Analysis of Time Dependent Effects in Radiation Epidemiology

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1. Background

Starting with radium watch dial painters in the 1920s, numerous diverse populations have been monitored following significantly-above-background radiation exposures. It is well founded that doses exceeding 100 mGy have potential to induce negative health outcomes in humans. Health effects resulting from radiation doses below this level are not as well understood. Consequently, risks for outcomes in the 0-100 mGy low-dose range are often approximated by linear extrapolation to zero dose. This practice is known as the "linear no-threshold" model. Existing research related to the linear no-threshold model is discussed thoroughly in NCRP Commentary 27 (NCRP 2018).

Studies analyzing radiation-related health effects have grown in scope and complexity during the 21st century due to an increased focus on low dose and low dose rate exposures. Because health effects induced by low doses are few relative to background rates, a very large amount of data is needed to prove that outcomes are caused by radiation. So, advanced methods are being developed to link records and pool cohorts of exposed individuals (Kitahara et al. 2015). Pooling low dose and low dose rate cohorts of healthy individuals representative of today's population is the primary mission of the Million Person Study of low-dose health effects (Boice Jr. et al. 2019).

Further complexities are being introduced as researchers question the validity of existing results and seek to better define risks for greater extents of the human population. One outstanding topic to be addressed primarily in this analysis is the dependence of radiation-induced health effects on time. Specifically, the role of age at exposure in radiation epidemiology is not fully developed.

Studies of the atomic bomb survivors quickly revealed a strong dependence of radiation-induced health effects on age at exposure. This was primarily noted for individuals exposed during childhood, exhibiting a much higher risk of carcinogenesis for most solid cancers (Little et al. 1998). This effect is further supported by the National Academies' report BEIR VII phase 2, which presented preferred risk models allowing for age at exposure effects before age 30 (National Research Council 2006).

Although well-founded for childhood exposures, there is controversy surrounding the effect of age at exposure on adults. Many instances of increased relative risk per dose for those exposed in middle- to late-ages have been observed. Achieving statistical significance in studies that observe this effect is challenging, as few late-age exposures are captured by epidemiological studies. Still, many instances of this correlation exist and are presented in this analysis. Increase in radiosensitivity with age is also supported by many biological mechanisms. Biological factors relating to radiation-induced carcinogenesis are discussed in detail.

Currently, studies in radiation epidemiology rely on cumulative dose values. Given the strong age-dependence of radiation-induced health effects, this may not be the best method of accounting for doses throughout a lifetime. Also, it is plausible that radiation doses may lose their effect at long times since exposure. Consequently, new modeling techniques may need to be developed to handle time effects in radiation epidemiology. Reviewed in this analysis are various methods for handling time-varying covariates in risk models. Conclusions are drawn from the existing literature and approaches for developing time-dependent radiation risk models using data from chronically exposed populations are formulated.

2. Role of Age at Exposure in Existing Studies

Existing epidemiologic and biological studies provide support for and against the plausibility of increased radiosensitivity with age. The studies presented are simply observations related to the effect and are not intended to prove the effect exists. There is much variability surrounding radiation induced health risks based on exposure type, dose

magnitude, dose rate, and outcome of interest. Future epidemiological studies have the potential to provide statistical significance to the effect of increases in radiation-induced risk with age at exposure. As cohorts begin to be combined in the effort to better understand low dose and low dose rate health effects, greater numbers of individuals exposed at older ages will exist in single analyses. Pooled studies will open many doors for researchers to discover nuances in radiation carcinogenesis that were previously undetectable.

2.1 Epidemiological outlook

Age at exposure is sparsely considered in modern low dose and low dose rate studies. The studied populations that experience chronic, low dose exposures to radiation are almost exclusively exposed occupationally. So, the ages of exposure for these studies are concentrated in typical working years, leaving few exposure records of children or the elderly.

As a result, age at exposure is rarely considered for dose-response effect modification in low dose and low dose rate studies. This is true of the International Nuclear Workers (INWORKS) study. The most recent publication presenting results for over 309,000 exposed international workers made no mention of age at exposure (Richardson et al. 2023). Interestingly, mortality from circulatory diseases and other non-cancer outcomes was previously analyzed with respect to age at exposure for the INWORKS cohort (Gilles et al. 2017). No significant trend in risk per dose with age at exposure is evident for circulatory, cerebrovascular, or ischemic heart diseases.

