# Understanding Radiation Risk Through Deep Learning: Promise and Challenges

**Gilbert W. Beebe Symposium on AI and ML Applications**

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**Hiroshima, Japan**

# Exposure to Ionizing Radiation: Health Risks and Uncertainties

- Exposure to ionizing radiation from natural and man-made sources is inevitable. Accurate risk assessment is essential for radiation protection.

- While high-dose IR effects are well-known, the health risks of low-dose IR (<100 mGy) remain uncertain and debated.

- Epidemiological studies are crucial, but significant uncertainties persist, especially in assessing low-dose risks.

# Excess Relative Risk (ERR) Model

- Nonlinear parametric (NLP) models with Poisson loss:

$$\mu = \mu_0\ (1 + ERR)\ =\ \mu_0\ (1 + \rho(d)\gamma).$$

$$ERR = \rho(d)\gamma = \rho(d)\varphi(aa, ax, sx).$$

$\mu_0 =$ background rate (or mean count) function of sex, age, city, and NIC.

$\rho(d) = \tau_1 d + \tau_2 d^2$ (LQ), and $\gamma = \varphi(aa, ax, sx)$ is the age-related effect modification term

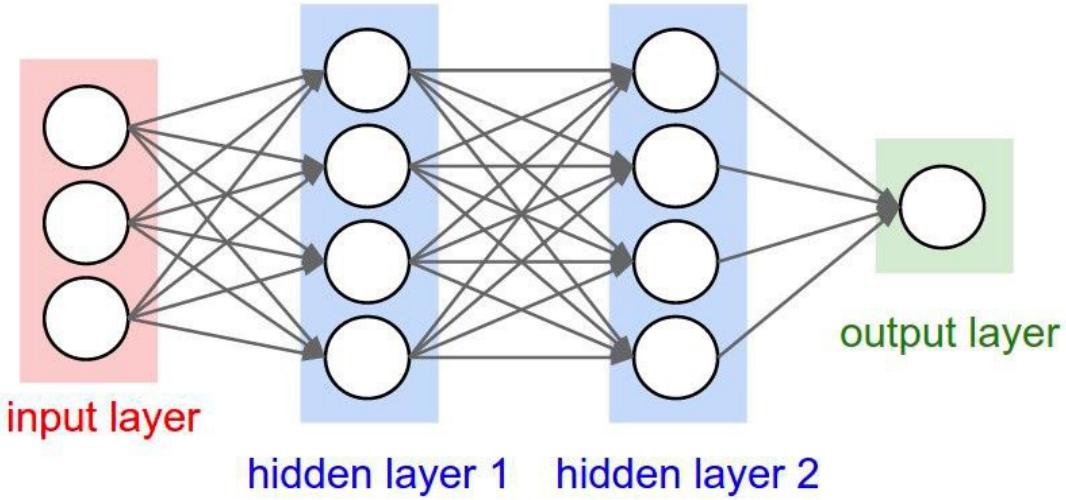
- A model has been used for radiation risk estimation over the last 40-50 years
- Simple and easy to interpret.

# Motivation and Objective

- **Challenges in Parametric Radiation Dose-Response Models:**
  - Parametric models have been critiqued for inadequately addressing uncertainties in the low-dose range.
  - Age-related modifications in radiation risk are typically constrained by specific functional forms
- **Exploring Deep Learning for Radiation Risk Assessment:**
  - **Potential:** Greater accuracy and flexibility.
  - **Challenges:** Identifying and addressing limitations with DNN.
  - **Future Directions:** Integrating deep learning into risk models.
- **Investigating AI-Guided Parametric Models for Low-dose Radiation Risk Assessment**
  - Exploring how AI can enhance low-dose risk assessment.

# Deep Learning

- **Deep learning, or deep neural networks (DNNs),** is a key area of modern AI. Neural networks with multiple hidden layers are "deep," while those with one hidden layer are "shallow."
- **Types of Neural Networks:**
  - **Feed-Forward Neural Network (FNN):** Information flows from input to output.
  - **Recurrent Neural Network (RNN):** Models sequential data, ideal for time series.
  - **Convolutional Neural Network (CNN):** Processes spatial/temporal data, used in image recognition like chest X-rays.



# The Two Datasets

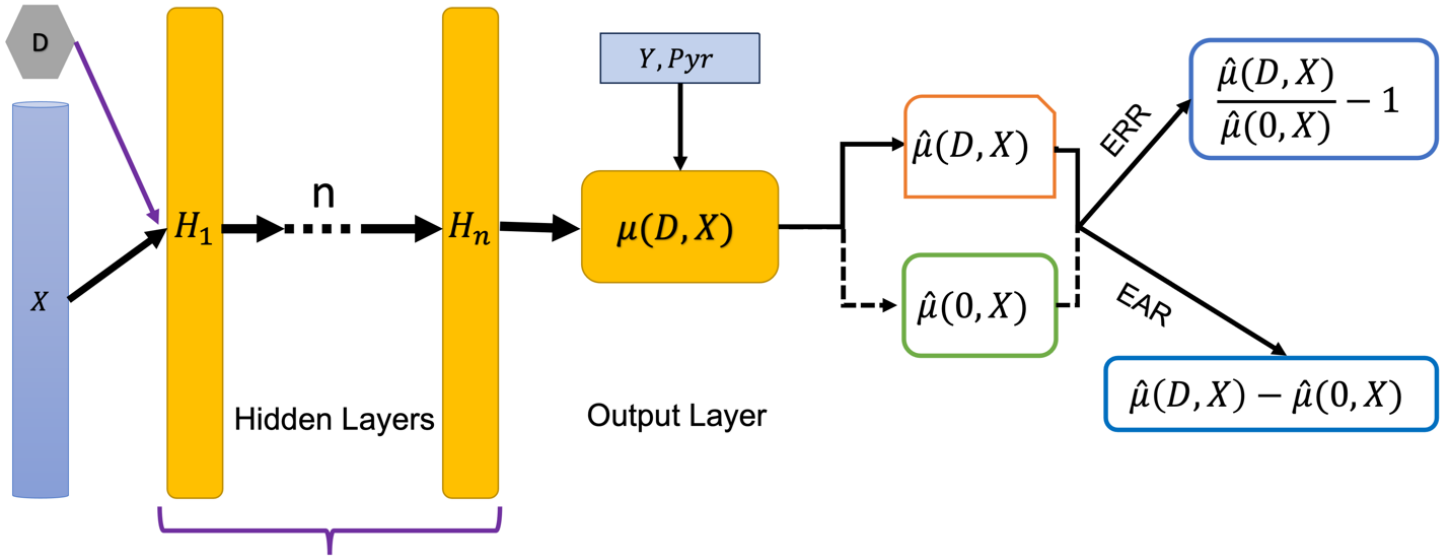
- **Solid Tumor Incidence Data**
  - **Dataset**: 25,570 person-year cells, covering 2,764,735 person-years of follow-up.
  - **Cases**: 17,448 solid tumor cases among 105,427 survivors.
  - **Radiation Risk Estimation**: Based on person-year weighted, adjusted, and truncated colon dose.
- **Leukemia Data (1950–2001)**
  - **Cases**: 491 leukemia cases among 113,011 survivors.
  - **Stratification**: Age at exposure, attained age, time since exposure, gender, city, and NIC (Not in City).
  - **Radiation Risk Estimation**: Based on person-year weighted, adjusted, and truncated marrow dose.
- **References:**

  - [1]. D. L. Preston, E. Ron, S. Tokuoka, et al. (2007), Solid Cancer Incidence in Atomic Bomb Survivors: 1958 – 98. Radiat.Res. 167 (2007).
  - [2]. Hsu WL, Preston DL, Soda M, et al. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. Radiat Res 2013; 179(3):361–82.

# DNN Models for Estimating ERR and EAR

## Model Architecture

- **Structure**: A DNN with three hidden layers, an input layer, and an output layer.
- **Hidden Layers:** 64, 32, and 16 nodes in $H_1, H_2,$ and $H_3$, respectively.
- **Model Selection**: 5-fold cross-validation.
- **Loss function**: Negative Poisson log-likelihood.



# DNN Models for Radiation Risk Estimation

- **Data-Driven and Model-Free:**
  - Feedforward deep neural networks (DNNs) are model-free, meaning they approximate the underlying function without encoding any specific functional form.
- **Nonlinear:**
  - DNNs are inherently nonlinear and do not rely on predefined parametric settings.
- **Learning from Data:**
  - The models infer the dose-response relationship directly from data, without imposing a predefined functional form.

