Assessing diet-health relationships: Focus on dietary components consumed daily by nearly all persons

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In recognition of his internationally renowned contributions to the field of nutrition epidemiology and his commitment to understanding measurement error associated with dietary assessment.

Presenters and Collaborators

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Objectives

Learning objectives

- Understanding:
  - That measurement error leads to bias in estimated diet-health associations
  - Concepts involved in regression calibration, a method to correct for this bias
  - The role of calibration studies in regression calibration
- Learning how to apply regression calibration in diet and health studies

Main results on impact of measurement error

From webinar 6,

- When there is a single dietary exposure measured with error in a diet-health model:
  1) Estimated diet-health relationship (risk) is attenuated (underestimated)
  2) Power to detect relationship is decreased
  3) Statistical tests are still valid
- Same conclusions seem to hold approximately when several dietary exposures are included in a model
- In this webinar we will (mostly) address problem 1

Why adjust the risk estimate?

- Unadjusted estimates will underestimate
  - True health risk due to unhealthy eating
  - True health benefit due to healthy eating
- As a result:
  - Public health impact of dietary change would be underestimated
  - Health officials could mistakenly ignore the potential impact
Methods of adjusting the risk estimate

- Regression calibration
- SIMEX
- Maximum likelihood
- Multiple imputation
- Moment reconstruction
- ... and more!

Regression calibration for univariate exposures

**Linear equations and linear functions**

- The equation for a line in two dimensions is
  \[ Y = a_0 + a_1X \]

- The equation for a line in k dimensions is
  \[ Y = a_0 + a_1X_1 + a_2X_2 + \ldots + a_kX_k \]

- This relationship can be expressed as a function
  \[ f(Y) = a_0 + a_1X_1 + a_2X_2 + \ldots + a_kX_k \]

- A function of this form is called a linear function

Risk model

- Risk model (logistic regression):
  \[ \log \{ \text{Odds}(Y=1) \} = a_0 + a_1T + a_2Z_1 + \ldots + a_pZ_p \]

  - \( Y \) = health outcome variable (0 or 1)
  - Odds(\( Y=1 \)) = Prob(\( Y=1 \)) / Prob(\( Y=0 \))
  - \( T \) = true dietary intake
  - \( Z_1, \ldots, Z_p \) = other variables in disease model
  - \( Z = \{Z_1, \ldots, Z_p\} \)
  - \( \alpha_T, \alpha_{Z_1}, \ldots, \alpha_{Z_p} \) = regression coefficients
  - \( = \) log odds ratios

- Risk model:
  \[ \log \{ \text{Odds}(Y=1) \} = a_0 + a_1X + a_2Z_1 + \ldots + a_pZ_p \]

- Problem:
  - We are unable to measure true intake \( T \)
  - Instead, we obtain reported intake \( Q \) which is subject to measurement error
  - If we use \( Q \) instead of \( T \) in the risk model, the estimate of \( \alpha_T \) will be biased (attenuated)

Regression calibration

- Risk model:
  \[ \log \{ \text{Odds}(Y=1) \} = a_0 + a_1X + a_2Z_1 + \ldots + a_pZ_p \]

- Regression calibration method:
  - Step 1: Calculate \( E(T|Q, Z) \) = conditional expectation of \( T \) given \( Q \) and \( Z \)
  - \( E(T|Q, Z) \) is the “predicted value” of \( T \) given \( Q \) and \( Z \)
  - Step 2: Replace \( T \) with \( E(T|Q, Z) \) in risk model
### Regression calibration

- **Risk model:**
  \[
  \log(\text{Odds}(Y=1)) = a_0 + a_x Q + a_{Z_1} Z_1 + \ldots + a_{Z_p} Z_p
  \]

- **Regression calibration assumption:**
  - Q has "nondifferential error" with respect to disease Y
  - Q has no information about Y beyond that provided by T and Z

- Under this assumption, regression calibration estimates are (approximately) unbiased

