Prediction Model: Breast Cancer in Women Irradiated for a Pediatric Malignancy

Working Groups: Second malignancy, Biostatistics/Epi, Cancer Control

Principal investigator: Chaya Moskowitz, PhD

The following figure lists the members of the research team, consultants, and CCSS investigators.

RESEARCH TEAM

Memorial Sloan-Kettering Cancer Center

Chaya Moskowitz, PhD	Biostatistics
Kevin Oeffinger, MD	Cancer Survivorship
Suzanne Wolden, MD	Radiation Oncology
Colin Begg, PhD	Biostatistics
Peter Bach, MD, MAPP	Health Outcomes
Jonine Bernstein, PhD	Epidemiology
Monica Morrow, MD	Breast Surgery

CCSS Coordinating Center (St. Jude)

Gregory Armstrong, MD	CCSS Project Director
Christopher Vukadinovich	Data/Systems Director
Christie Cooper	Lead CRA
Blaire Benavides	Lead CRA
Jola Dowdy	CRA

Dutch Childhood Oncology Group LATER Cohort

Flora van Leeuwen, PhD	Epidemiology
Cecile Ronckers, PhD	Epidemiology
Birgitta Versluys, MD	Medical Oncology

CONSULTANTS

Study Design/Data Analysis

Mitchell Gail, MD, PhD	National Cancer Institute
Peter Inskip, PhD	National Cancer Institute
Lois Travis, MD, ScD	University of Rochester Medical Center
Sarah Donaldson, MD	Stanford
Patricia Ganz, MD	UCLA
Leslie Robison, PhD	CCSS/St. Jude
Helena van der Pal, MD	Academic Medical Center, Amsterdam

Dissemination

Michael Kattan, PhD	Case Western
Robert Smith, PhD	American Cancer Society
Michael Fordis, MD	Baylor College of Medicine
Frank Sculli, MS	BioDigital Systems, LLC
Brandon Smith	BioDigital Systems, LLC

Background: This is a currently funded study that was approved as an ancillary study (R01 CA136783). As per discussions with Greg Armstrong, the following concept proposal consists of the grant application Aims page and the statistical analysis. As this grant has been in process for several years and has already completed secondary data collection, information regarding other steps has not been included. References or other information is available upon request.

Specific Aims

Breast cancer following chest radiation for the treatment of pediatric cancer is a common and serious late effect of therapy. It is associated with significant morbidity, mortality, and diminished quality of life. Onset of breast cancer can occur at a relatively young age in this population and has been noted as early as eight years post radiation. Survival rates are strongly associated with the stage of disease at the time of diagnosis. Early-stage breast cancer is curable in this population. Thus, international groups recommend initiation of breast cancer screening at a young age. The Children's Oncology Group (COG), considered to be the standard of care in the United States (US) and Canada, recommends annual mammography and breast MRI starting at age 25 or eight years after completion of radiation therapy. Importantly, there are several key gaps in the literature that limit the quality of this recommendation.

The COG guideline recommends screening women treated with chest radiation $\geq$ 20 Gy. For women who were treated in the 1970s - 1980s with high dose (35 - 50 Gy) mantle radiation, this recommendation is quite appropriate. However, it is well known that the risk of breast cancer increases linearly with dose of radiation. Approximately one-quarter of women with breast cancer were treated with doses of chest radiation < 20 Gy. This recommendation also does not address differences in risk based upon the volume of breast tissue exposed, reflecting more contemporary therapy that has reduced not only the dose but also the volume of radiation. Non-therapy factors, such as a first degree relative with breast cancer, early age at menarche, and late age at menopause, likely increase risk. In contrast, ovarian toxic therapy with pelvic radiation or high dose alkylating agent therapy decreases risk. Thus, a risk prediction model that includes relevant modifying factors to estimate the 5- and 10-year absolute risk of breast cancer would provide a tool to individually communicate

risk and would improve upon our current crude recommendation. Such a model would be applicable to women treated with contemporary therapy which generally aims to limit the dose of radiation to 10 - 25 Gy. Importantly, providing absolute risk may also improve the rate of screening among women treated with higher dose radiation, as the majority of women with this exposure are not being regularly screened.