# Assessing ERR with DNN

**Relative Risk (RR) Estimation**

- **Expected Incidence**: $\hat{\mu}_i = E(Y_i \mid \phi(x_i, W)) = Py_i e^{\phi(x_i, W)}$
- **Baseline Risk:**
  - Compute $\hat{\mu}_{i0}$ by setting the radiation dose to zero.
  - Estimate baseline absolute risk as $\hat{\mu}_{i0} / Py_i$.
- **Calculating RR and ERR:**
  - **Relative Risk (RR):** $RR_i = \hat{\mu}_i / \hat{\mu}_{i0}$,
  - **Excess Relative Risk (ERR):** $ERR_i = \hat{\mu}_i / \hat{\mu}_{i0} - 1$.
- **Model Performance Evaluation**:
  - **Primary Metric**: Average negative log-likelihood on test data
  - **Additional Metrics**: RMSE, MAE, mean Pearson residuals, and mean Poisson deviance loss.

# Two standard NLP Models to Compare

- **Solid Tumor:**

$$\mu = Pyrk \times exp\{\alpha_1 M + \alpha_2 F + \alpha_3 H + \alpha_4 mlage70 + \alpha_5 flage70 + \alpha_6 \text{lagesq} + \alpha_7 me30 + \alpha_8 fe30 + \alpha_9 nic\}\left(1 + \beta_1 \text{D} \times exp\left(\gamma_1\left(\frac{ax-30}{10}\right) + \gamma_2 log\left(\frac{aa}{70}\right)\right)\right).$$

- **Leukemia:**

$$\mu = Pyr10k \times exp\left\{\alpha_0 + \alpha_1 F + \alpha_2 Ng + \alpha_3 yob + \alpha_4 yob^2 + \alpha_5 \log\left(\frac{aa}{70}\right) + \alpha_6\, hnic + \alpha_7 nnic\right\}\left(1 + (\beta_1 \text{D} + \beta_2 D^2)\, exp\left(\gamma_1 log\left(\frac{sx}{40}\right) + \gamma_2 log\left(\frac{aa}{70}\right)\right)\right).$$

# Performance Comparison of DNN and NLP Models for Tumor Incidence

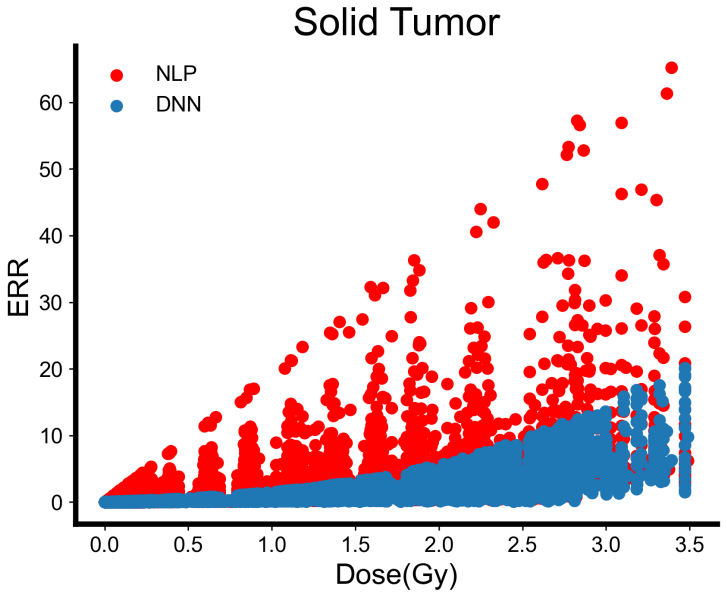
| Tumors | Models | MNLL | MPDL | MPR | MAE | RMSE |
|---|---|---|---|---|---|---|
| Leukemia | NLP | 0.044 | 0.070 | 0.152 | 0.019 | 0.095 |
| | DNN | 0.044 | 0.070 | **0.151** | **0.018** | 0.095 |
| Solid Tumors | NLP | 0.619 | 0.587 | 0.567 | 0.413 | 0.849 |
| | DNN | **0.618** | **0.585** | **0.566** | **0.409** | **0.839** |

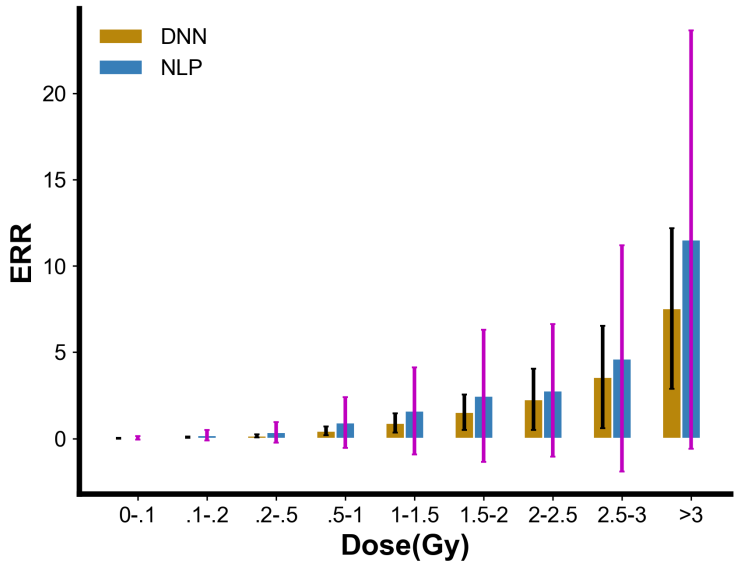
Table 1: MNLL: mean negative log-likelihood; MPDL: mean Poisson deviance loss; MPR: mean Pearson residuals; MAE: mean absolute error; and RMSE: root mean square error. A bolded smaller number denotes better performance.

- DNN achieves comparable performance in predicting leukemia incidences and better performance in predicting solid tumor incidence.

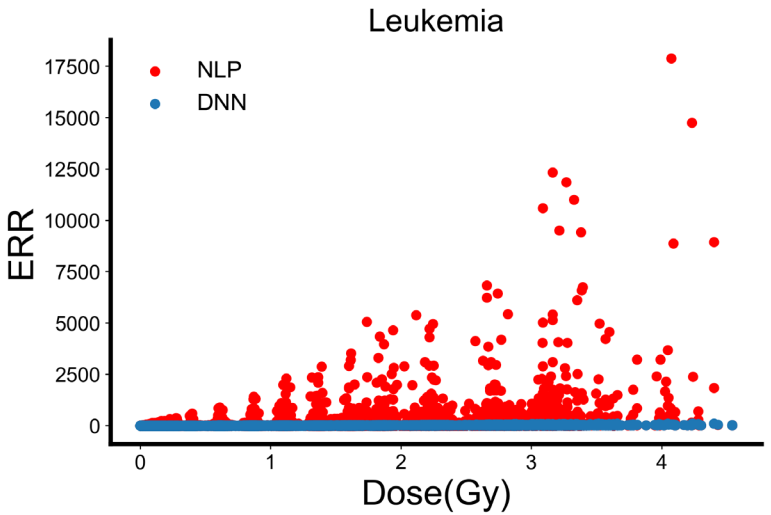
# Differences in ERR Estimation

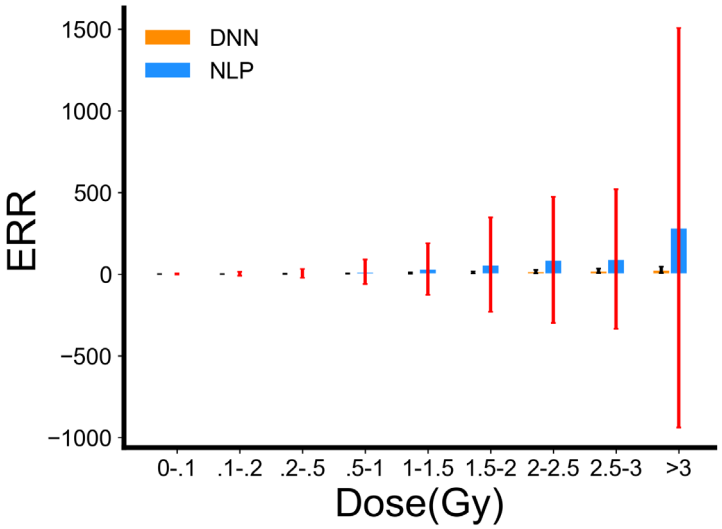
- DNN and NLP models yield significantly different ERRs across dose ranges, despite similar performance in predicting mean incidence ($\mu$).
- The functional form of a parametric model can significantly impact ERR estimation.
- Good tumor incidence prediction doesn't guarantee accurate ERR estimation.
- The ground truth for ERRs is unknown.




$$ERR = 0.426159D\ exp\left(-0.156699\left(\frac{ax-30}{10}\right) - 2.10184log\left(\frac{aa}{70}\right)\right)$$