### How do we calculate \( E(T|Q, Z) \)?

- **In order to predict T, we need to develop a “prediction equation”**

- **Example:** linear prediction equation

  \[
  E(T|Q, Z) = \lambda_0 + \lambda_Q Q + \lambda_{Z_1} Z_1 + \ldots + \lambda_{Z_p} Z_p
  \]

- If T were observable in a sample of participants, could estimate the parameters in prediction equation by regressing T on Q and Z

### Summary of regression calibration

- Regression calibration involves 2 regressions:
  - Step 1: Regress R on Q and Z to get prediction equation \( E(T|Q, Z) \)
  - Step 2: Regress health outcome Y on \( E(T|Q, Z) \) and Z

- Regression calibration makes 2 assumptions:
  - Q has nondifferential error with respect to Y
  - R is unbiased for T

### Linear regression calibration

- **We will focus on linear regression calibration**

- In linear regression calibration:
  - Predicted value of T is a linear function of Q and Z

  \[
  E(T|Q, Z) = \lambda_0 + \lambda_Q Q + \lambda_{Z_1} Z_1 + \ldots + \lambda_{Z_p} Z_p
  \]

  - Parameters in prediction equation \((\lambda_0, \ldots, \lambda_{Z_p})\) are estimated by linear regression of R on Q and Z

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### Calibration studies

- **Prediction equation (calibration equation) is developed in a sample on which the reference instrument is measured**

- A sample collected for this purpose is called a “calibration study”

- We will learn more about calibration studies later in this webinar
Dietary components that are consumed daily by most persons

Sometimes we want to fit a risk model where $T$ is on a transformed scale.

Risk model:
\[
\log \left\{ \text{Odds}(Y=1) \right\} = \alpha_0 + \alpha_1 g(T) + \alpha_2 Z_1 + \ldots + \alpha_p Z_p
\]

Examples of transformation $g(T)$:
- Log transformation: $g(T) = \log(T)$
- Square root transformation: $g(T) = \sqrt{T}$

Potential problem with linear regression calibration

Risk model:
\[
\log \left\{ \text{Odds}(Y=1) \right\} = \alpha_0 + \alpha_1 g(T) + \alpha_2 Z_1 + \ldots + \alpha_p Z_p
\]

Prediction equation is also on transformed scale
\[
E\{g(T)|Q, Z\} = \lambda_0 + \lambda_1 g(Q) + \lambda_2 Z_1 + \ldots + \lambda_p Z_p
\]

Estimate parameters in prediction equation by regressing $g(R)$ on $g(Q)$ and $Z$.

Example: dietary fat and breast cancer

Thiebaut et al. (J Nat Cancer Inst, 2007)

Nested case-control analysis

3501 invasive breast cancer cases, with 4 matched controls per case:
- Age at entry (+/- 1 year)
- Person-years at risk (≥ years for case)
- Hormone use (never/former, current)

Logistic regression of breast cancer status ($Y$) on log total fat intake ($T$)

Other covariates ($Z$)
- Body mass index (< 25, 25-30, ≥ 30)
- Age at first birth / number of children (nulliparous, <30 / 1-2, <30 / 3+, ≥30 / 1+)
- Hormone use (never/former, current)
- Age at entry
Dietary components that are consumed daily by most persons

Regression calibration:

Step 1: Estimate prediction equation by linear regression of $R$ on $Q$ and $Z$ in calibration study

$E(T|Q,Z) = 4.5 + 0.28 \times Q + 0.06 \times BMI_1 + 0.04 \times BMI_2 + 0.01 \times AFBI + 0.03 \times AFBI_2 + 0.05 \times AFBI_3 + 0.01 \times Hormone - 0.002 \times Age$

Use prediction equation to predict intake for each subject in main study

Regression calibration for univariate exposures

Example: dietary fat and breast cancer

Step 2: Logistic regression of $Y$ on $E(T|Q,Z)$ and $Z$ in main study

$\log\{ \text{Odds}(Y=1) \} = 2.4 + 0.11 \times E(T|Q,Z) + 0.06 \times BMI_1 + 0.17 \times BMI_2 + 0.26 \times AFBI + 0.36 \times AFBI_2 + 0.01 \times AFBI_3 + 0.01 \times Hormone + 0.002 \times Age$
Dietary components that are consumed daily by most persons

