

# Diabetes and Breast Cancer in Asian-Americans

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## Diabetes Mellitus and Breast Cancer

- Diabetes – an established risk factor for cancers of pancreas, liver and endometrium
- Wolf et al (2005) conducted a meta-analysis of published studies on diabetes and breast cancer in western populations
  - 6 cohort studies
    - Effect of diabetes: RR 1.25 (1.19-1.31)
  - 4 case-control studies
    - Effect of diabetes: RR 1.13 (0.99-1.28)
- Role of obesity not resolved in published studies

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## Diabetes Mellitus and Breast Cancer

- Diabetes and breast cancer – complex relationship
  - Effect of high body weight and breast cancer
  - Effect of high body weight and diabetes
  - Is the effect of diabetes on breast cancer risk independent of weight and other risk factors?

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## Population-Based Case-Control Study of Breast Cancer in Los Angeles County Asian-Americans

- BCRP 1RB-0287, BCRP 3PB-0102, BCRP 5PB-0018
- Cases:
  - Chinese, Filipino, Japanese
  - 20-75 years of age at diagnosis of incident, histologically confirmed breast cancer, on or after January 1, 1995
  - Residents of Los Angeles County
- Controls:
  - Frequency matched to cases on neighborhood, Asian ethnicity and age
  - No history of breast cancer

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## Main Objectives

- To test the hypothesis that high intake of soy foods ↓ the risk of breast cancer
- To examine the roles of:
  - menstrual and reproductive factors, including use of exogenous hormones
  - other dietary factors
  - physical activity
  - body characteristics
  - other factors, e.g., smoking, family history, use of specific medications
- To examine the roles of selective metabolism genes

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## Statistical Analysis

- Case-control analysis
  - Use conditional logistic regression methods with matched sets defined jointly by age and specific Asian ethnicity
  - Include other covariates (birthplace, years of residence in the US, age at menarche, parity, menopausal status, physical activity, family history, and others) in the regression model

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## Study Population

		Cases (n=1277)	Controls (n=1160)
Race	Chinese	35%	42%
	Japanese	28%	27%
	Filipino	37%	31%
Age	<=39	8%	15%
	40-49	34%	37%
	50-59	29%	26%
	60-69	20%	16%
	70+	9%	7%
	Mean (sd)	52.9 (10.5)	50.6 (10.6)

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## Established Risk Factors

- Age at menarche
- Parity, Age at first birth
- Family history of breast cancer
- Physical activity
- Body size (weight, waist/hip circumferences)
- Menopausal hormone therapy
  - Soy intake (adolescence and adult life)
  - Green tea

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## Assessment of Diabetes Mellitus

- Ever told by a doctor you have diabetes?
  - If 'yes' – type of diabetes (Type 1, Type 2, gestational diabetes)
  - Age or year at diagnosis
  - Treated for diabetes

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## Prevalence of Diabetes Mellitus-Asian American Women

- Among control women, the prevalence of diabetes was 4.3%
  - Prevalence increased significantly with age
    - 11.3% in women aged >64 years of older vs 1.2% in women aged <45 years of age
  - Prevalence increased significantly with increasing body size
    - 7.9% in women in with body mass index (BMI) >24.6 vs 0.7% in women with BMI <=20.4
  - Prevalence decreased significantly with increasing physical activity
    - 2.8% in women who had regular physical activity for 20+ yrs vs 6.3% in women with <4 years of regular activity

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## Diabetes and Breast Cancer Risk in Asian Americans

		Control %	Adj OR*	BMI/WHR+ Adj OR
All subjects	No	95.7	1.00	1.00
	Yes	4.3	1.68	1.71 (1.1-2.5)
Premenopausal	No	98.3	1.00	1.00
	Yes	1.7	1.55	1.49 (0.6-3.6)
Postmenopausal	No	93.0	1.00	1.00
	Yes	7.0	1.74	1.67 (1.1-2.6)

\*Adjusting for age, race, years in US, education, age at menarche, parity, years of physical activity, age at menopause and type of menopause (in analyses including all subjects and postmenopausal women).

+ Additional adjustment for weight, WHR, soy and tea intake.

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## Diabetes and Breast Cancer Risk in Asian Americans

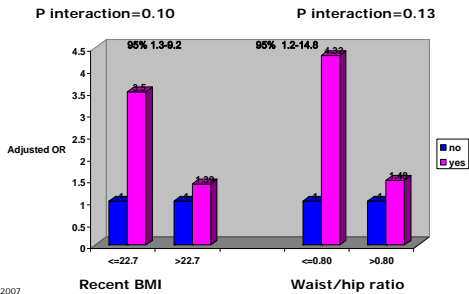
		Control %	BMI /WHR+ Adj OR
Years since first diagnosis	No	95.7	1.0
	<=7	2.2	1.4 (0.9-2.5)
	8-14	1.1	2.0 (0.9-4.4)
	>14	1.0	2.0 (0.9-4.5)
	P trend		0.007
Treated	No	0.8	2.1 (0.9-4.7)
	Yes	3.5	1.6 (1.1-2.4)

Adjusting for age, race, years in US, education, age at menarche, parity, years of physical activity, age at menopause and type of menopause, BMI, WHR and others.

