Breast Cancer Risk Prediction

Impact of Time-Dependent Risk Factors and Heterogeneity by ER/PR Receptor Status

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I. Nature of Risk Prediction

1. Breast cancer is a complex disease that has many risk factors.

2. The nature of the risk factors and their magnitude of effect changes over time.

3. We've chosen to quantify the effects of each risk factor by developing a calendar over time for that risk factor from menarche to pre-menopause to post-menopause and summarizing effects over the calendar (e.g., average BMI before menopause; average BMI after menopause)

II. Metrics of Risk (annual incidence vs. cumulative incidence)

ANNUAL INCIDENCE

- Most risk prediction algorithms are based on (annual) incidence (I.e. short-term risk) – e.g., 50 year old women – what is the risk of breast cancer over the next year

- However, annual incidence is usually low and of perhaps more relevance is cumulative incidence over longer periods of time (e.g. age 50 to age 70)

II. Metrics of Risk (annual incidence vs. cumulative incidence)

CUMULATIVE INCIDENCE

1. Cumulative incidence
   A) Requires a Kaplan-Meier type calculation
   B) If risk factors change over time (which is likely for BMI, PMH use and possible BBD and family Hx as well) then cumulative incidence will change as a function of these variables

2. Risk prediction in terms of cumulative incidence is not simply a single estimate of risk but rather a collection of possible risks, according to possible changes in risk factor status (perhaps over long periods of time)

III. Age-specific and cumulative incidence of breast cancer by weight profile, Nurses' Health Study, 1976-1994

	Weight percentile								Cumulative incidence age 30-70 ($x10^{-5}$)	RR
	18 years		50 years		60 tears		70 years			
	%	BMI	%	BMI	%	BMI	%	BMI		
Average woman	50	21	50	24	50	25	50	25	6083	1.0 (ref)
Stable weight	50	21	10	20	10	20	10	20	5564	0.92
Above average weight gain	50	21	90	31	90	32	90	31	7023	1.19
Consistently lean	10	18	10	20	10	20	10	20	6027	1.00
Consistently obese	90	25	90	31	90	32	90	31	6387	1.06

Age at menarche=13 years; parity=2; ages at birth=20 and 23 years; age at menopause=50 years; type of menopause=natural; no postmenopausal hormone therapy; women with no benign breast disease, no family history, average height (I.e., height before menopause= 64.5 inches (163.8 cm); height after menopause= 64.4 inches (163.6 cm), lifetime nondrinkers.

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IV. Breast cancer subtypes

1. Virtually all risk prediction for breast cancer assumes that breast cancer is a homogeneous disease, i.e. all types of breast cancer have the same risk profiles

2. Recent work (Colditz et al, JNCI 2004) has indicated that risk factor profiles may vary according to both ER status and PR status for some risk factors, but are the same for other risk factors

3.

Risk factor		**ER+/PR+**	**ER-/PR-**
Age	Duration of premenopause	11%/yr p<.001	5%/yr p=0.001
	Duration of natural menopause	5%/yr p<.001	1%/yr p=0.13
		RR (95% CI)	**RR (95% CI)**
Age at menopause	45	1.0	1.0
	55	1.50 (1.27-1.77)	1.24 (0.99-1.55)
Pregnancy History	Nulliparous	1.0	1.0
	20,23,26,29	0.71 (0.60-0.84)	1.07 (0.77-1.69)
	35	0.86 (0.69-1.08)	1.39 (0.89-2.17)
PMH use (10 yrs)	Estrogen	1.18 (1.00-1.38)	0.96 (0.78-1.17)
	Estrogen + progesterone	1.67 (1.33-2.10)	1.21 (0.87-1.68)

3. (con't)

Risk factor		**ER+/PR+**	**ER-/PR-**
		RR (95% CI)	**RR (95% CI)**
Body Mass Index	Avg. woman*	1.0	1.0
	Above avg. wt.gain Woman+	1.27 (1.15-1.39)	0.96 (0.83-1.11)
BBD	No	1.0	1.0
	Yes	1.64 (1.46-1.85)	1.54 (1.24-1.90)
Family Hx of breast cancer	No	1.0	1.0
	Yes	1.45 (1.25-1.68)	1.70 (1.32-2.19)

* 50 percentile at age 18 (123 lbs), 50 (142 lbs), 60 (146 lbs), 70 (145 lbs)

+ 50 percentile at age 18 (123 lbs), 90 percentile at age 50 (185 lbs), 60 (190 lbs), 70 (185 lbs)

V. Implications of heterogeneity of risk for breast cancer subtypes on risk prediction

1. Different risk model for breast cancer-specific subtypes (e.g. ER+/PR+, ER-/PR-)

2. Risk model for total breast cancer is no longer a simple Poisson regression model, but is instead a mixture of different risk models for different disease subtypes

3. A polychotomous logistic regression (PLR) model is required to fit the data.

4. One implication of this model is that some properties of Poisson regression – e.g. constant relative risk over the full range of risk factor X are no longer valid

V. Implications of heterogeneity of risk for breast cancer subtypes on risk prediction

5. Instead, a risk surface has to be developed based on specified combinations of risk factors:

- Age at menarche
- Age at menopause
- Parity
- AAfB
- BBD
- Family Hx
- Anthropometric variables
- PMH use

Etc.

Summary

1. Breast cancer is a complex disease with many possibly time dependent risk factors
2. Short-term risk prediction involves current and past levels of risk factors
3. Long-term risk prediction is also determined by how risk factors will change prospectively and may involve more than a single estimate of risk
4. Risk factor profiles for different types of breast cancer may vary according to ER/PR status
5. Short-term absolute risk is low; relative risk between age-specific extreme deciles is 5-7 fold for ER+/PR+ breast cancer; 4 fold for ER-/PR- breast cancer, making risk stratification viable at least on a group level.