INWORKS combines cohorts of workers in nuclear power, fuel cycle, and weapons focused facilities from the US, France, and the UK (Hamra et al. 2015). Another occupational group of interest for radiation epidemiology is medical workers. A review of epidemiological studies on 11 health professional cohorts exposed to ionizing radiation from 1975 to 2019 had a single mention of age at exposure, noting a lack of information in one cohort (Chartier et al. 2020). The remaining cohorts presented no results related to age at exposure.

Some other existing studies that analyze age at exposure for chronically exposed cohorts do exist. Most notably, recent results from the Pooled Uranium Miners Analysis (PUMA) indicate increasing excess relative risk per working level month (ERR/WLM) with increasing age at exposure for both the full, 119,000-person pooled cohort, and the 1960+ subcohort, which translates better to today's population (Kreuzer et al. 2024).

Workers hired at Oak Ridge National Laboratory (ORNL) from 1943 through 1972 were monitored through a 1990 follow-up (Richardson et al. 1999). In this study, it was found that doses received after age 45 were associated with a 5.9±1.7% increase in cancer mortality per 10 mSv, relative to doses received before age 45.

26,389 workers hired at a plutonium production factory in Hanford, Washington from 1944 to 1978 were followed until 1994 (Wing & Richardson 2005). The results show strong evidence of an increase in ERR/Sv in the age at exposure category of 55-82. The increase is heavily driven by lung cancers. Smoking status was not routinely tracked for the Hanford workers. So, a high probability of confounding exists due to smoking-induced lung cancers. Atomic bomb survivor cohort studies that address the effect of smoking on cancer rates are discussed later in this analysis.

Much analysis surrounding age at exposure was conducted related to the atomic bomb survivors. The Radiation Effects Research Foundation (RERF) study of the atomic bomb survivors is known as the Life Span Study (LSS). A large-scale analysis of LSS solid cancer incidence data through 1998 follow-up suggested that solid cancer relative risk exhibits a U-shaped relationship with age at exposure, initially decreasing then increasing at older exposure ages (Preston et al. 2007).

Following this finding, two papers were published commenting on results related to age at exposure. Both publications reanalyzed the solid cancer incidence data for the LSS cohort. The first found a marginally statistically significant variation in the relative risk with age at exposure for all incident solid cancers (p=0.033). Stratification by cancer type weakens the relationship slightly below statistical significance (p=0.060). It is concluded that chance cannot be excluded as an explanation for this finding (Little 2009). The second response, published in the same issue of Radiation and Environmental Biophysics, again reanalyzes the data. Figures are presented for comparison of ERR/Gy by age at exposure. The addition of error bars representing likelihood-based 95% confidence intervals provides great visual context to the uncertainties associated with risks at later exposure age, shown in Figure 1 (Walsh 2009). The high uncertainties are a result of few records of exposures at later ages.

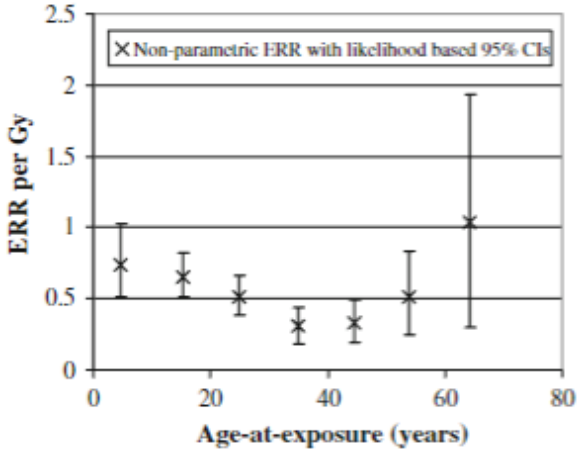

Figure 1. Age at exposure effects on solid cancer incidence risks at 70 years after a dose of 1 Gy. Reproduced from (Walsh 2009) Fig. 2.

At the time of these publications, follow-up was complete for age at exposure groups of more than 50 years. So, for the LSS, no further data in high age at exposure categories will be available. Thus, any further evidence of the U-shaped trend will need to be generated from more modern populations exposed to ionizing radiation.

A recent analysis of the LSS cohort has presented results that challenge the validity of the U-shape (Grant et al. 2017). The exclusion of autopsy-only cases greatly reduced the increase in ERR/Gy in late exposure ages for solid cancer incidence, presented as black solid dots Figure 2. So, it is believed that the U-shaped trend in LSS solid cancer incidence data is an artifact of autopsy findings of occult cancers. The 95% Wald confidence intervals indicate great uncertainty in the ERR estimate past 60 years, so it cannot be concluded that no effect of age at exposure exists. Additionally, the non-significant increase in ERR/Gy from age 45 to 55 is notable, though still perhaps due to random variation. Since the exclusion of autopsy-only cases was reported, one large-scale analysis of all LSS solid cancers has been conducted. The analysis stratified age at exposure in two categories: 0-19 and 20-83 (Brenner 2022).

