estimate ORs for the association of each factor with BPBD risk. Among nonusers of

hormone therapy, fasting serum insulin was associated with a statistically

significant increase in risk of BPBD (OR for highest vs. lowest quartile = 1.80;

95% confidence interval, CI, 1.16-2.79; Ptrend = 0.003) as were levels of

estradiol (OR for highest vs. lowest tertile = 1.89; 95% CI, 1.26-2.83; Ptrend =

0.02) and CRP (OR for highest vs. lowest quartile = 2.46; 95% CI, 1.59-3.80;

Ptrend < 0.001). Baseline adiponectin level was inversely associated with BPBD

risk (OR for highest vs. lowest quartile = 0.47; 95% CI, 0.31-0.71; Ptrend <

0.001). These associations persisted after mutual adjustment, but were not

observed among users of either estrogen alone or of estrogen plus progestin

hormone therapy. Our results indicate that serum levels of estrogen, insulin,

CRP, and adiponectin are independent risk factors for BPBD and suggest that the

estrogen, insulin, and inflammation pathways are associated with the early stages

of breast cancer development. PMID: 24755474

17. Mol Cell Endocrinol. 2014 Jan 25;382(1):673-82.

**The immune system and inflammation in breast cancer.** Jiang X, Shapiro DJ.

Author information: Department of Medicine, VA Palo Alto Health Care System/Stanford University

School of Medicine, Stanford, CA

During different stages of tumor development the immune system can either

identify and destroy tumors, or promote their growth. Therapies targeting the

immune system have emerged as a promising treatment modality for breast cancer,

and immunotherapeutic strategies are being examined in preclinical and clinical

models. However, our understanding of the complex interplay between cells of the

immune system and breast cancer cells is incomplete. In this article, we review

recent findings showing how the immune system plays dual host-protective and

tumor-promoting roles in breast cancer initiation and progression. We then

discuss estrogen receptor α (ERα)-dependent and ERα-independent mechanisms that

shield breast cancers from immunosurveillance and enable breast cancer cells to

evade immune cell induced apoptosis and produce an immunosuppressive tumor

microenvironment. Finally, we discuss protumorigenic inflammation that is induced

during tumor progression and therapy, and how inflammation promotes more

aggressive phenotypes in ERα positive breast cancers. PMID: 23791814

18. Adv Exp Med Biol. 2014;816:53-73.

**The role of inflammation in inflammatory breast cancer.** Fouad TM, Kogawa T, Reuben JM, Ueno NT.

Author information: Department of Breast Medical Oncology, Morgan Welch Inflammatory Breast Cancer

Research Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX

Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer.

Despite extensive study, whether inflammation contributes to the tumorigenicity

or aggressiveness of IBC remains largely unknown. In this chapter, we will review

the potential role played by inflammation in IBC based on the results of in

vitro, in vivo, and patient studies. Current evidence suggests that several major

inflammatory signaling pathways are constitutively active in IBC and breast

cancer. Among them, the NF-κB, COX-2, and JAK/STAT signaling systems seem to play

a major role in the tumorigenesis of IBC. Inflammatory molecules such as

interleukin-6, tumor necrosis factor alpha (TNF-α), and gamma interferon have

been shown to contribute to malignant transformation in preclinical studies of

IBC, while transforming growth factor-β, interleukins 8 and 1β, as well as TNF-α

appear to play a role in proliferation, survival, epithelial-mesenchymal

transition, invasion, and metastasis. In this chapter, we also describe work thus

far involving inhibitors of inflammation in the development of prevention and

treatment strategies for IBC. PMID: 24818719

19. Cancer Epidemiol Biomarkers Prev. 2013 Jul;22(7):1319-24.

**Adipocytokines, inflammation, and breast cancer risk in postmenopausal women: a prospective study.**

Gross AL, Newschaffer CJ, Hoffman-Bolton J, Rifai N, Visvanathan K.

Author information: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health,

Baltimore, MD

Obesity is a known risk factor for postmenopausal breast cancer; it has been

postulated that adipocytokines may mediate this association. We explored the

relationship between three markers altered by obesity: leptin, adiponectin, and

soluble tumor necrosis factor receptor 2 (sTNF-R2), an inflammatory marker, with

breast cancer risk in postmenopausal women. A nested case-control study of

postmenopausal women was conducted within CLUE II, a prospective population-based

cohort. Baseline plasma levels of leptin, adiponectin, and sTNF-R2 were assayed

in 272 female breast cancer cases and 272 controls matched on age, date, and hour

of blood draw. Conditional logistic regression was used to estimate matched odds

ratios (OR) and 95% confidence intervals (CI). sTNF-R2 and leptin were

independently positively associated with breast cancer risk in adjusted models.

The OR for breast cancer comparing the highest to lowest tertile was 2.44 (95%

CI: 1.30-4.58) for sTNF-R2 and 1.98 (95% CI: 1.20-3.29) for leptin. While higher

levels of adiponectin were protective (OR for the lowest tertile = 1.63; 95% CI:

1.02-2.60), there was no dose response. A 20% reduction in the breast cancer risk

associated with overweight/obesity was observed when sTNF-R2 alone was included

in multivariable models. Including both sTNF-R2 and adiponectin in the models

resulted in a 29% reduction in the OR. Adipocytokines and sTNF-R2 are important

factors in the etiology of postmenopausal breast cancer due to adiposity. This

study informs our understanding of the relationship between obesity,

inflammation, and postmenopausal breast cancer and identifies potential

biomarkers. PMID: 23651666

20. Asian Pac J Cancer Prev. 2013;14(1):243-8.

**Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies.**

Guo YZ, Pan L, Du CJ, Ren DQ, Xie XM.

Author information: Department of Respiratory Medicine, Xuzhou Central Hospital, Affiliated Xuzhou

Hospital of Medical College of Southeast University, China.

BACKGROUND: Associations between elevated C-reactive protein (CRP) and cancer

risk have been reported for many years, but the results from prospective cohort

studies remains controversial. A meta-analysis of prospective cohort studies was

therefore conducted to address this issue.

METHODS: Eligible studies were identified by searching the PubMed and EMBASE up

to October 2012. Pooled hazard ratios (HR) was calculated by using random effects model.

RESULTS: Eleven prospective cohort studies involving a total of 194,796

participants and 11,459 cancer cases were included in this meta-analysis. The

pooled HR per natural log unit change in CRP was 1.105 (95% confidence interval

(CI): 1.033-1.178) for all-cancer, 1.308 (95% CI: 1.097-1.519) for lung cancer,

1.040 (95% CI: 0.910-1.170) for breast cancer, 1.063 (95% CI: 0.965-1.161) for

prostate cancer, and 1.055 (95% CI: 0.925-1.184) for colorectal cancer.

Dose-response analysis showed that the exponentiated linear trend for a change of

one natural log unit in CRP was 1.012 (95% CI: 1.006-1.018) for all-cancer. No

evidence of publication bias was observed.

CONCLUSIONS: The results of this meta-analysis showed that the elevated levels of

CRP are associated with an increased risk of all-cancer, lung cancer, and

possibly breast, prostate and colorectal cancer. The result supports a role of

chronic inflammation in carcinogenesis. Further research effort should be

performed to identify whether CRP, as a marker of inflammation, has a direct role

in carcinogenesis. PMID: 23534731