The proposed study will thus fill a critical gap in existing knowledge. Our goal is to quantify the long-term risk of breast cancer by taking into account information on treatment exposure and traditional risk factors for breast cancer, first focusing on the factors' association with the risk of breast cancer and then focusing on obtaining predictions of the individualized risk of breast cancer based on the relevant factors. For these purposes we plan to use the unique resources of the North American Childhood Cancer Survivor Study (CCSS) and the Dutch LATe Effect Registry (LATER) cohorts. These two cohorts include the largest assembled group in the world of women with and at risk for breast cancer following therapeutic chest radiation.

Aim 1: Derive a breast cancer risk prediction model using chest radiation, additional treatment-related factors, traditional breast cancer risk factors, and other potential risk factors to predict the probability of breast cancer among women who have previously been treated with chest radiation for a childhood malignancy.

The treatment-related factors to be studied are the dose/volume/fraction of chest radiation, treatment with pelvic or abdominal radiation, treatment with an alkylating agent, and primary cancer diagnosis. The traditional risk factors to be included in this analysis include the Gail model factors (age at menarche, age at first live birth, number of first degree female relatives with breast cancer, number of previous breast biopsies, biopsy with atypical hyperplasia). Other risk factors to be studied are age at menopause (or number of years with intact ovarian function following cancer therapy), hormone replacement therapy/oral contraceptive use, and body mass index. Possible interactions between risk factors will be studied. The study population will be women in the original CCSS cohort who were diagnosed with a childhood cancer from 1970-1986 and treated with chest radiation.

Aim 2: Validate the model derived in Aim 1 on an independent validation data set.

We will validate the model using women in the Dutch LATER cohort (diagnosed with childhood cancer from 1970-1999) and women in the expanded CCSS cohort (diagnosed from 1987-1999).

Aim 3: Develop a risk calculator that will predict an individual's absolute risk of breast cancer.

By incorporating the prediction model into user-friendly software, we aim to create a tool that provides computer-assisted risk prediction in a format that can be easily used in clinical practice. A long-term objective of this research project is to establish a basis for building future absolute risk tools to predict other outcomes for which survivors of cancer are at risk.

D8. Statistical Methodology

D8.1 Aim 1 Analysis Methods

Aim 1: Derive a breast cancer risk prediction model using the dose of chest radiation, additional treatment-related factors, and the traditional breast cancer risk factors to predict the probability of breast cancer among women who have previously been treated with chest radiation for a childhood malignancy.

Basic modeling approach: The Cox proportional-hazards model[115] will be used to evaluate the association between each of the predictor variables and the risk of breast cancer. The Cox model is a standard statistical tool for time-to-event multivariate models. It takes the form

$$\lambda(t \mid \mathbf{Z}) = \lambda_0(t) e^{\boldsymbol{\beta}' \mathbf{Z}}$$

where $\lambda(t \mid \mathbf{Z})$ is the hazard (risk) of breast cancer for an individual of age *t* years old with risk factors **Z**=(Z_1, Z_2, …, Z_p), $\lambda_0(t)$ is the baseline hazard function, and **β=(**β_1, β_2, …, β_p) is the vector of regression coefficients. With this approach we assume that there is a common baseline risk of breast cancer ($\lambda_0(t)$) which is adjusted for individual cases to have either higher or lower risk than the common baseline risk. The regression coefficients quantify the association between the risk of breast cancer and variables in the model. They are interpreted in terms of the relative risk (hazard ratio). That is, $\lambda(t \mid \mathbf{Z}) / \lambda(t \mid \mathbf{Z}^*) = \exp(\sum_{k=1}^{p} \beta_k (Z_k - Z_k^*))$ is the risk of breast cancer for a group of women with risk factors **Z** compared with the risk of breast cancer for a

group of women with risk factors **Z***. We judge whether potential prognostic factors are associated with the risk of breast cancer by making inferences about **β**.

