COMMENTARY

Biologically-based models of cancer risk in radiation research

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ABSTRACT

Purpose: In radiation risk analysis the state-of-the-art approach is based on descriptive models which link excess rates of cancer incidence and mortality to radiation exposure by statistical association. To estimate the number of sporadic and radiation-induced cases descriptive models apply parametric dose response function which directly determine the radiation risk. In biologically-based models of cancer risk (BBCR models) dose responses are implemented for key events on the biological level such as early mutations or clonal expansion of initiated cells. Influenced by radiation these events then shape the risk response on the epidemiological level. Although BBCR models facilitate a more comprehensive consideration of biological processes for risk assessment, their range of application in radiation research remains limited. Therefore, we emphasize their ability to improve understanding of radiation-related carcinogenesis by integrating molecular biology with epidemiology. We highlight the potential of BBCR models to harness information from adverse outcome pathways (AOPs) for risk estimation with closer links to radiobiology. The AOP concept originates from toxicology and may be applied profitably in radiation research.

Conclusion: The conceptual design of BBCR models can be guided by the high-dimensional data environment provided by AOPs. Risk estimates from BBCR mod-

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els pertain not only to classical radioepidemiological covariables such as radiation dose or attained age but also to well characterized molecular pathways. By additionally deploying biological information BBCR models facilitate finer risk stratification for a more personalized risk assessment. They leave behind the one-size-fits-all approach of descriptive modeling with the downside of more involved model development. Importantly, predictions from BBCR models can be validated against molecular measurements. Validated predictions would confirm the model design and strengthen the link between molecular biology and epidemiology. But the availability of cancer tissue in good quality from patients with known radiation exposure constitutes a major bottleneck. More ambitious initiative is needed to recover stored tissue samples and make them available for molecular investigations. To conclude, risk estimation will not only on rely on statistical association but will be quantitatively informed with radiobiological insight. Combined with the AOP framework BBCR models could improve accuracy and reduce uncertainty of radiation risk estimates in future research.

KEYWORDS

biologically-based models of cancer risk; radiation epidemiology; molecular biology; integrative modeling; adverse outcome pathways

Introduction

Increasing grasp of disease processes leading to cancer and concomitantly the establishment of observational data sets for the general population prompted the development of biologically-based models of cancer risk (BBCR models) (Armitage and Doll 1957; Moolgavkar et al. 1980; Moolgavkar and Knudson 1981). In radiation epidemiology the first deployment of BBCR models occurred with the Life Span Study (LSS) of Japanese a-bomb survivors decades after their application to observational cancer data (Little et al. 1992; Little 1996; Kai et al. 1997; Heidenreich et al. 1997). Since the late 1990s the scope of mechanistic modeling of radiation-induced cancer risk has been extended to a growing number of epidemiological cohorts which were exposed to different radiation fields of acute and protracted exposure (Shuryak 2019). Rühm et al. (2017) have extensively reviewed the application of BBCR models to the LSS, post-Chernobyl cohorts and cohorts of uranium miners from Europe and North America.

Early pioneering studies of radiation risk in the LSS were based on descriptive models which linked excess rates of cancer incidence and mortality to radiation exposure by statistical association (Wakabayashi et al. 1983; Thompson et al. 1994). Descriptive models have been refined with longer follow-up for many cancer sites and remain the mainstay of cancer risk assessment at low doses and dose rates (Preston et al. 2007). Updates of the LSS analysis with additional risk factors such as smoking have been published in a series of studies for all solid cancers combined (Grant et al. 2017) and site-specific for cancers of the thyroid, lung, breast and colon (Furukawa et al. 2013; Cahoon et al. 2017; Brenner et al. 2018; Sugiyama et al. 2020).

To estimate the number of sporadic and radiation-induced cases in radio-epidemiological cohorts descriptive models rely on convenient functional forms of dose responses interpreted either additively as Excess Absolute Rates (EARs) or multiplicatively as Excess Relative Risks (ERRs). In a dose range between about 0.1 - 2 Gy a linear response in both risk measures often yields a good description of the observational data. For purposes of radiation protection the linear response is extrapolated to very low doses according to the linear no threshold (LNT) paradigm based on plausible radiobiological arguments (Brenner 2009). Dose response functions in descriptive mod-

els directly determine age-risk patterns, possibly moderated by dose effect modifiers such as attained age or age at exposure. Against it, BBCR models[1] facilitate a more comprehensive consideration of biological processes for risk assessment. Compared to descriptive models dose responses are predicated on biological events such as early mutations. In this case risk responses are not easily expressed with simple parametric functions, although linearity at low doses is mostly maintained.