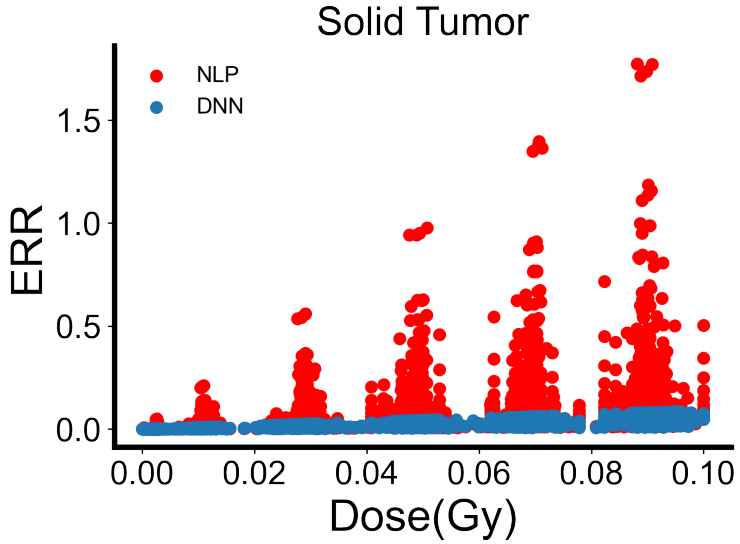


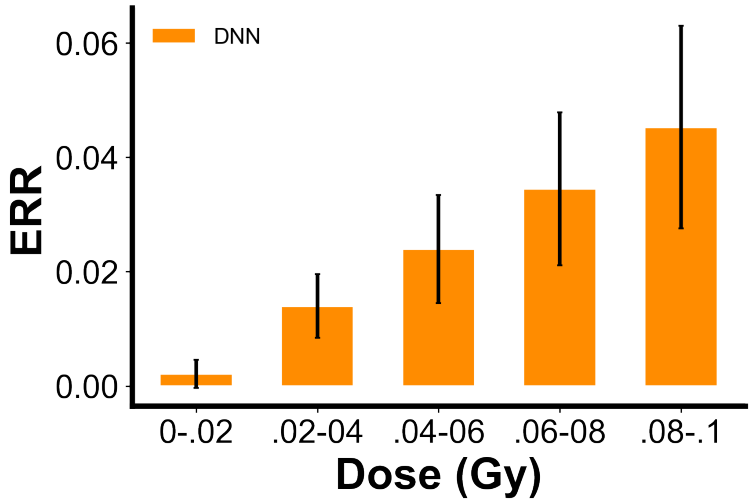



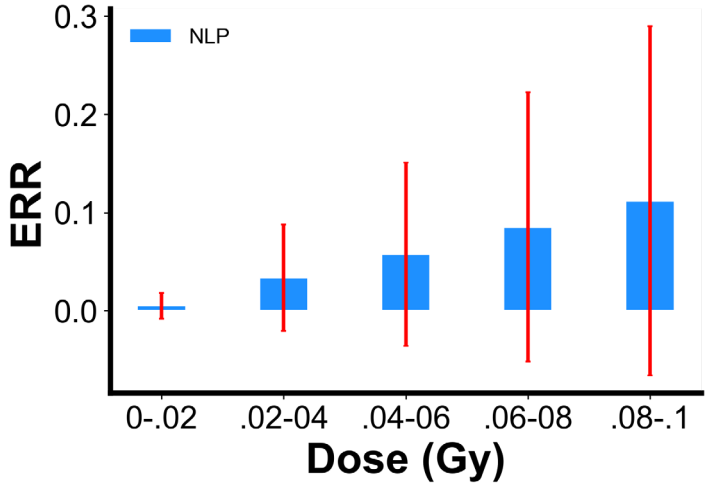

$$ERR = (0.5071\mathrm{D} + 0.2510D^2)exp\left(-0.5762log\left(\frac{sx}{40}\right) - 3.0655log\left(\frac{aa}{70}\right)\right)$$

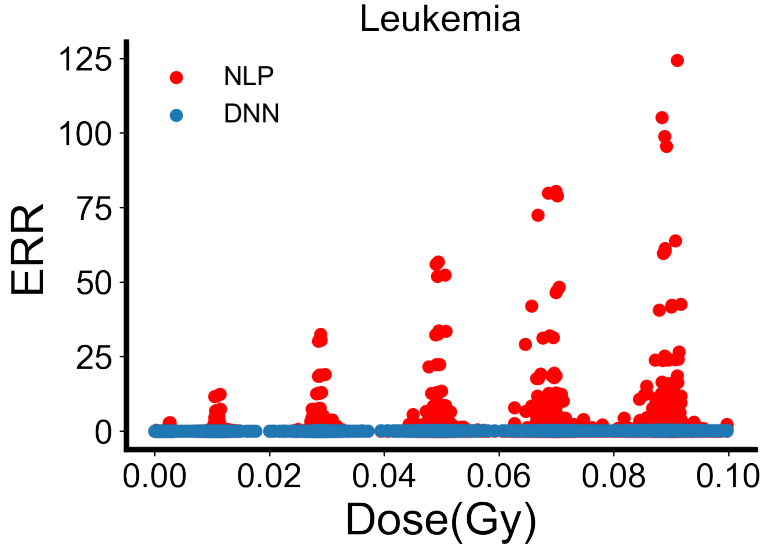
# Differences in ERR Estimation at Low-doses

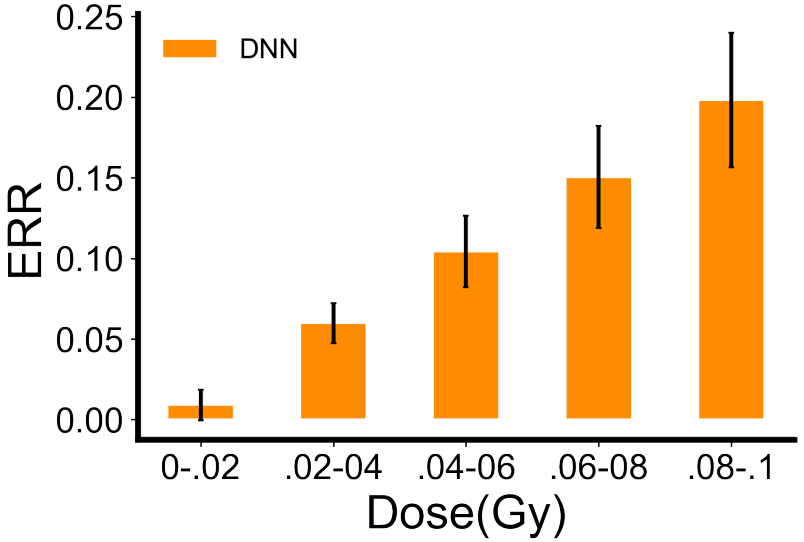
- Similar results are observed in the low-dose range (<100 mGy).

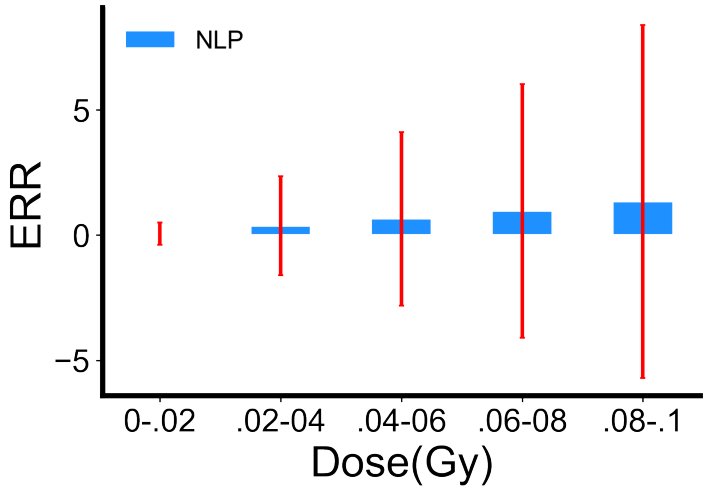


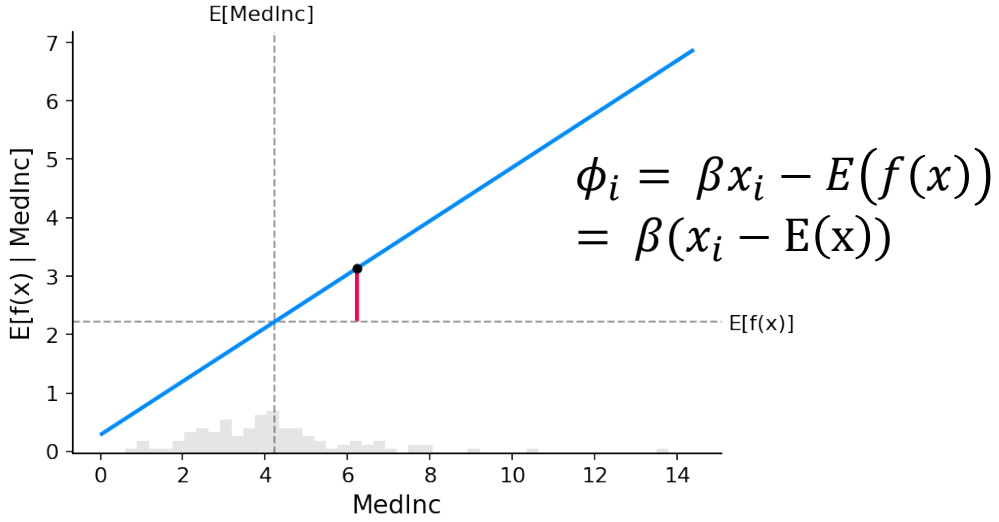



# Explainable AI with SHAP Values

**SHAP (SHapley Additive exPlanations) values, derived from game theory, quantify the contribution of each variable to a model's prediction.**