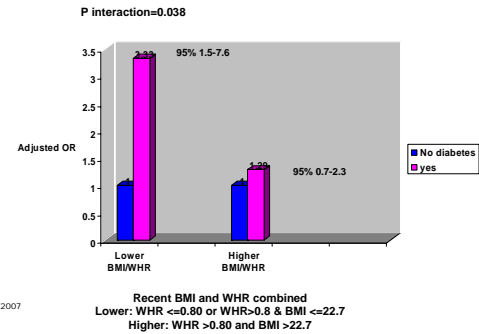
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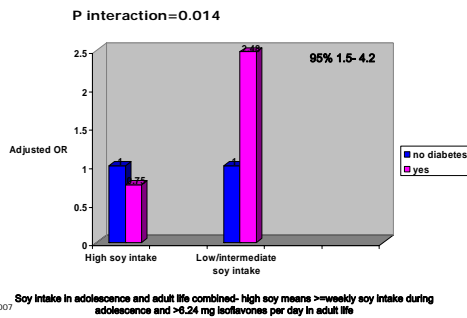
## Diabetes and Breast Cancer Risk By Recent Weight and by Waist/hip Ratio



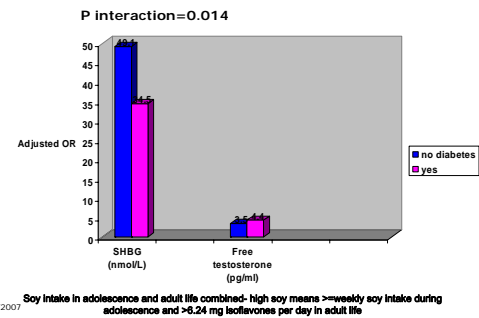
## Diabetes and Breast Cancer Risk By Recent Weight and WHR combined



## Diabetes and Breast Cancer Risk By Soy Intake



## Hormone Levels by History of Diabetes in Control Women



## Diabetes, Soy and Breast Cancer

- Soy consumers did not have increased risk associated with history of diabetes- why?
- Peroxisome proliferator-activated receptor gamma (PPAR) is highly expressed in adipose tissue and in breast tissues
  - PPAR may have a tumor suppressor role in breast cancer - use of PPAR ligands can inhibit proliferation and induce differentiation and apoptosis
- Ligands for PPAR include
  - Polyunsaturated fatty acids
  - Common antidiabetic drugs (fibrates, glitazones)
  - Soy genistein and daidzein
- These synthetic ligands decrease insulin resistance and serve as antidiabetic drugs

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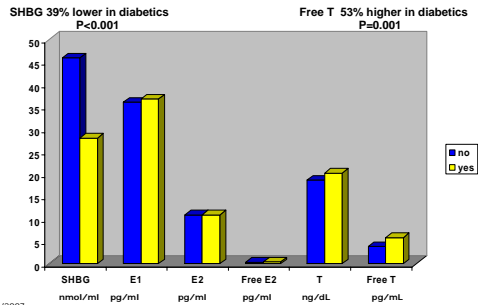
## Substudy- Hormone Profiles in Controls by History of Diabetes

- Measured sex hormone levels in a subgroup of postmenopausal women who were non-hormone users and reached menopause naturally
- Compared sex hormone levels in women with diabetes (n=34) and women without diabetes (n=178)
- Hormones measured
  - Total and free estradiol (E2), estrone (E1)
  - Total and free testosterone (T), androstenedione
  - Sex hormone-binding globulin (SHBG)

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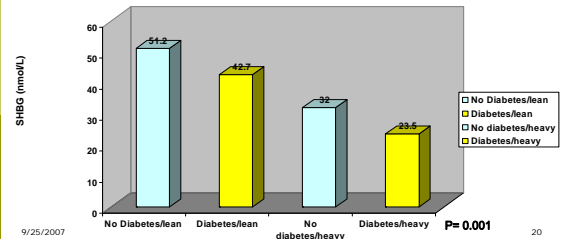
### Diabetes and Mean Circulating Hormone Levels in Postmenopausal Control Women



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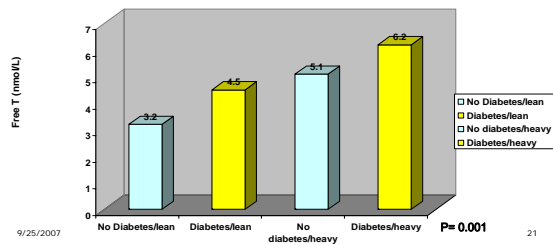
### Diabetes, Body Size and Mean SHBG Levels in Postmenopausal Control Women



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### Diabetes, Body Size and Mean Free Testosterone Levels in Postmenopausal Control Women



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### Diabetes Mellitus and Breast Cancer

- Larsson et al (2007) conducted a meta-analysis of published studies on diabetes and breast cancer in western populations
  - 15 cohort studies
    - Effect of diabetes: RR 1.20 (1.11-1.30)
  - 5 case-control studies
    - Effect of diabetes: RR 1.18 (1.05-1.32)

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### Diabetes, Body Size, and Breast Cancer

- Independent effects of diabetes and body size on sex hormone pathway
  - Marked reduction in SHBG levels
  - Marked increase in free T levels
- Independent role of SHBG and breast cancer
  - Insulin inhibits the production of SHBG which results in an increase in free steroid hormone
- Independent role of androgens and breast cancer

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### Diabetes and Breast Cancer

- Hyperinsulinemia may increase breast cancer risk
  - Direct effects on breast tissues
  - Indirect effects by increasing circulating estrogens, testosterone and IGF
- Effects very similar in case-control and cohort studies

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Reference

Wu AH, Yu MD, Tseng DD, Stanczyk FZ, Pike MC. Diabetes and risk of breast cancer in Asian American women. *Carcinogenesis* 28: 1561-66, 2007

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