- Step 2: Logistic regression of Y on Q and Z in the main study
  
  \[
  \log\{\text{Odds}(Y=1)\} = -1.7 + 0.03Q + 0.08\times\text{BMI} + 0.18\times\text{BMI} - 0.26\times\text{AFB} - 0.37\times\text{AFB} + 0.02\times\text{AFB} + 0.26\times\text{Hormone} + 0.003\times\text{Age}
  \]

- Attenuated log odds ratio: \( \hat{\alpha}_0 = 0.03 \)
- Standard error: \( \text{s.e.}(\hat{\alpha}_0) = 0.03 \)

- Step 3: Divide attenuated log odds ratio by attenuation coefficient
  
  \[
  \hat{\alpha} = \frac{\hat{\alpha}_0}{\hat{\lambda}^Q} = \frac{0.03}{0.28} = 0.11
  \]

- Rosner’s method and regular linear regression calibration: estimates are the same

- Step 4: Estimate standard error using delta method
  
  \[
  \text{s.e.}(\hat{\alpha}) \approx \sqrt{\left(\frac{\text{s.e.}(\hat{\alpha}_0)}{\hat{\lambda}^Q}\right)^2 + \left(\frac{\hat{\alpha}_0\text{s.e.}(\hat{\lambda}^Q)}{\hat{\lambda}^{2Q}}\right)^2}
  \]

  = 0.09

- Bootstrap and delta method standard errors are similar but not exactly the same

Example: Dietary fat and breast cancer

Dietary fat intake and breast cancer risk in NIH-AARP

<table>
<thead>
<tr>
<th>Correction for Measurement Error</th>
<th>Log Odds Ratio (s.e.)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected</td>
<td>0.03 (0.03)</td>
<td>1.03 (0.98, 1.09)</td>
</tr>
<tr>
<td>Regression calibration</td>
<td>0.11 (0.10)</td>
<td>1.12 (0.93, 1.35)</td>
</tr>
<tr>
<td>Rosner’s method</td>
<td>0.11 (0.09)</td>
<td>1.12 (0.94, 1.33)</td>
</tr>
</tbody>
</table>

Summary of Rosner’s method

- Advantage: standard errors can be computed quickly and easily
- Limitation: Only applies when the regression calibration model is linear
- Next webinar (webinar 8) will focus on situation where regression calibration model is nonlinear

Summary

Regression calibration for univariate exposures

Regression calibration for multivariate exposures

REGRESSION CALIBRATION FOR MULTIVARIATE EXPOSURES
**Motivation: energy-adjusted analysis**

- Researchers often perform an “energy-adjusted” analysis by adding total energy intake to model.
- Sometimes, the main exposure variable is also modified.
  - Example: Percent energy from fat.
- Reasons for energy adjustment:
  - Interest in association between dietary composition and health.
  - Energy-adjustment often decreases measurement error in reported intake.

**Regression calibration with two dietary exposures**

- Disease model:
  \[
  \log\left( \text{Odds}(Y=1) \right) = \alpha_T + \alpha_1 T_1 + \alpha_2 T_2 + \alpha_3 Z_1 + \ldots + \alpha_p Z_p
  \]
- Replace \( T_1 \) and \( T_2 \) with \( E(T_1|Q_1,Q_2,Z) \) and \( E(T_2|Q_1,Q_2,Z) \).
- \( E(T_1|Q_1,Q_2,Z) \) is the predicted value of \( T_1 \) given reported intakes \( Q_1 \) and \( Q_2 \) and explanatory variables \( Z_1, \ldots, Z_p \).
- Confidence intervals for odds ratios calculated using the bootstrap method, exactly as described for a single exposure.
Dietary components that are consumed daily by most persons

- NIH-AARP Diet and Health Study
- Logistic regression of breast cancer status (Y) on log total fat intake (T₁) and log non-alcohol energy intake (T₂)
- Substitution effect: adding fat intake while keeping non-alcohol energy constant
- Other covariates (Z) same as for univariate fat and breast cancer example