- SHAP Values decompose model predictions into additive contributions from different variables, offering a clear measure of feature importance.
- In linear models, variable importance is assessed by the magnitude of coefficients.
- SHAP values generalize this concept to any machine learning model, capturing both linear and nonlinear effects.





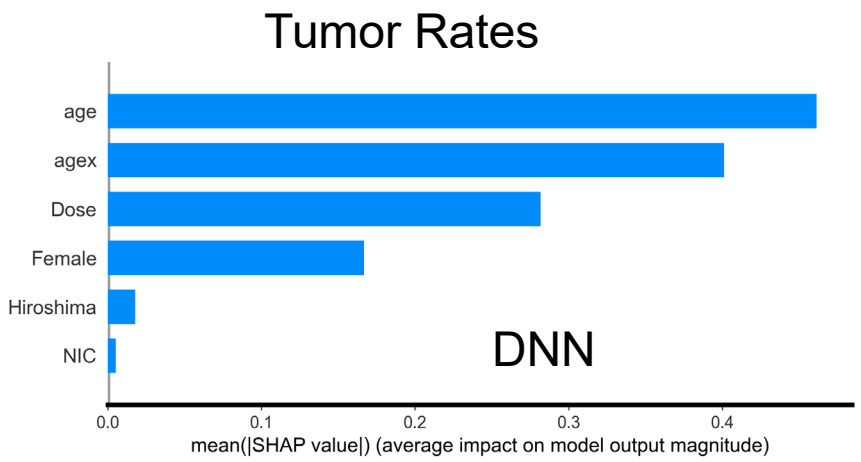
**Reference**

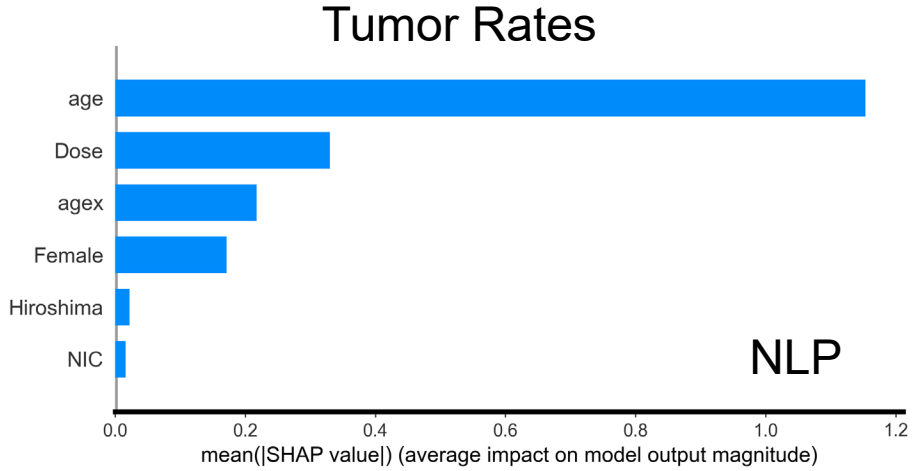
[1] Lundberg, Scott M., and Su-In Lee. "A unified approach to interpreting model predictions." Advances in Neural Information Processing Systems (2017)

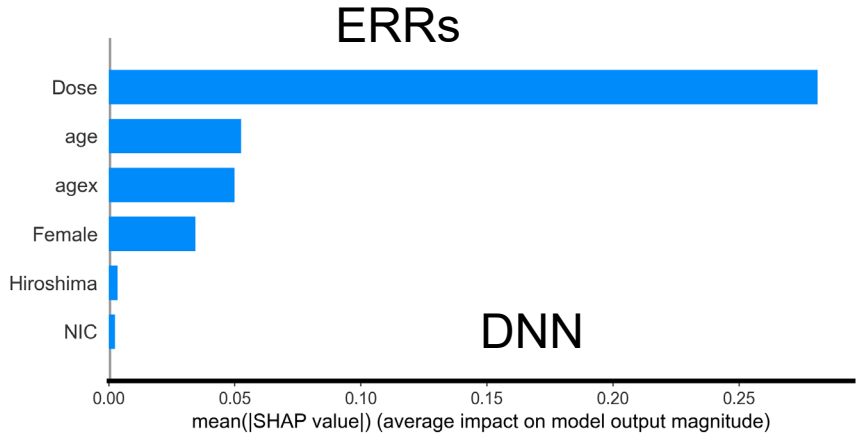
[2]. Janzing, Dominik, Lenon Minorics, and Patrick Blöbaum. "Feature relevance quantification in explainable AI: A causal problem." International Conference on Artificial Intelligence and Statistics. PMLR (2020).

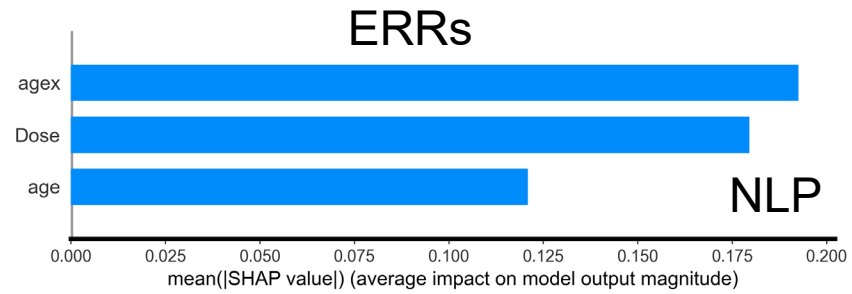
# SHAP Values for Solid Tumor Rates and ERRs

- The top four factors influencing tumor incidence (rates) in both the DNN and NLP models are age, agex, radiation dose, and gender, with age being the most significant factor.
- Despite the similarity in feature importance for tumor incidence between DNN and NLP models, the feature importance for ERR differs significantly between the two models.
- The results from the DNN model align well with intuitive expectations.
- The age modification term may contribute to the observed discrepancies.