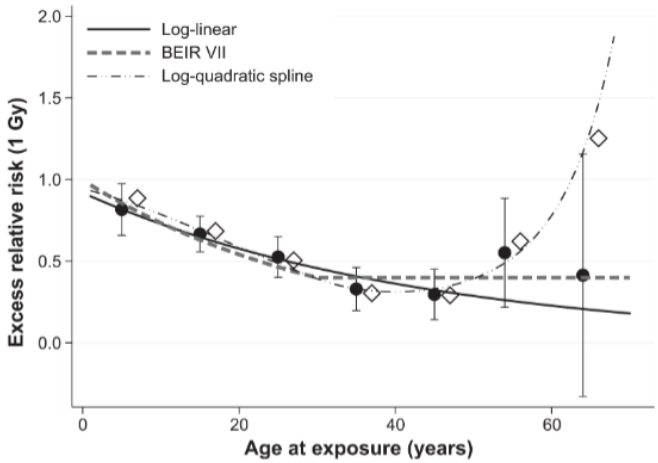

Figure 2. Age at exposure effects on radiation risk and the impact of autopsy only cases. Sex-averaged ERR estimates at an attained age of 70 years. Solid dots are nonparametric estimates when excluding autopsy-only cases and open diamonds (offset by two years to avoid overlap) are nonparametrix estimates when including autopsy-only cases (both with Wald 95% confidence intervals). The dot-dash line is fit to autopsy-only included estimates and the solid line is is fit to autopsy-only excluded measurements. The dotted line follows BEIR VII models accounting for age at exposure before age 30. Reproduced from (Grant et al. 2017) Fig. A2.

An additional LSS analysis provides useful insight on the subject of smoking as a confounder for lung cancer incidence. Within the LSS cohort, ERR/Gy for lung cancer has shown to increase with increasing age at exposure. It has been suggested that this may be a consequence of the failure to adjust for the effects of smoking (Preston et al. 2007). After making proper adjustments for smoking status, it was found that radiation risks were not significantly higher for smokers in the cohort (Furukawa et al. 2010). The results of this analysis confirmed that the age at exposure effect for lung cancer incidence was not an artifact of failure to adjust for smoking.

2.2 Biological outlook

The biological mechanisms behind induction of disease in humans are very complex and the theories for a single mechanism can be numerous. It is even more difficult to understand the influence of radiation on mechanisms taking place in the body.

Theories of aging provide context to the cellular processes that take place within the human body as it ages. The free radical theory of aging suggests that the gradual accumulation of oxidative cellular damage is the fundamental driver of cellular aging (Harman 1956). This theory suggests that the population of reactive oxygen species (ROS) in the body increases as we age, progressively causing damage in cells throughout the body. Increase in ROS population and decline in adenosine triphosphate (ATP) production greatly weakens antioxidant defense capabilities, allowing for damage to the cell, organelle membranes, DNA, lipids, and proteins (Maldonado et al. 2023). ROS also have an important role in regulating bodily signaling pathways related to control of various disease states (Schieber & Chandel 2014). The positive role of ROS has required expansion of the original free radical theory. Resulting is a model in which ROS immune response signaling moderates bodily function while inevitable ROS buildup creates oxidative stress capable of cellular and DNA damage.

Cellular changes with age take numerous forms, many of which have the potential to increase the carcinogenic effects of radiation. Highlighted in this section are the age-related mechanisms of most concern, often triggering threats to the genomic integrity of human cells.

The first process of interest, closely related to the theory of aging described above, is oxidative stress arising from a combination of aging and radiation. Reactive oxygen species can be endogenously generated by normal cellular metabolism or arise from exogenous exposures to radiation and chemical compounds (Valko et al. 2007). The hydroxyl radicals formed then lead to oxidative stress, which is linked to a variety of diseases. It is well-founded in animal studies that a diet of antioxidant nutrients leads to protection against radiation effects (Weiss & Landauer 2003). Irradiation of blood samples has led to observation of a sharper decrease in antioxidant protective capacity per dose for women after 58 years of age, substantiating greater effectiveness of exposure-induced oxidative stress at older ages (Kasapovic et al. 2011). With aging cells already exhibiting an unbalanced oxidant-antioxidant population, irradiation of aged cells would unequivocally contribute to overload of the antioxidant system (Hernandez et al. 2015).