**Example: energy-adjusted fat and breast cancer**

**Example: energy-adjusted fat and breast cancer**

Dietary fat intake and breast cancer risk in NIH-AARP

- Adjusted for non-alcohol energy intake

**Correction for Measurement Error**

<table>
<thead>
<tr>
<th></th>
<th>Log Odds Ratio (s.e.)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected</td>
<td>0.15 (0.05)</td>
<td>1.16 (1.05, 1.29)</td>
</tr>
<tr>
<td>Regression calibration</td>
<td>0.29 (0.11)</td>
<td>1.34 (1.09, 1.66)</td>
</tr>
<tr>
<td>Alternate method</td>
<td>0.29 (0.10)</td>
<td>1.34 (1.10, 1.64)</td>
</tr>
</tbody>
</table>

**Calibration studies**

- Studies performed to “calibrate” the main study instrument (Q) to a reference instrument (R)
- To calibrate Q means to develop a prediction equation to predict R given Q
- The information from these studies can be used as the basis for regression calibration

**Types of calibration studies**

- Internal calibration study: random subsample of main study participants
- External calibration study: separate study of participants that are similar to those participating in the main study
- Participants must complete the same study instrument (Q) that is used in the main study
- Internal calibration is preferable

**Reference instrument: ideal properties**

- Unbiased measure of individual true usual intake
- Errors uncorrelated with true usual intake
- Errors uncorrelated with errors in study instrument
Dietary components that are consumed daily by most persons

- Doubly labeled water for energy intake
- 24-hour urinary nitrogen for protein intake
- 24-hour urinary potassium for potassium intake

**Reference instrument: examples**

- Instruments that are usually used as a reference
  - 24-hour recalls (one or more)
  - Multiple-day food records
- Problems
  - Biased for true intake
  - Errors correlated with true intake
  - Errors correlated with errors in FFQ

**Performance of 24HR as reference**

OPEN Study: Attenuation factors estimated using recovery biomarker or 24HR as reference
(Freedman et al., J Nat Cancer Inst, 2011)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Gender</th>
<th>Reference Biomarker</th>
<th>Reference 24HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>Men</td>
<td>0.06 (0.03)</td>
<td>0.21 (0.04)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.03 (0.03)</td>
<td>0.09 (0.05)</td>
</tr>
<tr>
<td>Protein Density</td>
<td>Men</td>
<td>0.43 (0.07)</td>
<td>0.35 (0.07)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.33 (0.08)</td>
<td>0.45 (0.06)</td>
</tr>
<tr>
<td>Potassium Density</td>
<td>Men</td>
<td>0.57 (0.08)</td>
<td>0.59 (0.05)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.61 (0.08)</td>
<td>0.62 (0.07)</td>
</tr>
</tbody>
</table>

**Design of calibration studies**

- Two important factors:
  - Number of participants in calibration study
  - Number of reference measures per participant

**Size of calibration study**

\[
\text{s.e.} (\hat{\alpha}) \approx \frac{\sigma_\lambda}{\hat{\lambda}} \left[ \frac{\text{s.e.} (\hat{\alpha})}{\sigma_\lambda} \right]^2 + \left( \frac{\text{s.e.} (\hat{\lambda})}{\lambda_0} \right)^2
\]

- 1st term is uncertainty of estimating attenuated log odds ratio in main study of size N
- 2nd term is uncertainty of estimating attenuation factor in calibration study of size n

\[
\text{s.e.} (\hat{\lambda}) = \frac{\sigma_\lambda^2}{\sqrt{n \sigma_\lambda^2}}
\]

\[\hat{\alpha} \] = residual variance in regression of R on Q
Measurement Error Webinar Series

**Dietary components that are consumed daily by most persons**

- Choose $n$ so that 2nd term is a small fraction of 1st term, say $1/10^{th}$

$$\frac{\sigma_2^2}{n \lambda_0^2 \sigma_0^2} = \frac{1}{10} \left( \frac{s.e.(\hat{a}_0)}{a_0} \right)^2$$