In particular, for our analysis we will model the risk of breast cancer as a function of the variables listed in Section D3. Initially the variables will be explored in univariate analyses. Different forms of the factors, such as categorizing or dichotomizing continuous variables and more sophisticated methods such as restricted cubic splines will be considered. Estimates of the relative risk and corresponding 95% confidence intervals will be calculated. In addition, the Wald test statistic will be used to formally test associations.

To build a multivariate model, we plan to begin by considering the full model incorporating all variables and interactions listed in Section D3. Decisions over which variables to exclude will be based on judgment, with additional guidance from an assessment of the predictive accuracy of the model. For instance, we may remove variables for which the estimated association with breast cancer risk is very small and the variable has little impact on the predictive accuracy of the model. The predictive accuracy from any reduced models will be compared to the predictive accuracy of the full model to ensure that precision of the risk predictions is not lost.

For this purpose, predictive accuracy will be quantified using the c-index, which is a measure of concordance.[116] The c-index measures how well the model discriminates between subjects with the outcome and those without it, in our case between women who will develop breast cancer and those women who will not. In the situation where there is no censored data, the c-index is equivalent to the area under the receiver operating characteristic (ROC) curve. A useless model that is incapable of discriminating between those subjects with the outcome and those without it will have a c-index of 0.5. A perfect model that discriminates between subjects with and without the outcome with no errors will have a c-index equal to 1.0.

In addition, when assessing predictive accuracy we are ultimately interested in how well the model makes predictions for new patients, not patients who contributed data to the model building process. Thus, simply using data on all women in our cohort to build multiple models and then choosing a final model (equivalently, a final set of predictor variables) by calculating the c-index directly from this same data is not appropriate. To correct for this problem, we will use a procedure called 10-fold cross validation.[117] This methodology involves randomly dividing the data into 10 mutually exclusive sets. One at a time, each subset is removed and the model is built on the remaining 9 combined sets. The c-index is then calculated on the removed subset, in effect simulating “new” patients. This process is repeated for each subset and then the median of the c-indices is taken as the corrected measure of predictive accuracy.

Missing data: We do not expect to have a substantial amount of missing data. Note that the outcome, breast cancer status and the date of breast cancer diagnosis, will be known for all women in the cohort. Further, information on all treatment-related factors will be available for virtually all participants to be included in the analysis. The only possible place that missing data may arise is in the information collected on the traditional breast cancer risk factors. During data collection, however, every effort will be made to ensure that there are no missing data for these predictors. Therefore, we do not expect missing data to be an issue for this analysis.

Competing risks: A consideration in building an absolute risk prediction model is the presence of competing risks. The projected risk of developing breast cancer may be affected by the risk of death from causes other than breast cancer. Specifically, the risk of breast cancer is likely to be reduced by the possibility of dying from another cause before breast cancer develops. In our analysis we will take into account the competing risk of death due to other causes using methodology developed in Fine and Gray[118] and described further in Kattan, Heller and Brennan.[119] By using the conditional cumulative incidence function and estimating the cumulative baseline subdistribution hazard with a weighted version of Breslow’s estimate,[120] this approach allows us to model covariate effects on the hazard subdistribution for breast cancer and the hazard subdistribution for non-breast cancer deaths separately. Advantages of this method include that it will allow us to assess factors that are predictive of death due to causes other than breast cancer directly from our data and that it does not restrict these factors to be the same as the factors that are included in the model for predicting breast cancer.[118] In contrast to the model developed by Travis et al. where the competing hazard of death due to other causes was obtained from external data (registries that participate in the Surveillance Epidemiology and End Results [SEER] Program), we will be able to evaluate whether other factors such as radiation dose are associated with the risk of non-breast cancer death from data particularly suited to this specific population and then incorporate the relevant information into our risk prediction model.