Another cellular process that promotes radiogenic effects at older ages is telomere shortening. It is well-founded that

telomeres, DNA protein structures at the end of the chromosomes, shorten with age (Shammas 2011). Mouse studies have shown that shortened telomeres lead to hypersensitivity to chromosomal damage relating to ionizing radiation (Goytisolo et al. 2000). Additionally, in-vitro analysis has shown that irradiation of cells from healthy individuals with short telomeres resulted in higher frequencies of radiation-induced micronuclei (indicative of DNA damage) compared to irradiated cells of long telomere individuals (Castella 2007). The inevitable shortening of telomeres with age promotes the susceptibility of cells to DNA damage often induced by ionizing radiation. It is likely that this mechanism contributes to increased radiosensitivity at older ages.

A third process of interest is the decline in DNA repair efficiency with cellular age. DNA damage response refers to the body's identification and repair of DNA damage while minimizing the number of heritable mutations. DNA repair involves activation of complex repair pathways that regulate responses such as cell-cycle arrest and apoptosis (Zhou & Elledge 2000). DNA repair efficiency is especially crucial for instances of DNA double-strand breaks which, if left unrepaired, can lead to mutations or chromosomal aberrations and eventually diseases such as cancer (Bekker-Jensen & Mailand 2010). In vitro studies have shown a delay in the recruitment of needed repair proteins to the damaged site (Rodriquez-Hernandez et al. 2014). In mice, it has been shown that B lymphocytes from old mice show poor double strand break repair efficiency and increased misrepair compared with younger mice (Puthiyaveetil & Caudell 2013). If a natural decline in DNA damage response success rate exists throughout the human lifespan, it is inherent that DNA damage-inducing incidents are more dangerous for aged individuals.

The literature surrounding the three processes mentioned above is dense and each mechanism seems to have clear implications for the sensitivity of cells to radiological damage. Other known age-related processes that can induce genomic instability exist but are less naturally related to the ways in which radiation can damage the body.

Understanding of the biological mechanisms related to radiation-induced disease is greatly informative to how risk assessment is conducted from an epidemiological perspective. As biological mechanisms are better understood and epidemiological methods progress, the two should continue to validify each other, benefiting the knowledge of concepts in both fields of science.

2.3 Relevance of age effects in today's population

Radiation exposures common in the world today are vastly different than those experienced by the atomic bomb survivors and some heavily exposed occupational cohorts of the 20th century. A new challenge exists today to better define risks and outcomes resulting from low dose and low dose rate exposures. Limits and standards are in place to restrict the doses received by those exposed routinely to radiation, usually through their occupation.

For medical radiation exposures, usually imaging or radiotherapy, the exposure levels involved are less of a concern, as a net benefit is achieved, or at least perceived, by the patient and treatment planners. However, measures are taken to limit exposures to as low as reasonably achievable (ALARA) for medical exposures. If a heightened radiosensitivity at older ages does exist, new considerations must be taken to balance the benefits of imaging and radiotherapy procedures with the radiosensitivity and increased risks of aged individuals who are often in most need of medical intervention.

3. Statistical Modelling

Epidemiological analyses are typically conducted using risk models containing various parameters and testing their fit to the data of interest. Popular methods for estimating risk in radiation epidemiology are Poisson regression and Cox proportional hazards regression. Additionally, models from committee-level publications, such as the BEIR VII report, are sometimes used in more specific cases.

Statistical models for radiation-induced risks usually seek an excess relative risk (ERR) or excess absolute risk (EAR) of an outcome or event as a function of radiation dose. Almost exclusively, the dose value used is cumulative dose. Naturally, many other factors besides dose exist that affect the risk value. Common to radiation epidemiology are models accounting for biological sex, attained age, and age at exposure effect modification. Other factors such as smoking status and socioeconomic status may also be used depending on the study. Risk models are often comprised of linear, quadratic, and logarithmic combinations of the parameters involved. With so many possible combinations, flexibility is a major benefit of using parametric risk models.

Options become somewhat restricted when certain survival models are used. Choice of statistical model is also dependent on the dataset, as each model relies on certain assumptions. For example, if survival time follows an exponential distribution and the count of events follows the Poisson distribution, then Poisson regression can be used. If these assumptions are not appropriate, then use of another model is likely necessary (George et al. 2014).