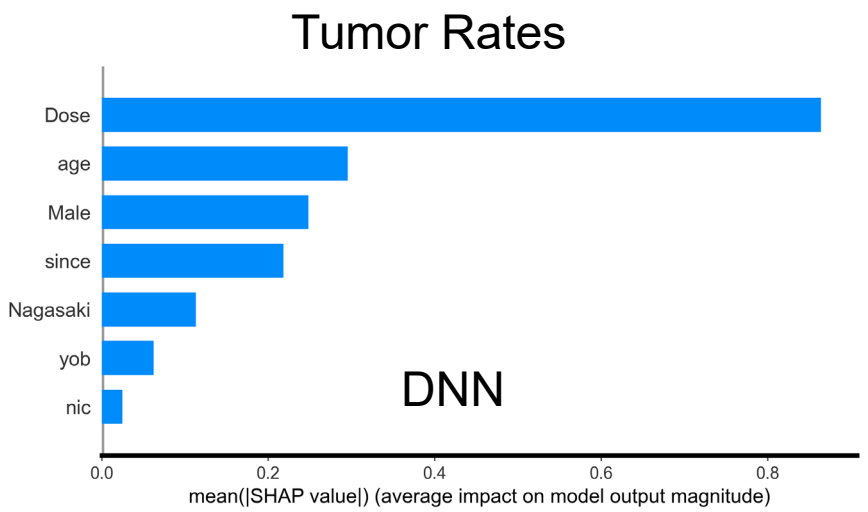



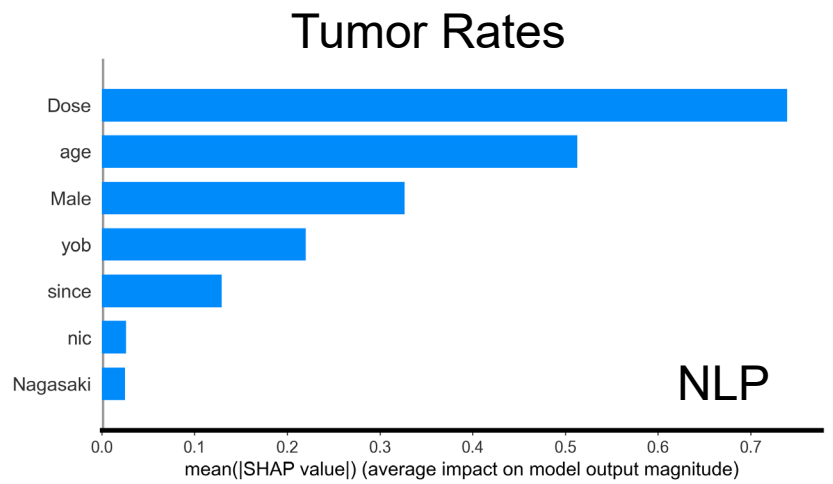



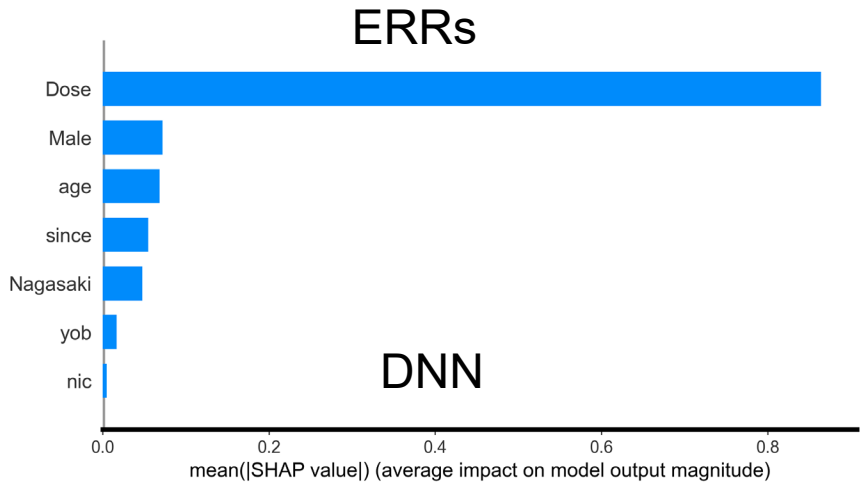

$$ERR = 0.42616D \times exp\left(-0.1567\left(\frac{ax-30}{10}\right) - 2.1018log\left(\frac{aa}{70}\right)\right)$$

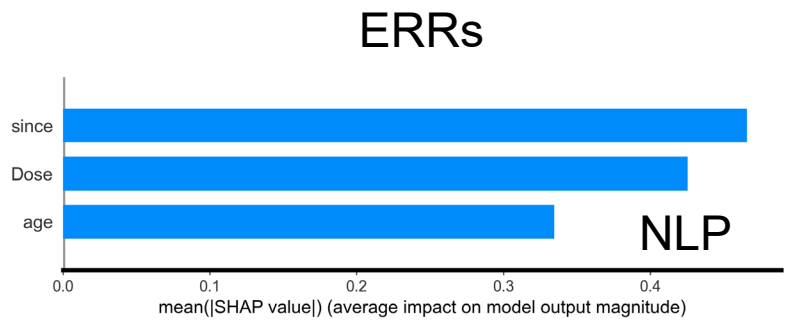
# SHAP Values for Leukemia Rates and ERRs

- The top three factors influencing tumor incidence (rates) in both the DNN and NLP models are radiation dose, age, and gender, with radiation dose being the most significant factor.
- Despite the similarity in feature importance for tumor incidence between DNN and NLP models, the feature importance for ERR differs significantly between the two models.
- The results from the DNN model align well with intuitive expectations.
- The age modification term in parametric model may contribute to the observed discrepancies.




$$ERR = (0.5071\mathrm{D} + 0.251D^2) \times exp\left(-0.5762log\left(\frac{sx}{40}\right) - 3.0655log\left(\frac{aa}{70}\right)\right)$$

# Discrepancies in ERR Estimates Between DNN and NLP Models Despite Similar Tumor Risk Predictions

- Radiation Risk is estimated indirectly as part of the tumor Risk:

$$\mu = \mu_0\ (1 + ERR) = \mu_0\ \left(1 + \rho(d)\varphi(aa, ax, sx)\right).$$

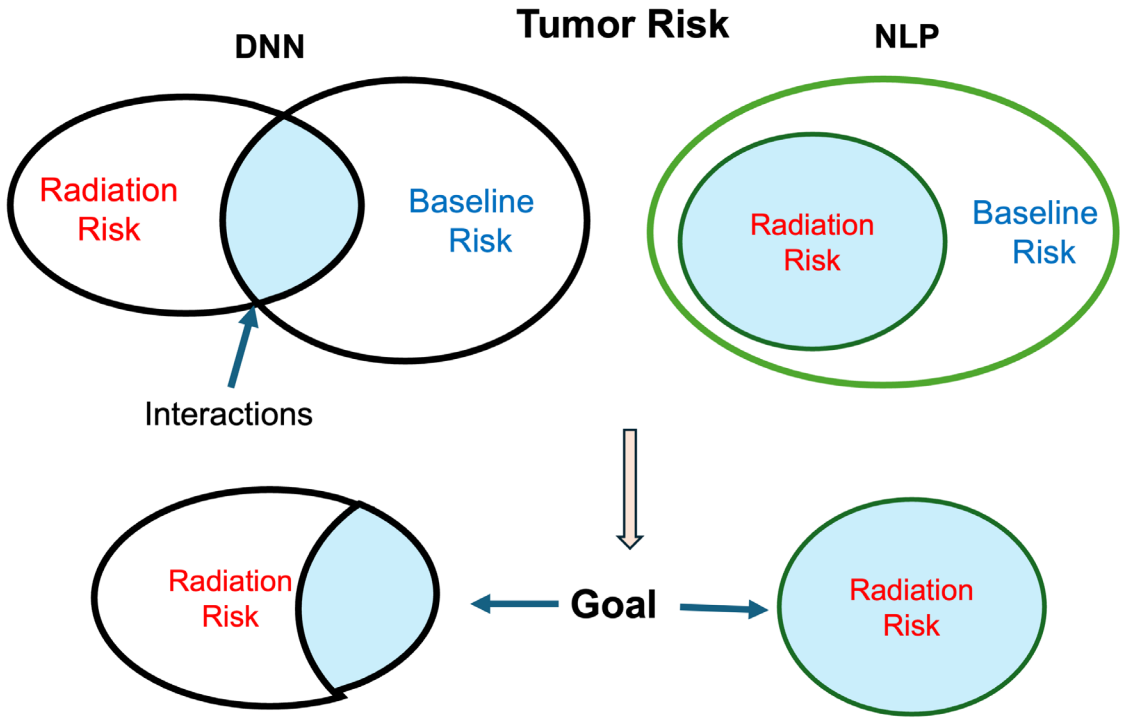
Even if two models have similar tumor risk, differences in the baseline function form of $\mu_0(X)$ or variations in effect modification (interaction) terms in a parametric model can lead to substantial differences in radiation risk assessments.

**Assumptions of NLP Models**

- Radiation affects tumor risk only through the interaction of age and dose: ERR = 0.42616D $\times exp\left(-0.1567\left(\frac{ax-30}{10}\right) - 2.1018log\left(\frac{aa}{70}\right)\right)$.
- Radiation risk depends on dose in a linear or linear-quadratic manner, while its association with age follows an exponential or power function.

**What Do SHAP Values of the DNN Model Reveal?**

- Radiation contributes to tumor risk both independently and through interactions with baseline variables.
- After adjusting for baseline effects on tumor risk, the contribution of baseline variables to tumor (radiation) risk will be smaller, aligning well with intuitive expectations.



# Barriers for DNN in Radiation Risk Estimation

**Prediction vs. Inference**

- Prediction:
  - **Goal**: Accurately estimate or forecast unknown outcomes using complex models.
  - **Focus**: Maximizing predictive accuracy, often at the cost of interpretability.
- Inference:
  - **Goal**: Estimate parameters and test hypotheses to understand relationships.
  - **Focus**: Prioritizes interpretability and understanding the data-generating process.

**Baseline Risk and Effect Modifications**

- **Challenge**: Identifying the sources of baseline risk and effect modification in a parametric model.
  - **Learning from Data**: Can we relay on DNNs to detect baseline risk and model effect modifications automatically ?
  - **Domain Knowledge**: Should modifications be guided by radiation physics or biology?
  - Impact: Balancing data-driven learning with domain expertise remains a key challenge.