Evaluating the model: The Cox proportional hazards model assumes that the predictor variables are linearly related to the log hazard function. To help determine the best functional form for each variable, plots of the

martingale residuals against the predictor variable will be used to evaluate this assumption.[121,122] Smoothed lines will be fit to these scatter plots to assess linearity. If there is evidence that this assumption is not met, different transformations of the variables will be considered, including restricted cubic splines and various categorizations. When considering interaction terms, multiplicative and additive interactions will be explored.

The Cox model is a multiplicative model that assumes that the hazard rates of two individuals with different values of a covariate are proportional. To evaluate whether this assumption is appropriate we will use graphical methods and formal statistical tests. The graphical methods will include the log(-log(survival)) plot, which is a plot of the logarithm of the cumulative hazard functions for different groups of individuals with different values of the covariate (where continuous variables will be categorized for this purpose) versus the logarithm of time. The formal tests will include the scaled Schoenfeld residual test[123] and the time-dependent covariate test.[115] If there is evidence that the proportional hazards assumption is violated, we will explore other options for modeling the variable appropriately such as including it as a time-dependent covariate in the proportional hazards model, stratifying by the covariate, and using other regression models. In particular, we will evaluate whether an additive hazards regression model is more appropriate for the data. In an additive hazard model, the conditional hazard at time t is modeled as a linear combination of the covariates

$$\lambda(t \mid \mathbf{Z}(t)) = \beta_0(t) + \sum_{k=1}^{p} \beta_k(t) Z_k(t).$$

This model assumes that there is an unknown baseline hazard rate which is adjusted in an additive manner for individual cases to have either a higher or lower risk. The coefficients are written as functions of time to accommodate covariates that may change over time.

Overall model fit will be evaluated by using the Cox-Snell residuals.[124,125] We will compute the Nelson-Aalen estimator of the cumulative hazard rate for the residuals and then plot this estimated hazard rate against the residuals. To study leverage points, the influence of each observation on the estimation process will be checked by plotting Schoenfeld's partial residuals for each predictor against the case number.[126] To further help identify possible outliers, the deviance residuals will be plotted against the fitted model values.[125] Finally, Fine and Gray[118] also suggest a procedure for obtaining confidence intervals for the individualized risk projections. We will follow their suggestion and use a simulation method to evaluate the distribution of the cumulative incidence function in order to obtain point-wise confidence intervals.

Final model: *Once the model has been validated in Aim 2 (described below), if the model is well-calibrated we will refit the model (using the same variables and functional forms decided upon during the model building process) to the original CCSS cohort data combined with the two validation cohorts to determine final coefficient magnitudes and confidence intervals. If the model is not well-calibrated, we will recalibrate as described in detail below in Section D8.3 to obtain the final model.*

D8.2 Sample Size Justification for Aim 1

We explore here the power we will have to determine the association between the relative risk of breast cancer and several predictor variables. While our final goal is to have a model that estimates absolute risk rather than relative risk, the relative risk model is the first step in building the absolute risk model, so it may be helpful to understand how well we will be able to detect associations with *187* breast cancer cases. Because our goal is not to study each predictor variable independently but instead assess them in combination, here we evaluate the power we will have to detect an association between a predictor variable and the risk of breast cancer in the presence of other possibly correlated predictor variables.