- Solve for $n$

$$n = 10 \left( \frac{\sigma_2^2}{\lambda_0^2 \sigma_0^2} \right) \left( \frac{a_0}{s.e.(\hat{a}_0)} \right)^2$$

**Calibration studies**

**Size of calibration study**

- Calculation of the size of a calibration study

$$s.e.(\hat{a}_0) \approx \frac{\sigma_a}{\lambda_0} \sqrt{\frac{s.e.(\hat{a}_0)}{a_0}^2 + \frac{\sigma_2^2}{n \lambda_0^2 \sigma_0^2}}$$

**Example: size of calibration study**

- Example calculation of the size of a calibration study

$$n = 10 \left( \frac{\sigma_2^2}{\lambda_0^2 \sigma_0^2} \right) \left( \frac{a_0}{s.e.(\hat{a}_0)} \right)^2$$

- 95% CI: $\hat{a}_0 \pm 1.96 \times s.e. \hat{a}_0$

- Choose $s.e.(\hat{a}_0) = a_0 / 2$

$$n = 40 \left( \frac{\sigma_2^2}{\lambda_0^2 \sigma_0^2} \right)$$

**For fat intake in AARP**

- $\lambda_0 = 0.28$, $\sigma_0^2 = 0.25$, $\sigma_2^2 = 0.34$

- $n = 694$

**Number of reference measurements**

- Example calculation of the number of reference measurements

$$\sigma_{ik}^2 = \sigma_{ik}^2 + \sigma_{ik}^2 - \sigma_{ik}^2 / k - \lambda_0^2 \sigma_0^2$$

- $\sigma_{ik}^2$ is the variance of a single R and $\sigma_{ik}^2$ is the covariance between repeat R's

**Example: number of reference measurements**

- Example calculation of the number of reference measurements

$$n = \frac{\sigma_{ik}^2}{\lambda_{ik}^2} \left( \frac{\sigma_{ik}^2}{\lambda_{ik}^2} \right)$$

- Gain in precision due to additional reference measurements depends on the size of $\sigma_{ik}^2 - \sigma_{ik}^2$

**Example: number of reference measurements**

- Example calculation of the number of reference measurements

- Relative sample size required in a calibration study with $k$ repeats of R per participant

<table>
<thead>
<tr>
<th>$k$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1000</td>
</tr>
<tr>
<td>2</td>
<td>672</td>
</tr>
<tr>
<td>3</td>
<td>563</td>
</tr>
<tr>
<td>4</td>
<td>508</td>
</tr>
</tbody>
</table>

(Based on fat intake in AARP)
Dietary components that are consumed daily by most persons

- Performing regression calibration when regression calibration model is linear
  - Minimum number = 1
- Performing regression calibration when regression calibration model is nonlinear
  - Minimum number = 2
- Estimating correlation of Q and T
  - Minimum number = 2
  - Estimating power
- Assessing the quality of Q (validity)

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### Summary

**STATISTICAL TESTING AND REGRESSION CALIBRATION**

- Univariate exposures
- Multivariate exposures
- Calibration studies
- Statistical testing

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### Hypothesis testing

- Null hypothesis: no association between dietary intake and the health outcome ($\alpha_T = 0$)
- Wald test statistic: estimated log odds ratio divided by its standard error
  $$ W = \frac{\hat{\alpha}_T}{s.e.(\hat{\alpha}_T)} $$
- W is approximately normal with
  - mean = $E(\hat{\alpha}_T) / s.e.(\hat{\alpha}_T)$
  - standard deviation = 1

---

### Validity of statistical tests

- A statistical test is valid if probability of a type I error really is at the chosen significance level
- For Wald test, condition holds only if the mean of $W = 0$ under the null hypothesis
- Since mean of $W = E(\hat{\alpha}_T) / s.e.(\hat{\alpha}_T)$, Wald test is valid only if
  $$ E(\hat{\alpha}_T) = 0 \text{ whenever } \alpha_T = 0 $$
- If estimator is unbiased (i.e., if $E(\hat{\alpha}_T) = \alpha_T$), then Wald test is valid

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### Is the uncorrected test valid?