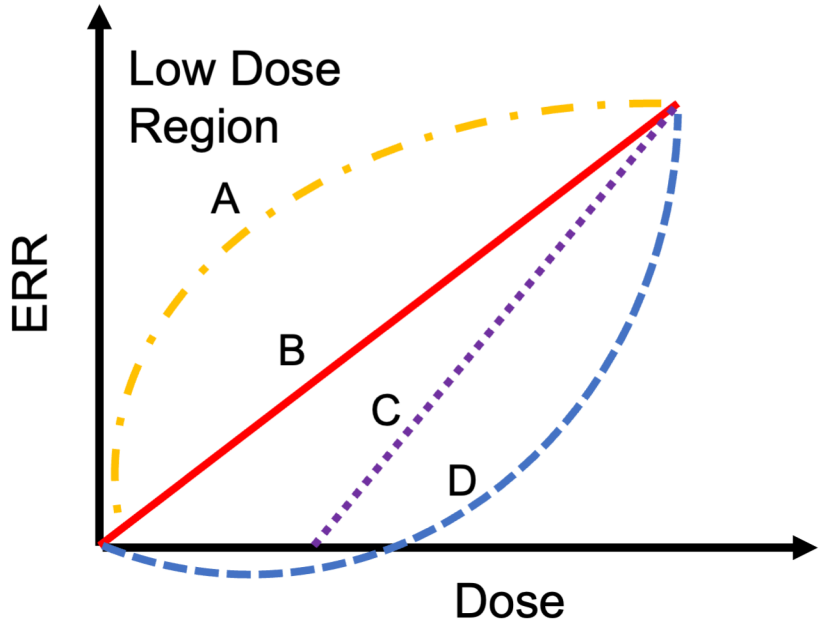
**Complexity in Modeling:** DNNs are intricate and less interpretable; Require substantial computational resources; Estimating confidence intervals in DNNs is non-trivial.

# Low-Dose Radiation Risk Estimation Guided by DNN

- Individual tumor risks vary significantly.
- Radiation risks at low doses (<100 mGy) are also likely heterogeneous.
- Epidemiological evidence on low-dose radiation risk is crucial for radiation protection and policymaking, but its carcinogenic effects remain unclear.
- Standard parametric models struggle to detect statistically significant ERRs at low-doses.

**Goal: Leverage DNN-learned individual risk heterogeneity to improve low-dose radiation risk assessment.**

# Four Candidate Models at Low-Dose

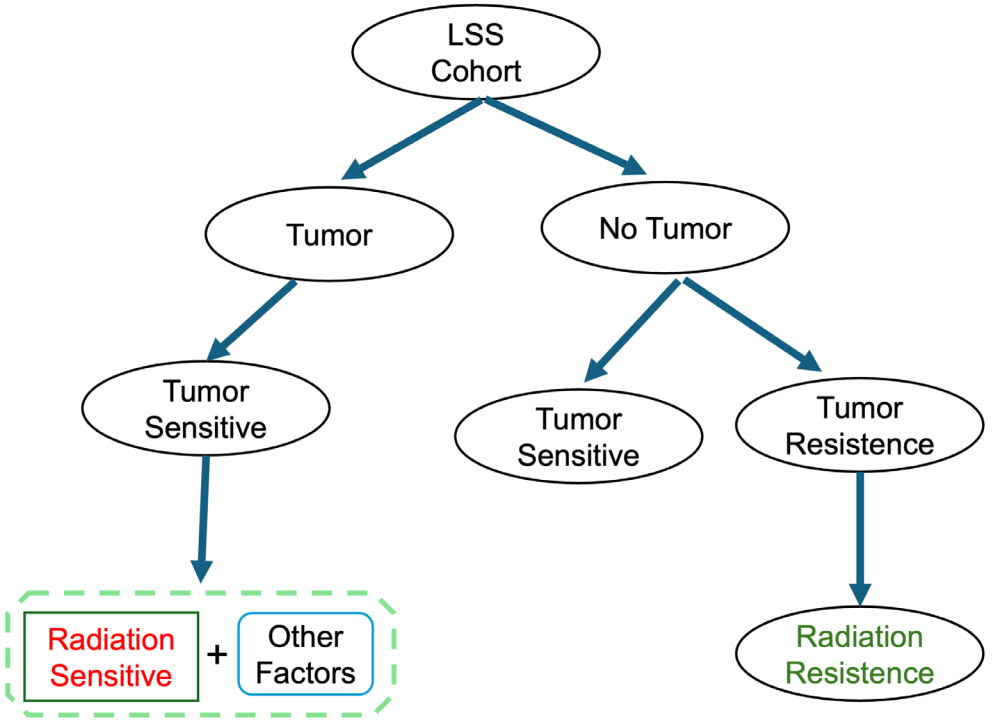



- A: Supra-linear
- B: Linear no threshold (LNT)
- C: Threshold
- D: Hormesis

- Linear-no-threshold (LNT) model is the most widely adapted model by regulatory bodies.
- It relies on low-dose extrapolation.
- Threshold model has zero (or near zero) ERR at low dose. It believes that very small IR exposures are harmless. It has made more noises in recent years
- Most epidemiological studies analyze data as a whole and overlooking the heterogeneity

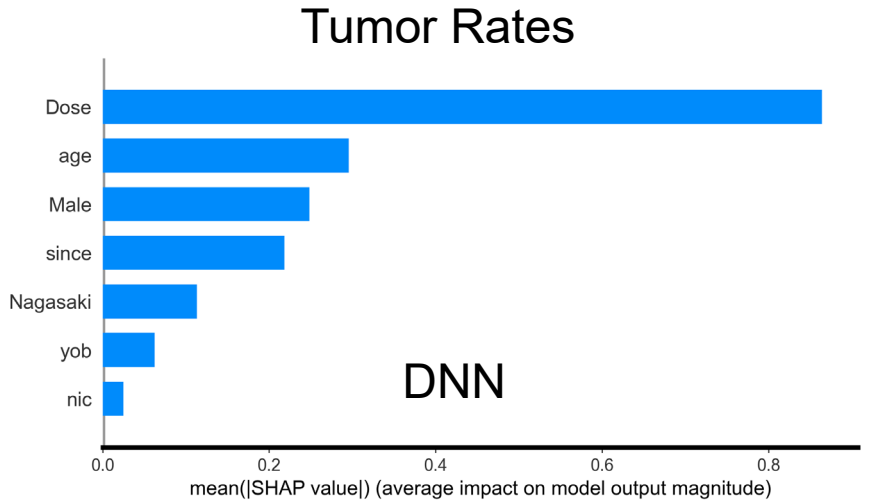
# Tumor Sensitivity vs. Radiation Sensitivity: Resistance and Susceptibility

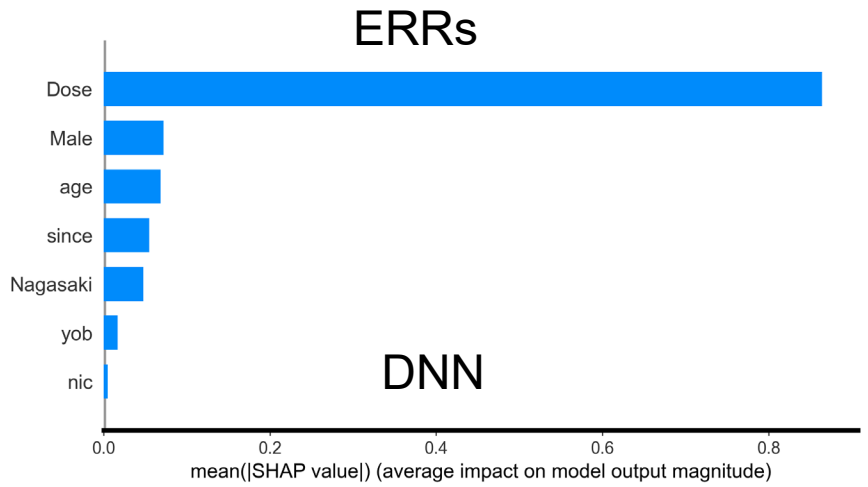
- **Tumor-Sensitive Individuals**: Develop tumors and are influenced by various risk factors, including radiation.
- **Tumor-Resistant Individuals**: Never develop tumors despite exposure to all potential risk factors, including radiation.
- **Uncertainty in Tumor-Free Cases**:
  - Some tumor-free individuals may still be **tumor-sensitive** but have not developed a tumor yet.
  - Others are truly **tumor-resistant**, meaning they are also **radiation-resistant**.