We first consider the case of binary predictor variables. It has been shown that in this situation, the power to detect an association depends in part on the number of events (the number of women with breast cancer), the proportion of subjects with the risk factor Z, denoted p_z, (for instance, the proportion of women with a family history of breast cancer), the strength of the association quantified by the hazard ratio (HR), and the correlation between the multiple predictor variables.[127,128] Because we have no way of knowing prior to analysis exact values for each of these parameters, we consider a range of different scenarios that we expect might reasonably arise. Using a formula presented in Hseih and Lavori,[127] in the table below we show the power we will have to detect an association between a predictor variable and the risk of breast cancer in the presence of other predictor variables that are correlated with the predictor variable under investigation using a two-sided 0.05 level test for:

(1) different levels of this correlation (0.1 represents a small degree of correlation, 0.5 a moderate degree of correlation, and 0.7 a high degree of correlation),

(2) different values of p_z (0.1 represents a small proportion, 0.3 a slightly larger proportion, and 0.5 a moderate proportion),
(3) different HRs (with 1.6 and 2.0, and 2.2 representing different degrees of a modest association).

The highlighted cells in Table 5(a) indicate the situations in which we will have at least 80% power to detect an association. For evaluating the expected power to detect an association between a continuous covariate and the risk of breast cancer in the presence of other potentially correlated variables, the quantity p_z is no longer relevant. In its place, the power now depends upon the variance of the continuous covariate, which is again difficult to know in advance. In Table 5(b), we show scenarios similar to those used above except that now the second column of the table represents the hypothetical standard deviation of a continuous covariate.

Table 5. Power to detect an association between (a) a binary variable and (b) a continuous variable with the risk of breast cancer in the presence of other correlated variables *(Numbers updated for this submission)*

Hazard ratio	(a) Binary variable				(b) Continuous variable			
	p_z	Correlation			Standard Deviation	Correlation		
		0.10	0.50	0.70		0.10	0.50	0.70
1.6	0.1	0.48	0.39	0.30	0.3	0.48	0.39	0.30
	0.3	0.83	0.73	0.56	0.5	0.89	0.80	0.63
	0.5	0.89	0.80	0.63	0.7	0.99	0.98	0.93
2.0	0.1	0.81	0.69	0.53	0.3	0.81	0.69	0.53
	0.3	0.99	0.96	0.87	0.5	> 0.99	0.98	0.93
	0.5	> 0.99	0.98	0.92	0.7	> 0.99	> 0.99	> 0.99
2.2	0.1	0.90	0.80	0.64	0.3	0.90	0.80	0.64
	0.3	> 0.99	0.99	0.94	0.5	> 0.99	> 0.99	0.97
	0.5	> 0.99	> 0.99	0.97	0.7	> 0.99	> 0.99	> 0.99

For comparison, Inskip et al. estimated an odds ratio (relative risk) for breast cancer of 1.9 for women who received doses of chest radiation between 0.14 and 1.29 Gy relative to women who did not receive chest radiation with the odds ratio increasing to 10.8 for doses between 30-60 Gy.[17] Kenney et al. estimate the relative risk of breast cancer associated with a family history of breast cancer to be 2.6 in women treated with chest radiation.[9] Therefore, from both tables we see that we expect to have sufficient power to detect modest associations in a variety of different plausible scenarios that we anticipate will arise in our analysis.

D8.3 Aim 2 Analysis Methods

Aim 2: Validate the model derived in Aim 1 on an independent validation data set

Quantifying model performance: There are two components of model performance that we will use to evaluate the final risk prediction model. The first component is discrimination, that is, the ability of the model to discriminate between a woman who will develop breast cancer and one who will not develop breast cancer. We will measure discriminatory ability primarily with the c-index, described above. The prediction model will be applied to the validation cohort to obtain the predicted probability of breast cancer for each member of the cohort. These predicted probabilities will then be compared to the observed breast cancer outcomes of the validation cohort using the c-index to quantify how well the model differentiates between women with and without breast cancer. While the c-index is the most widely used measure of discrimination in the applied literature, we recognize that it is not without limitations. In particular, the c-index is biased when there is a large amount of censored data. In our setting, any participant who has not developed breast cancer is "censored." Consequently, for comparison we will also compute a recently proposed measure of concordance probability that is not affected by the degree of censoring in the data.[129]