The Cox proportional hazards (PH) model works under the assumption that the hazard for the event of interest and the baseline hazard are proportional throughout the model. As a result, the model presents risk in the form of a hazard ratio (HR), a ratio of the hazard for the event of interest to the baseline hazard. Thus, HR greater than one means an excess risk exists for the event of interest. The primary advantage of the Cox PH model is that no specification of the baseline hazard function is required. Consequently, because the

baseline hazard can take any form, the model is classified as semi-parametric.

Accelerated failure time (AFT) models are a popular alternative to the Cox PH model in survival analysis. An important feature of this method is the ability to estimate time to an event without knowing its distribution (Orbe 2002). It also is independent of the proportional hazards assumption of the Cox model. The results of AFT models are relatively easy to interpret, as they are not affected by the choice of a probability distribution. From known hazards and any number of covariates, a survival time is estimated using this model.

3.1 Time-varying covariates

When covariates of interest are changing in time, complexities in modeling techniques must be introduced. Methods for handling time-varying covariates are well tested and documented in literature. The present analysis will present diverse use cases for both the Cox PH model and the AFT model.

A simple way to show the effect of time-varying covariates on a model is to frame the model in a piecewise notation (Zhou 2001). Consider a situation where an outcome C with covariate z_1 behaves differently before and after a time of interest t_i. The two models needed to represent this situation are, chronologically:

$$C_1 = \exp[\beta_1 D]$$
$$C_2 = \exp\left[\beta_1 D + \beta_2\right]$$

Now, assume that a second, time-dependent covariate $z_2(t)$ is introduced with values of 0 if $t \geq t_i$ and 1 if $t > t_i$. Now, the sing model with a time varying covariate can be written as

$$C = \exp\left[\beta_1 z_1 + \beta_2 z_2(t)\right]$$

In practice, more complexities often arise. An analysis of time-dependent covariate use in the Cox PH regression model provides examples for selecting the form of a time-dependent covariate (Fisher & Lin 1999). Sometimes the covariates can be modeled as simple, binary, piecewise functions. For example, if smoking status was measured over a series of years, each year could yield a status of "yes" or "no" (0 or 1) for smoking. This is much like the simplified example above. Next, consider a drug therapy trial where lipid values are assumed to improve over time after therapy is introduced. In this case, it may be advantageous to model a linear increase with time for the lipid value covariate. Continuing in complexity, the time varying function could take on a sinusoidal, parabolic, or exponential form. If the covariate can be defined at each calculated point in the analysis, it can be of use in the Cox PH model.

An issue that arises with handling of time-varying covariates is that the value of the time-varying covariate is often conditional on the survival of the subject, as is the case for covariates generated from yearly follow-up appointments or interviews. To handle this, models with time-varying covariates can include an additional parameter indicating observation time. So, if observation (follow-up) is discontinued, the subject will be censored. This prevents faulty estimation due to incomplete measurements of the time-dependent covariate being used.

Assumptions of the AFT model make the use of time-varying covariates very challenging. The model assumptions that time ratios are constant over time and that covariates have linear relationships with the logarithm of the event time make time-varying covariate implementation undesirable within the AFT model. However, a recent extension of the accelerated failure time model has been proposed for use with time-varying covariates (Pang et al. 2021).

An interesting use case for time-varying covariates is within competing risk regression models, such as the Fine-Gray subdistribution hazard model. Competing risk models track alternative outcomes precluding the occurrence of a primary outcome. The use of time-varying covariates in these models is possible, but caution is advised. The primary challenge of using time-varying covariates is that following a competing risk, the subject must remain in the risk set (Austin et al. 2019). If death is a competing risk, the subject will stay in the risk set postmortem, possibly with nonzero time-varying covariate values. This would cause for continuing risk modification after death, which is improbable.

In summary, implementation of time-varying covariates is possible in many common survival analysis models. However, the implementation quickly becomes challenging as complexity of the covariate or statistical model increases. So, for complex statistical analyses, much caution must be taken with the use of time-varying covariates.

4. Conclusion

Proper estimation of risks for radiation-induced health effects is no easy task due to the myriad factors that play into both epidemiological and biological outlooks. Ideally, advancements in statistical methods and resources for radiation epidemiology will be accompanied by further development of our understanding of the biological mechanisms involved in radiation-induced health effects.

As cohorts within radiation epidemiology are combined, it is important that statistical models to handle new discoveries are available. The current analysis emphasizes the importance of time dependencies in epidemiological risk modeling. Many routes exist for handling of time-varying covariates, some of which have the potential to be adapted or improved for use in radiation epidemiology. Exploration of additional methods for handling of time effects within and outside of survival analysis could generate new ideas surrounding time dependent analyses in radiation risk modeling.

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