An Estrogen Model: the Relationship between Body Mass Index, Menopausal Status, Hormone Replacement Therapy, and Breast Cancer Risk

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Introduction

The Body Mass Index (BMI) and Hormone Replacement Therapy (HRT) Enigma

Premenopausal	Postmenopausal	
	No HRT	HRT users
High BMI = Low Risk	High BMI = High Risk	Little to no effect of BMI

Estrogen may hold the key to explaining the enigma

- Estrogen is known to stimulate growth of normal and malignant tissue. Abundance of estrogen increases risk of breast cancer.
- For postmenopausal women, adipose tissue is the major source of estrogen for women not taking HRT. Hence, higher BMI corresponds to higher estrogen levels and higher breast cancer risk
- For premenopausal women, adipose tissue stores estrogen, and consequently, reduces estrogen exposure of breast tissue. Hence, higher BMI protects against breast cancer.

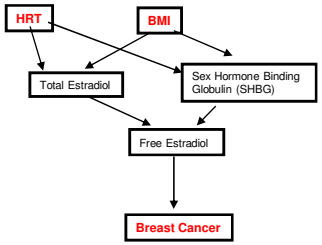
Objective

To quantitatively evaluate the relationship between BMI, menopausal status, HRT, and breast cancer risk.

Methods

We develop a mathematical model of the relationship between BMI, menopausal status, HRT and breast cancer risk through the following steps:

- Construct a mathematical representation of simplified hormonal pathways
- Relate BMI and HRT use to concentration of hormones in premenopausal and postmenopausal women
- Relate concentration of free estradiol to breast cancer risk.



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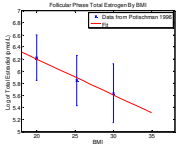
Key assumptions/relationships

- Experimental data are used to quantify the relationship between BMI and total estradiol and between BMI and sex hormone binding globulin (SHBG).
- Concentration of free estradiol is calculated based on concentration of total estradiol and SHBG through law of mass action.
- A doubling of concentration of free estradiol increases risk of breast cancer by a factor of 2.08 in premenopausal women and by a factor of 1.50 in postmenopausal women (Eliassen et al., 2006; Key et al., 2003) (Estimates based on logistic regression of case-control sets taken from nine prospective studies, including only never-users of HRT)

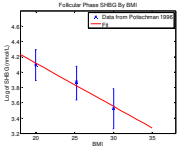
Premenopausal Women

- Hormone levels vary with phase of menstrual cycle
- Model uses hormone levels during follicular phase, because breast cancer risk is most strongly associated with estrogen levels during this phase.

Total estradiol decreases with BMI

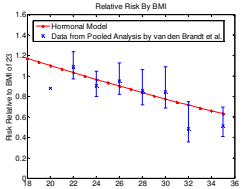


SHBG decreases with BMI



- Using law of mass action, calculate that free estradiol decreases with BMI
- Lower concentration of free estradiol leads to lower risk of breast cancer

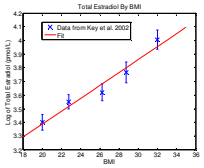
Validation



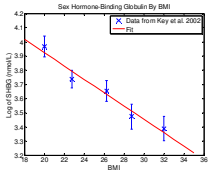
- In independent validation, model agrees with data.
- Note that the 95% confidence interval is absent in the data for BMI of 20 because a BMI of 20 was used as a reference value for calculating relative risks in the Van den Brandt analysis.

Postmenopausal Women (Non-HRT Users)

Total estradiol increases with BMI

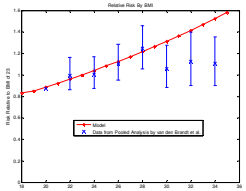


SHBG decreases with BMI



- Free estradiol increases with BMI
- High concentration of free estradiol is correlated with high risk of breast cancer.

Validation



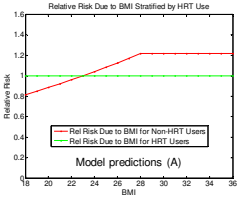
- In independent validation, model agrees with data for BMI less than 28.
- In order to match the plateau of breast cancer risk observed in the data for BMIs over 28, we introduce idea of a saturation level, above which additional amounts of free estradiol do not incur additional risk.

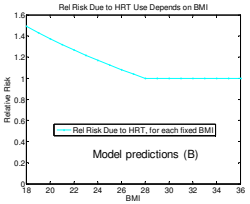
References:

Eliassen, H. et al. (2006). Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. *Journal of the National Cancer Institute* , 1406-1413.
Key, T. et. al (2002). Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *Journal of the National Cancer Institute* , 606-616.
Key, T. et. al. (2003). Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *Journal of the National Cancer Institute* , 1218-1226.
Nachtigall, L. et al. (2000). Serum estradiol-binding profiles in postmenopausal women undergoing three common estogen replacement therapies. *Menopause* , 7 (4), 243-250.
Potishman, N. et. al. (1996). Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *Journal of the National Cancer Institute* , 756-758.
Slater, C. et. al. (2001). Comparison of estrogen and androgen levels after oral estrogen replacement therapy. *Journal of Reproductive Medicine* , 1052-1056.
Van den Brandt, P. et. al. (2000). Pooled analysis of prospective cohort studies on height, weight, and breast cnacer risk. *American Journal of Epidemiology* , 514-527.

Postmenopausal Women (HRT Users)

- Model includes combined hormone replacement therapy only
- Combined hormone replacement therapy has greater impact on breast cancer risk than estrogen only hormone replacement therapy
- For HRT users, we relate BMI to levels of total estradiol and SHBG using summarized data on HRT users (Nachtigall et al., 2000, Slater, 2001)
- We calcuate free estradiol level and associated breast cancer risk as for non-HRT users
- We use the saturation assumption





- Because of the saturation assumption, the model produces the correct qualitative interactions between BMI, HRT use, and breast cancer risk for postmenopausal women: there is no increase in breast cancer risk due to high BMI among HRT users (A), and the increase in breast cancer risk due to HRT user disappears for women with high BMI (B).
- The model underpredicts the effect of HRT use on breast cancer risk (data not shown).

Limitations

- The model is a simplified representation of actual physiology. There may be other hormonal pathways through which BMI and HRT influence breast cancer risk.
- The model of premenopausal hormones and breast cancer risk is based on limited data.
- The model of the effects of HRT on free estradiol and SHBG levels is based on limited data.
- Measurements of hormone levels are inaccurate and depend on the assay used. A more precise model could be built in the future if additional data using standardized assays becomes available.

Conclusions

- In order to match the leveling off of risk for post-menopausal women with high BMI, we found it necessary to assume a saturation level beyond which additional free estradiol did not influence breast cancer risk. This saturation assumption also produced the correct interactions between BMI and HRT use. The idea of a saturation level makes an interesting hypothesis for future research.
- The ability of this mathematical model to validate against experimental data supports the idea that estrogen levels are responsible for the relationship between BMI, HRT, menopausal status, and breast cancer risk.