Recently growing awareness of BBCR models is motivated by deeper understanding of the molecular landscape for many tumor types gained with advanced omics technologies. Outside radiation sciences research under the The Cancer Genome Atlas (TCGA) programme of the National Institutes of Health in the United States has comprehensively characterized molecular properties of cancer tissue from e.g. the breast, colon, lung or thyroid (Koboldt et al. 2012; Muzny et al. 2012; Agrawal et al. 2014; Campbell et al. 2016). This characterization provides valuable guidance for the design of mechanistic model concepts. In the wake of these molecular investigations the search for radiation biomarkers has been pursued with increased effort (Hall et al. 2017). Such markers have the potential to improve risk assessment when integrated into radioepidemiological analysis (Kaiser et al. 2016, 2020).

The added value of BBCR models has been pointed out by researchers for a variety of topics in radiation biology and epidemiology, and in clinical context. Dainiak et al. (2018) recommend the application BBCR models within a systems biology approach to explore radiation-induced biological effects on multiple length scales of molecular, cellular and tissue levels. Boice (2019) reports an interest in integrating the Million Person Study with BBCR models to improve risk estimates at low doses. Shore et al. (2019) argue that the analysis of radio-epidemiological cohorts informed by biological concepts produces more reliable risk estimates compared to estimates from mere statistical association. McMahon and Prise (2019) envisaged a role for biologically-based models to describe dose responses in radiotherapy. During long-range space missions astronauts are exposed to a mixed field of ionizing radiation which includes neutrons and heavy ions, and BBCR models could help to predict

[1]In radiation research they are often termed Biologically-Based Dose Response (BBDR) models (Preston 2015, 2017). Since not only radiation-induced but in principle *all* carcinogenic processes are addressed by this model type the abbreviation BBCR is suggested.

space-relevant low dose-rate risks of cancer (Shuryak and Brenner 2019).

Against the backdrop of increasing interest in BBCR models their range of application in radiation research remains still limited. Therefore, in the present paper we emphasize their ability to integrate molecular biology with epidemiology in the field of radiation-induced carcinogenesis. We discuss how BBCR models can harness information compiled for adverse outcome pathways (AOPs) for more accurate risk estimation. The AOP concept originates from toxicology and has been proposed recently for application in radiation research (Ankley et al. 2010; Preston 2015, 2017; Vinken et al. 2017; Chauhan et al. 2019). BBCR models for animals are not considered since main progress in the last years has been achieved for models involving humans. We comment on potential benefits for risk assessment with BBCR models related to the AOP concept and in combination with radiation biomarkers. Data needs and an optimal study design are laid out. The relevance of biologically-based modeling for experimental strategies, characterization of persistent radiation effects such as chronic inflammation and improved determination of risk quantities will be illustrated.

Discussion

Adverse outcome pathways

Concept

The concept of adverse outcome pathways (AOPs) originates from toxicology and describes disease development with a multi-scale approach (OECD 2013). Ankley et al. (2010) and Vinken et al. (2017) have summarized the AOP framework for toxicologists. The depiction of a generic AOP structure (Figure 2 of Vinken et al. (2017)) involves different levels of biological organization over several length scales. Disease development to an adverse outcome is understood as a chain of causes and effects which is triggered by a molecular initial event (MIE). An adverse outcome typically involves the tissue or organ level and should be subject to epidemiological risk assessment. Several key events are lined up along the path to an adverse outcome. In general key events denote biological footprints of disease development and are accessible for ex-

perimental or observational investigation. In the radiation context a radiation marker would constitute a pertinent key event.

Two key events are linked together by a key event relationship (KER) defining one event as upstream and the other as downstream of the adverse outcome. To integrate parallel processes within a single AOP, KERs may link both adjacent and non-adjacent key events. The web-based AOP wiki platform (https://aopwiki.org) offers a software to implement AOPs online and a compilation of radiation-related AOPs is already underway. The AOP effectopedia (https://www.effectopedia.org) is a tool for visual exploration and development of AOPs compliant with the OECD Users Handbook. The effectopedia intends to facilitate a quantification of AOPs. It offers an interface to enter dose-and-time response data which can be used for deriving response-to-response relationships and potentially for designing BBCR models.