# Insights from SHAP Values of DNN in Leukemia Risk Estimation

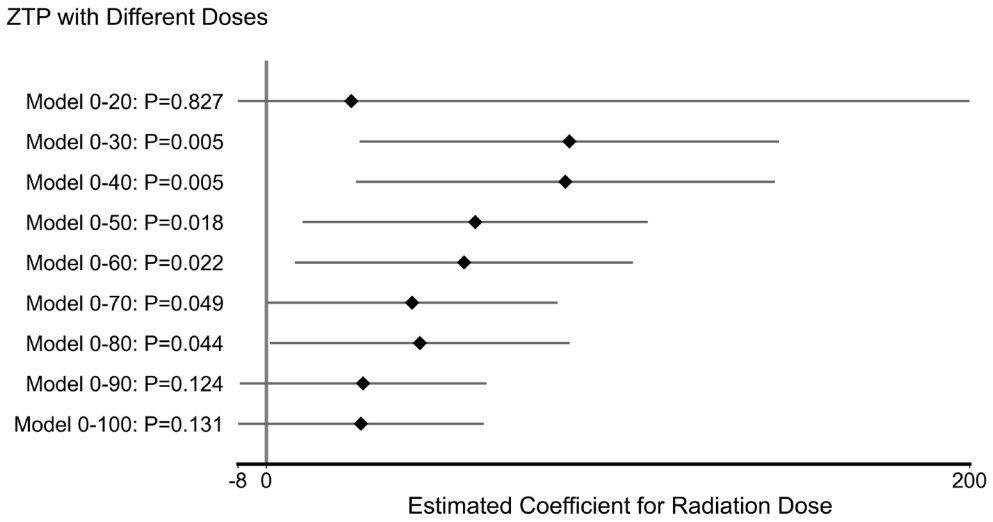
- SHAP values from DNN indicate that radiation dose is a dominant factor for both tumor rates and radiation risk (ERRs) in leukemia.
- Subjects with leukemia are likely more radiation-sensitive.
- Since we can not distinguish radiation sensitive from resistance in subjects without leukemia, we fit a zero-truncated Poisson (ZTP) model from dose = 0 to the given dose using only subjects with leukemia.
- **Goal**: Fit a ZTP model using only the known radiation-sensitive group.



# Low-Dose Radiation Risks for Leukemia

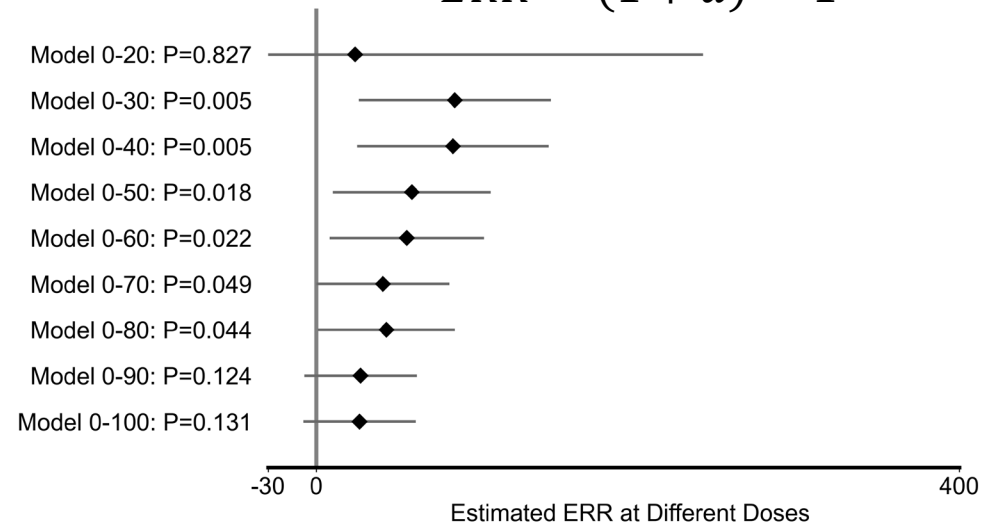
- Fitting a zero-truncated Poisson regression (log-linear) model from 0 to the given dose after transforming: $\log(1+d)$, $\log\left(\frac{agex}{30}\right)$, $and\ \log\left(\frac{since}{40}\right)$.
- Statistically significant coefficients and ERRs are detected for leukemia-sensitive subjects in the 30mGy–80mGy dose range.
- ERRs for leukemia at low doses are highly nonlnear, with $\beta \gg 2$.




Coefficients for Radiation Dose

| Coefficients | 95% CI |
|---|---|
| 24.218 | (-192.333, 240.768) |
| 86.204 | (26.555, 145.853) |
| 85.054 | (25.509, 144.599) |
| 59.435 | (10.365, 108.505) |
| 56.267 | (8.224, 104.31) |
| 41.484 | (0.142, 82.825) |
| 43.704 | (1.097, 86.31) |
| 27.548 | (-7.513, 62.61) |
| 26.93 | (-7.987, 61.847) |

$$ERR = (1+d)^{\beta} - 1$$




ERR at Radiation Dose

| Coefficients | 95% CI |
|---|---|
| 24.218 | (-192.333, 240.768) |
| 86.204 | (26.555, 145.853) |
| 85.054 | (25.509, 144.599) |
| 59.435 | (10.365, 108.505) |
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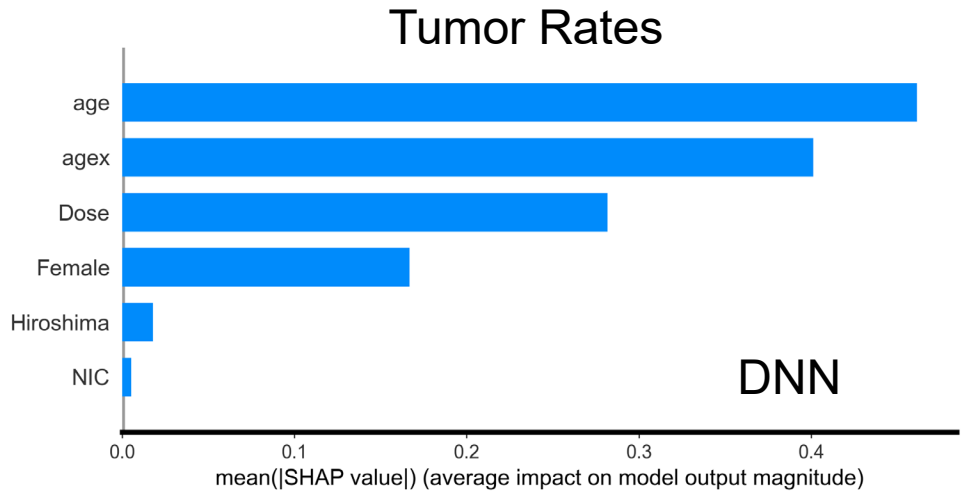
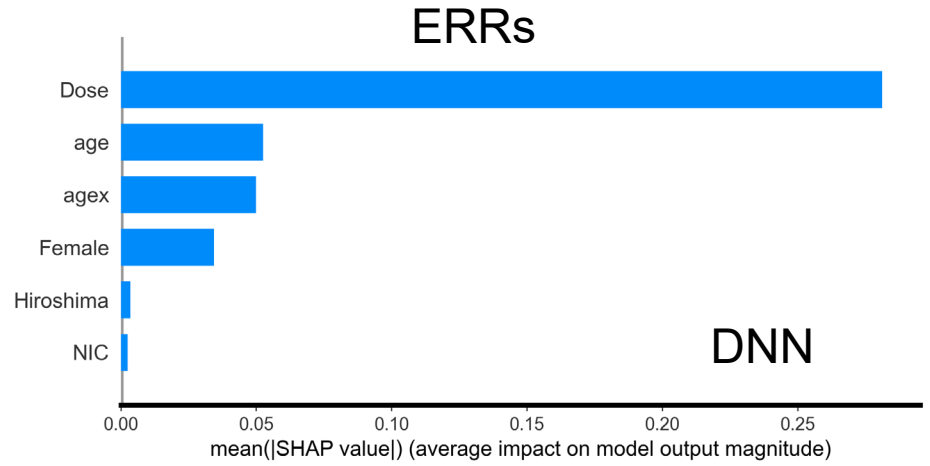
| 41.484 | (0.142, 82.825) |
| 43.704 | (1.097, 86.31) |
| 27.548 | (-7.513, 62.61) |
| 26.93 | (-7.987, 61.847) |

# Insights from SHAP Values of DNN in Sold Tumor Risk  Assessment

**SHAP Values from the DNN Model Indicate:**

- The top risk factors for solid tumors are **attained age** and **age at exposure (agex)**.
- **Radiation dose is the third most important factor** for tumor incidence.
- Individuals with solid tumors are **not necessarily radiation-sensitive**.
- Since **age and agex are strongly associated with tumor rates**, they may help distinguish **tumor-resistant vs. tumor-sensitive groups**.
- **Goal:** Exclude the tumor resistance group from the data analysis using zero-inflated Poisson (ZIP) regression.