The second component of model performance we will assess is calibration. The term calibration refers to how well the model predicts the risk of breast cancer across different subgroups of women with varying levels of risk. We will assess calibration graphically with a calibration plot.[119,130] To generate this plot, the model developed in Aim 1 will be applied to the independent validation data. For each subject in the validation data, the risk of breast cancer within a given time frame will be calculated from our model. These subjects will then be divided into deciles based on their predicted risks. The calibration plot will show the predicted and actual breast cancer rates for each decile. We will also calculate the Hosmer-Lemshow goodness-of-fit χ^2 statistic.[131]

Model recalibration: To further assess calibration, we will follow methods suggested in van Houwelingen (2000).[20] He describes an approach that involves fitting a "calibration model" to the validation cohort. The precise specification of the calibration model depends upon whether the prediction model is built assuming

proportional hazards or non-proportional hazards. In both cases, the model is a function of information from the prediction model together with parameters that are estimated from the validation data. If the estimated parameter values do not differ from the values specified under the relevant null hypotheses, then the model is considered to be well-calibrated. If the estimated parameters do differ from the null values, then the prediction model is re-calibrated by keeping the same covariates but re-estimating the regression coefficients only for those covariates whose effect appears to be different in the new data. The baseline hazard function is also re-estimated. The final re-calibrated prediction model then effectively combines data across the three cohorts.

Comparing model performance: We will also apply the Gail model and the Travis-Gail model to the validation cohort and compare the predictive accuracy of our model to the predictive accuracies of these two models. The Gail and Travis-Gail model are the two existing models that are most likely to be used to predict the risk of breast cancer in this population in the absence of the model we plan to develop. This exploratory analysis will allow us to assess whether our model improves even minimally upon what is currently available. By looking at the calibration curves and ranking the c-indices of the three models, we will evaluate which model most accurately predicts the risk of breast cancer in the validation cohort. If the c-index for our model is lower than the c-index for either the Gail or Travis-Gail model, we will not build the risk calculator described in Aim 3.

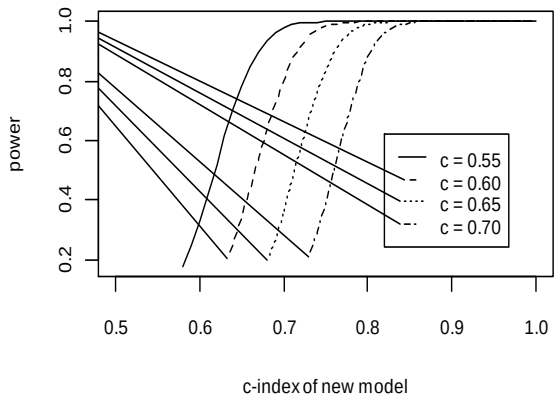
D8.4 Sample Size Justification for Aim 2

As part of the validation study, we will compare the predictive accuracy of the predictions made by the model we develop in Aim 1 with the accuracy of the predictions made by the Gail model and the Travis-Gail model when all three models are applied to the validation cohort, where predictive accuracy will be quantified by the c-index. Although our focus is not on finding a statistically significant difference between the models, here we explore the power we will have to detect differences in c-indices between two models assuming we will have data on 100 women with breast cancer and 1725 women without breast cancer. We concentrate on two comparisons, our model with the Gail model and our model with the Travis-Gail model.

A difficulty is that we have no prior data showing what a reasonable value of the c-index might be for either the Gail model or the Travis-Gail model when they are applied to a cohort of women who were irradiated as children. In validation studies using populations for whom the Gail model was developed, the c-index has been shown to be slightly below 0.60.[89,132] We expect it to be lower in our validation cohort. The Travis-Gail model has never been validated and so we have no preliminary estimate of a c-index.