- Wald test performed on the uncorrected log odds ratio will be called the “uncorrected test”
- For univariate exposures, the uncorrected log odds ratio is biased
  $$ E(\hat{\alpha}_Q) = \lambda_Q \alpha_T $$
- Nevertheless, if $\alpha_T = 0$, then $E(\hat{\alpha}_Q) = 0$
- Uncorrected Wald test for univariate exposure is valid
Dietary components that are consumed daily by most persons

- For bivariate exposures, the uncorrected log odds ratio has mean
  \[ E(\hat{\alpha}_{Q1}) = \lambda_{Q1} \alpha_{T1} + \lambda_{Q12} \alpha_{T2} \]

- When \( \alpha_{T1} = 0 \),
  \[ E(\hat{\alpha}_{Q1}) = \lambda_{Q12} \alpha_{T2} \]

- Uncorrected Wald test for bivariate exposures is not valid

- If contamination factor \( \lambda_{Q12} \) is sufficiently small, then uncorrected test is approximately valid

### Statistical testing and regression calibration

**Is the uncorrected test valid?**

- Contamination factors are generally small and not statistically significant
- Freedman et al. (2011) concluded that statistical tests for uncorrected test with multiple dietary exposures will be approximately valid
- Caveat: conclusion based on only three nutrients: protein, potassium and energy

### Statistical power

- Statistical power is the probability of rejecting the null hypothesis when the null hypothesis is false
- Equivalently, the probability of detecting an association as statistically significant
- Power depends on the size of true log odds ratio:
  - For \( \alpha_T \) close to 0, power is small
  - As \( |\alpha_T| \) increases, power increases

### Example: loss of power for uncorrected test

- NIH-AARP Diet and Health Study
- For fat intake, estimated \( \rho_{OT} = 0.40 \)
- In a study with \( N \) subjects:
  - If power = 90% using true intake \( T \), then power = 25% using \( Q \) instead of \( T \)
  - To get 90% power using \( Q \), would need a sample size of \( N / \rho_{OT}^2 = 6.25 \times N \)
- Similar loss of power for multivariate exposures measured with error
Regression calibration adjusts the estimated log odds ratio by dividing by the attenuation coefficient
\[ \hat{\alpha} = \frac{\hat{\alpha}_0}{\hat{\lambda}_0} \]

However, this adjustment changes the standard error of the estimate
\[ \text{se}(\hat{\alpha}) = \sqrt{\left( \frac{\text{se}(\hat{\alpha}_0)}{\hat{\lambda}_0} \right)^2 + \left( \frac{\hat{\alpha}_0 \text{se}(\hat{\lambda}_0)}{\hat{\lambda}_0^2} \right)^2} > \frac{\text{se}(\hat{\alpha}_0)}{\hat{\lambda}_0} \]

As a result:
- Expected value of test statistic W does not increase (it decreases slightly)
- Wald test based on regression calibration has slightly less power than the unadjusted test
- Regression calibration in its usual form corrects for bias, but does recover power lost due to measurement error

An enhanced version of regression calibration can sometimes be used to recover (some of) the power lost due to measurement error

Idea: predict T using E(T|Q, Z, C) instead of E(T|Q, Z), where C is a variable that:
1. Helps to predict true intake, but
2. Is not related to disease outcome conditional on true intake and covariates Z

See lecture 10 in the series for fuller discussion

### Summary

1. Measurement error causes attenuation of estimated risk parameters and loss of power to detect diet-health associations.
2. Regression calibration is an accessible method for adjusting these attenuated estimates to remove bias.
3. Calibration studies are needed to provide the information necessary to apply regression calibration.
4. In its usual form, regression calibration does not recover power lost due to measurement error.
5. Statistical tests of uncorrected risk estimates are, on current evidence, approximately valid.

### Questions & Answers

Moderator: Amy Subar

Please submit questions using the Chat function
Next Session

Tuesday, November 8, 2011
10:00-11:30 EST

Assessing diet-health relationships with FFQ:
Focus on episodically-consumed dietary components

Victor Kipnis
National Cancer Institute