Preston (2015, 2017) and Chauhan et al. (2019) proposed to transfer the AOP framework from toxicology to radiation research. Chauhan et al. (2020) present a case example for AOPs applied to radiation-related lung cancer. The customary scheme of multi-scale analysis with BBCR models of radiation-induced cancer is depicted in Figure 1 which also reproduces the generic AOP structure of human toxicology from Figure 2 of Vinken et al. (2017). Both approaches can be compared with some qualifications. The point of contact for a MIE imparted by e.g. a toxin is often well defined and located. On the other hand ionizing radiation acts on biological processes over many length scales and not all radiation effects are fully understood.

BBCR models in adverse outcome pathways

The AOP framework favors a process-oriented approach of causes and effects to explain pathogenesis but does not include risk prediction. The mechanistic concept of BBCR models appeals to the AOP framework which is, however, more comprehensive. It involves processes which are not explicitly addressed by BBCR models such as deregulated signaling pathways or radiation-induced transcriptomic and proteomic changes. AOPs are embedded in a network structure which is capable of highlighting connections between similar components in different AOPs. BBCR models are adjusted to observational data and can potentially connect AOPs with risk assessment. The AOP

effectopedia offers promising support for future model development. Figure 2 displays determining factors of a BBCR model. They include classical covariables of descriptive models, structural model elements and and elements which are interpretable as key events in AOPs.

Advanced BBCR risk models

Multiple radiation targets

A complex interaction of effects such as radiation-induced early and late mutations, tissue inflammation or other non-targeted effects may jointly drive healthy cells on a pathway to cancer. BBCR models offer various radiation targets which with some imagination can be identified with the above mentioned processes. The radiation risk results from multiple pathogenic effects which can be accommodated in different radiation targets of a BBCR model (Heidenreich et al. 2004; Kaiser et al. 2014).

Sometimes not all radiation targets can be implemented into a single model due to issues of low case numbers and parameters highly correlated by interaction. But *several* plausible BBCR models with different targets yield a good data description. In this case the radiation risk can be construed by a superposition of plausible models with the technique of multi model inference (Kaiser et al. 2012). The purpose of model superposition is not to generate a superior biological model but to provide are more comprehensive characterization of uncertainties in risk estimates which can also be achieved with descriptive models (Walsh and Kaiser 2011).

Multipath models

BBCR models involving radiation exposure have always profited from model development for specific cancer sites in the general population. Important progress was made for cancers of the digestive tract, notably in the colon following the genetic caretaker-gatekeeper paradigm (Kinzler and Vogelstein 1997; Luebeck and Moolgavkar 2002; Meza et al. 2008; Luebeck et al. 2013). For colon cancer Little and Wright (2003) have proposed a mathematical framework which generally applies to many cancer sites and provides the backbone of multipath models as the most advanced versions of BBCR

models.

The conceptual design of multipath models relies on broad molecular profiles which can often be subdivided into two major groups (Kaiser et al. 2014, 2016, 2020; Castelletti et al. 2019). The differential dynamics of disease development in molecular subgroups and differential dependence on risk factors facilitates the identification pathway-specific model parameters in observational data even in the absence of molecular information. Interestingly, multipath models have been initially applied to radioepidemiological cohorts but a transfer to cohorts exposed to other risk factors such as smoking appears possible.

Competing carcinogenic exposure

For many organs radiation exposure is not the most important carcinogenic agent. For example, in the LSS the majority of lung cancer cases is caused by smoking. Based on descriptive modeling it has been argued that lung cancer risk is increased interactively by smoking and radiation (Egawa et al. 2012; Cahoon et al. 2017). Castelletti et al. (2019) have developed a BBCR model which suggests that the risk for lung adenocarcinoma from smoking and radiation arises in distinct molecular pathways. Compared to descriptive models the BBCR model moderately improved goodness-of-fit. Genomic analysis of TCGA data strongly supported the conceptual model design of two independent pathways characterized by mutations in transducer-mutant (T^{mut}) genes vs. receptor-mutant (R^{mut}) genes (Campbell et al. 2016). In the T^{mut}-group the KRAS gene is most frequently mutated with a strong association to smoking. Mutations in the EGFR gene of the R^{mut}-group are probably caused by radiation. Based on biological plausibility gained from molecular analysis and on improved goodness-of-fit obtained with the BBCR model Castelletti et al. (2019) hypothesize that smoking and radiation do not influence the risk of adenocarcinoma interactively. Importantly, the BBCR model provides clear predictions on the distribution of T^{mut} vs. R^{mut} cases in strata of attained age, age at exposure and lung dose which can be tested by molecular measurements.