Figure 6 shows curves displaying the power we would have to detect a difference between a c-index for either of the existing models, represented by the individual curves corresponding to c=0.55, 0.60, 0.65, and 0.70, and our prediction model from Aim 1, represented along the horizontal axis. For instance, we expect to have at least 85% power to declare a statistically significant difference between a c-index of 0.55 for the Gail model or Travis-Gail model and a c-index of 0.66 for our new model, both values we might reasonably expect to see.

Figure 6. Power curves for Aim 2



For these calculations, we assumed a one-sided 0.10 level test for each comparison to maintain an overall level test of 0.05 across the two comparisons. The power depends on

several components including the correlation between the two models when applied to the same group of subjects. We assumed this correlation to be zero, which should give a conservative estimate of power.[133]

D9. Developing and Disseminating the Risk Calculator

Aim 3: Develop a risk calculator that will predict an individual's absolute risk of breast cancer.

Risk calculator: Our aim is to present the prediction model in the form of a risk calculator that can be easily used by clinicians and patients. We anticipate having a tool where the user can choose options from drop-down menus, input their individual values, and click buttons. The calculator will return the 5-year risk, 10-year risk, and 15-year risk of developing breast cancer together with the associated confidence intervals. Importantly, it will also allow the users to print out their results in a printer-friendly format.

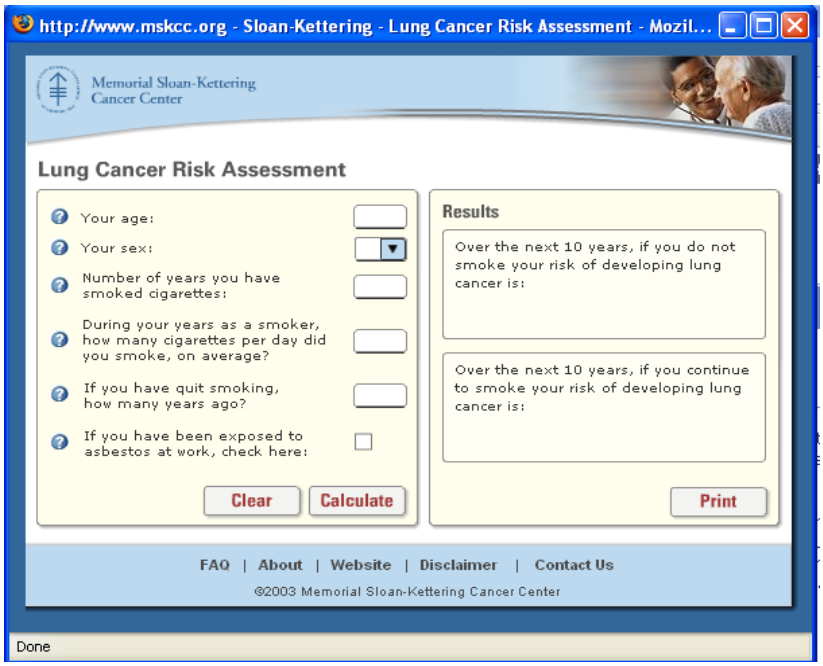
For example, a 32-year-old woman who was treated with 15 Gy of whole lung radiation when she was 3 years old, did not receive alkylating agents, was not exposed to pelvic radiation, had an age at menarche of 11 years, and has a mother with a history of breast cancer might use the calculator by typing in her current age, her age at menarche, the radiation dose she received and the age at which she received it, then *choosing whole lung radiation from a drop-down menu listing fields of radiation (to include mantle, mediastinal/IFRT, whole lung, total body, and spinal radiation fields) and no pelvic radiation exposure from a drop-down menu for pelvic radiation exposure (yes/no)*, as well as signifying one first-degree relative with breast cancer by choosing the corresponding option from a drop-down menu. She would then click a button at the bottom of the calculator that said "Calculate." In return the calculator would produce text that said "Your 5-year risk of developing breast cancer is 0.5%. Your 10-year risk of developing breast cancer is 2.1%. Your 15-year risk of developing breast cancer is 7.0%." The values used here are hypothetical and the exact form and layout of the calculator will of course depend upon the final model developed in Aim 1. Our goal with this example is simply to give an idea of what the final tool will look like.