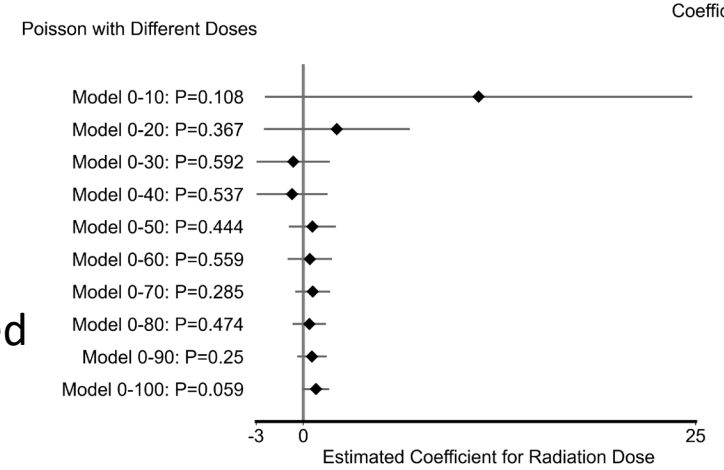



# Zero-Inflated Poisson (ZIP) Regression: Accounting for Heterogeneity in Solid Tumor

- Not everyone develops tumors, and some groups may have inherent resistance.
- The ZIP model assumes **two processes**:
  - A **binary process** where some individuals are not at risk at all (structural zeros).
  - A **Poisson-distributed count process** for individuals who are at risk.
- ZIP allows researchers to **distinguish tumor-sensitive individuals from tumor-resistant ones** based on covariates.
- SHAP value of DNN is useful for identifying factors (age and agex) that determine whether an individual belongs to the "at-risk" group.
- ZIP for person-year data is equivalent to Cure model for individual survival data

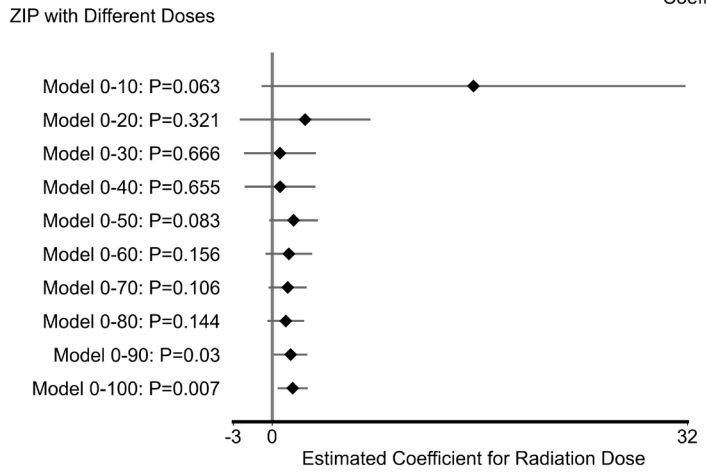
# Low-Dose Radiation Risk for Solid Tumor (ZIP vs Poisson)

- A ZIP model and a Poisson model were fitted using transformed variables: $\log(1+d)$, $\log\left(\frac{agex}{30}\right)$, $and\ \log\left(\frac{since}{40}\right)$.
- The ZIP model outperformed the Poisson model, yielding smaller AIC values.
- Statistically significant coefficients and ERRs were detected for solid tumors at 90 mGy and 100 mGy.
- ERRs for solid tumors at low doses follow a linear-quadratic pattern, with $1 < \beta < 2$.



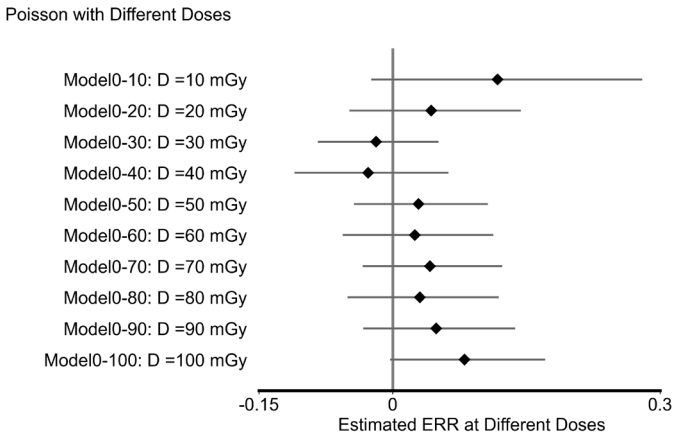

Coefficients for Radiation Dose

| Coefficients | 95% CI |
|---|---|
| 11.173 | (-2.441, 24.788) |
| 2.135 | (-2.508, 6.778) |
| -0.636 | (-2.965, 1.693) |
| -0.712 | (-2.974, 1.548) |
| 0.585 | (-0.911, 2.08) |
| 0.421 | (-0.992, 1.834) |
| 0.605 | (-0.503, 1.713) |
| 0.39 | (-0.678, 1.459) |
| 0.553 | (-0.39, 1.495) |
| 0.813 | (-0.031, 1.657) |




Coefficients for Radiation Dose

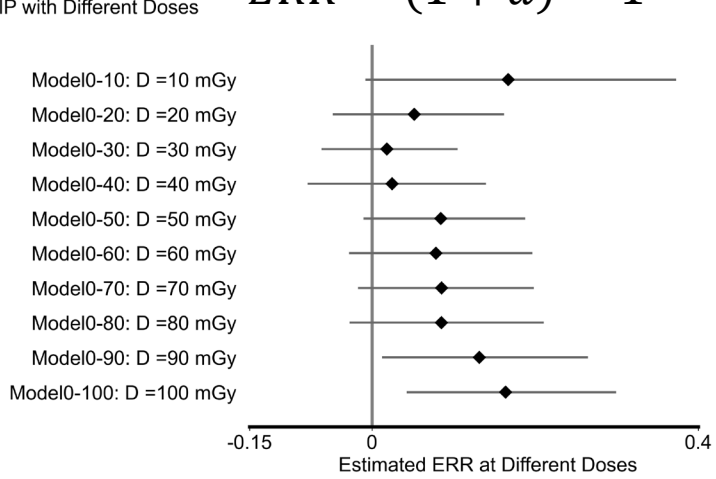
| Coefficients | 95% CI |
|---|---|
| 15.518 | (-0.814, 31.85) |
| 2.548 | (-2.489, 7.586) |
| 0.611 | (-2.162, 3.384) |
| 0.619 | (-2.099, 3.336) |
| 1.659 | (-0.214, 3.531) |
| 1.295 | (-0.493, 3.082) |
| 1.209 | (-0.256, 2.675) |
| 1.061 | (-0.362, 2.484) |
| 1.434 | (0.141, 2.727) |
| 1.591 | (0.437, 2.746) |




ERR at Radiation Dose

| ERRs | 95% CI |
|---|---|
| 0.118 | (-0.024, 0.28) |
| 0.043 | (-0.048, 0.144) |
| -0.019 | (-0.084, 0.051) |
| -0.028 | (-0.11, 0.063) |
| 0.029 | (-0.043, 0.107) |
| 0.025 | (-0.056, 0.113) |
| 0.042 | (-0.033, 0.123) |
| 0.03 | (-0.051, 0.119) |
| 0.049 | (-0.033, 0.138) |
| 0.081 | (-0.003, 0.171) |

$$ERR = (1+d)^{\beta} - 1$$




ERR at Radiation Dose

| ERRs | 95% CI |
|---|---|
| 0.167 | (-0.008, 0.373) |
| 0.052 | (-0.048, 0.162) |
| 0.018 | (-0.062, 0.105) |
| 0.025 | (-0.079, 0.14) |
| 0.084 | (-0.01, 0.188) |
| 0.078 | (-0.028, 0.197) |
| 0.085 | (-0.017, 0.198) |
| 0.085 | (-0.027, 0.211) |
| 0.132 | (0.012, 0.265) |
| 0.164 | (0.043, 0.299) |

# Conclusions

- DNN models may offer new insights into radiation risk assessment.
- SHAP values can help identify radiation-sensitive and radiation-resistant groups.
- Considering tumor heterogeneity may enhance low-dose radiation risk assessment for leukemia and solid tumors.
- Dose-response relationships at low doses may vary across tumor types and individuals.
- Identifying radiation-sensitive groups using epidemiological data alone is challenging, as tumor sensitivity does not always imply radiation sensitivity.
- If a low-dose threshold exists, it may vary by tumor type and individual.
- Integrating epidemiological data with insights from radiation biology and physics may improve identification of radiation-sensitive and resistant groups.
- Personalized radiation risk assessment holds promise for future advancements.

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