Weaknesses of BBCR models

Although BBCR models represent a step forward in linking molecular biology with radioepidemiology they possess obvious shortcomings.

State-of-the-art BBCR models keep track of transient changes in cell numbers and properties but lack a spatial dimension. Therefore, the use imaging data for model parametrization is not straightforward. In a first attempt a spatial component was involved in a simulation model to describe radon-induced growth of hyperplasia in the lung epithelium (Drozsdik and Madas 2019). For a three-dimensional model of the epithelium the impact of inhaled radon particles on the formation of hyperplasia was assessed in Monte-Carlo simulations. The aim was to provide a radiobiological explanation for the typical leveling of the clonal expansion rate with increasing rates of radon exposure, which has been reported for BBCR models in studies of uranium miners cohorts (Luebeck et al. 1999; Zaballa and Eidemüller 2016).

Little et al. (2010) showed that not all biological parameters of a BBCR model can be identified from observational data. Only composite model parameters pertaining to a combination of biological processes can be gleaned from observational data. Often fewer than ten parameters can be estimated which limits the complexity of models and their ability to describe biological processes in detail.

Most importantly, BBCR models cannot overcome the *black box* dilemma of modeling which also pertains to descriptive models. Different models could explain observational data almost equally well based on different mechanistic assumptions. A good fit to the data does not prove that the assumed underlying mechanisms are actually in force. On the other hand, knowledge from AOPs can support the conceptual design of BBCR models and thereby shed light into hitherto black boxes.

Radiation biomarkers

Radiation biomarkers have been studied intensively in the past to identify radiogenic disease pathways (Hall et al. 2017). Some studies report specific molecular signatures in cancer tissue as induced by radiation. The ratio of genomic inversions and deletions (indels) over single nucleotide variants was significantly enhanced in four different

tumor types, which were identified as independent second malignancies after radiotherapy (Behjati et al. 2016). Unfortunately, this genomic signature of irradiation was not further refined in a recent large-scale study (Alexandrov et al. 2020).

Thanks to the availability of tissue from the Chernobyl Tissue Bank (CTB) and other sources the search for radiation markers is probably most advanced for papillary thyroid cancer (PTC) in patients who were exposed to radioiodine as children and adolescents after the Chernobyl accident. Gene fusions seem to appear more often than point mutations in radiation-induced PTCs (Efanov et al. 2018). Overexpression of the CLIP2 gene has been proposed as an independent radiation marker in post-Chernobyl PTCs which exhibits a pronounced dose response (Selmansberger et al. 2015a,b). The radiogenic origin of RET/PTC rearrangements is not fully clarified in post-Chernobyl PTC but is supported in a-bomb survivors (Leeman-Neill et al. 2013; Hamatani et al. 2008).

Kaiser et al. (2016) have demonstrated with a two-path model for post-Chernobyl PTC that an estimate for the ERR can be derived from molecular biomarker data which is equal to the ERR estimate from radioepidemiological analysis. The model featured two pathways to PTC with distinct molecular profiles of which one was predominantly related to radiation. They showed that the dose response function from logistic regression on the prevalence of the molecular CLIP2 radiation marker in 141 Ukrainian PTC patients is directly equivalent to the ERR estimate in the Ukrainian-American cohort. This cohort consists of about 12,000 participants from Ukraine with age below 19 yr at the time of the accident. In this example a BBCR model links molecular biology with epidemiology most tangibly.