To further demonstrate the appearance of the proposed calculator, Figure 7 (following page) shows a Web-based risk calculator for lung cancer created from a model developed by Drs. Bach, Kattan, and Begg.[111] The precise questions and text on the screen will be different for our breast cancer risk calculator; however, our intent is to use a similar design. That is, we plan for the calculator to be in a professional yet understandable and accessible format that physicians and patients can easily use.

Further, the calculator will not be restricted to a Web-based application. We plan on providing downloadable software for use on desktop computers and mobile devices (such as the Blackberry and iPhone) which are increasingly used by physicians. This will facilitate use of the risk calculator in clinical practice.

Criteria to create the risk calculator: Whether we will proceed with the third aim of this study depends upon the results of Aim 2. As part of Aim 2, we will assess the predictive accuracy of our risk model using a calibration curve and the c-index statistic on the validation cohort. For comparison, we will also estimate the predictive accuracy of the Gail model and Travis-Gail model on the validation cohort. If our model shows better predictive accuracy than the two existing models, we will proceed with creating the risk calculator. Even a slightly higher c-index that is not statistically different from the c-indices for the existing models would suggest our model is an improvement over what is currently available and hence has clinical utility. Given the very different clinical setting of our study in contrast to the risks of a first primary breast cancer in older adult women and given the additional information that will be available and analyzed in our study in contrast to the Travis-Gail study, it will be very surprising if our model does not substantially outperform these models.

Figure 7. Proposed format for a risk calculator using an example from a lung cancer prediction model



Plans for Dissemination: MSKCC has a history of disseminating risk prediction tools for public use. Beginning with a nomogram developed by Dr. Michael Kattan (who will serve as a consultant for this project) for use in prostate cancer patients, we have had several prediction tools made available on different platforms, including free downloadable software for use on desktop computers and handheld devices. The web page http://www.mskcc.org/predictiontools offers multiple different risk calculators developed at MSKCC that are available to the public. In addition to adding our calculator to this page, we will provide free downloadable software for Blackberry and iPhone devices, allowing physicians to access the calculator in clinical practice.

The National Cancer Institute also has a web page devoted to cancer risk prediction models, http://riskfactor.cancer.gov/cancer_risk_prediction/about.html. We hope to have a link to our model included on this web page as well, allowing further dissemination of the model. The American Cancer Society (ACS) provides information to the public through a variety of methods, including through their website. Dr. Robert Smith, the ACS Director of Cancer Screening, will consult on the proposed study and explore methods to disseminate our calculator.

Lastly, Dr. David Poplack (Chief of Pediatric Hematology-Oncology at Baylor Medical College and Director of the Texas Children's Cancer Center in Houston) and Dr. Michael Fordis (Associate Dean and Director of the Center for Collaborative and Interactive Technologies, Baylor College of Medicine) have developed a novel internet-based program, called the *Passport for Care*, that is intended to facilitate the health care of pediatric cancer survivors. Co-investigator for the proposed study, Oeffinger, has served as a consultant in the development of *the Passport for Care* since its inception. Briefly, the *Passport for Care* integrates the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*[52] (www.survivorshipguidelines.org) into an algorithm-driven program that outputs individualized screening recommendations. The *Passport for Care* is currently being tested at Texas Children's Cancer Center, St. Jude Children's Research Hospital, and City of Hope Cancer Center and will soon be piloted at MSKCC. Following pilot testing, it will be provided to the COG cancer survivor programs located across the US, Canada, Australia, and New Zealand. The breast cancer risk calculator developed in the proposed study will be integrated into the *Passport for Care*, facilitating its use by clinicians in specialized survivor programs throughout the country. Dr. Fordis, who is overseeing the programming and development of the *Passport for Care*, will serve as a consultant on the proposed study.