Data needs

Public data bases

In many cases molecular profiles of cancer tissue are not available for radioepidemiological cohorts but have already been produced for cancer patients from the general population. Potentially interesting molecular data have been newly published by the International Cancer Genome Consortium (ICGC). The consortium have con-

tributed pan-cancer molecular analyses across multiple tumor types that provide insight into universal mutational processes and signatures of environmental agents in cancer genomes (Calabrese et al. 2020; Gerstung et al. 2020; Campbell et al. 2020; Li et al. 2020; Rheinbay et al. 2020; Alexandrov et al. 2020). Programmes TCGA and ICGC have at their disposal adequate molecular data which can be exploited to draft concepts for BBCR models. For example, for squamous cell carcinoma and adenocarcinoma in the lung distinct molecular profiles have been reported (Campbell et al. 2016). This fact is reflected in the mechanistic analysis of LSS data which has been performed exclusively for incidental adenocarcinoma by deliberately denouncing larger case numbers from all lung cancer cases combined (Castelletti et al. 2019).

Generally, large-scale genomics studies of diverse epidemiological cohorts combined with deep phenotyping and imaging provide an increasing number of publicly available data sets and generate insights into biological mechanisms of disease progression (Zeggini et al. 2019). From these multidimensional data sets blueprints for mechanistic models can be possibly gleaned with machine learning algorithms for later application in radioepidemiological cohorts.

Imputation of missing data

Usually risk factors other than radiation exposure are more influential for carcinogenesis in a specific organ. As a case in point tobacco consumption caused the majority of lung cancer cases in the LSS with radiation exposure in second place (Cahoon et al. 2017). Descriptive models can cope with missing smoking information by accounting for unknown smoking status at the cost of slightly biased risk estimates. BBCR models on the other hand depend upon complete information for major sources of exposure. Otherwise the claim of biologically-based modeling would make no sense. Consequently, the BBCR model for lung cancer from smoking and radiation in the LSS was developed with imputed smoking information (Furukawa et al. 2017; Castelletti et al. 2019).

Study design

Longitudinal cohort studies providing both individual epidemiological risk factors and cancer tissue for dedicated molecular profiling would form the optimal basis for mechanistic risk analysis involving BBCR models. Such conditions are realized for post-Chernobyl cohorts in collaboration with the CTB storing thyroid cancer tissue. Although the LSS facilitates high quality radioepidemiological analysis, effective interlock with molecular investigations has been achieved rarely. Systematic organization and preparation of material from LSS-related biobanks could possibly stimulate future research.

The design of case-control studies with focus on relative risks poses a difficulty for BBCR models which are parameterized to yield full hazard or survival functions. Heidenreich et al. (2002) have shown that BBCR models can still be applied in case-control studies when plausible assumptions on the parameters of the baseline hazard are made.

Quality management

Uncertainties of risk estimates are still large and efforts are made to reduce them. The most obvious approach is to increase sample size by pooling of cohorts (Leuraud et al. 2015; Laurent et al. 2016; Boice et al. 2019). However, inhomogeneities between cohorts may constitute a challenge for pooled data sets and insufficient understanding of incompatibilities could constitute a source for bias. Study protocols should apply comparable methods for all participants within and between cohorts. In general, the reliability and robustness of risk estimates is strongly influenced by the data component with the lowest quality. Hence, it is important to ensure similar levels of quality between components such as organ-specific dosimetry, case ascertainment and compilation of additional risk factors (or confounders) pertaining to socioeconomic status and lifestyle (Blettner 2015). The same diligence should be reserved for the generation of molecular profiles.

In radiation research two seemingly opposite requirements on data preparation need to be addressed. For general application, guidelines in radiation protection, e.g. on dose limits should be based on the largest possible body of evidence. This requires

aggregation of data from different sources which could be gained from pooled or meta analysis.

On the other hand, detailed investigation of radiobiological processes leading to cancer requires adequate resolution in space and time which under cost constraints can only be achieved with smaller sample size. Modeling of different subtypes of cancer is best performed with incidence data with precise diagnosis including histology. For mortality data different treatment modalities may cause an ambiguous interpretation of the outcome.

To sum up, mechanistic analysis would favor an approach of *well-balanced* data quality in all components over an approach which emphasizes the improvement of selected data features such as statistical power or dosimetry while neglecting others.

Impact on radiation protection

Probability of causation

Risk estimation with BBCR models has a direct impact on determining the probability of causation (POC). This risk measure is used in radiation protection to quantify the probability of radiation having caused a diagnosed cancer. It is routinely calculated to substantiate compensation claims with software packages such as IREP from the United States and the German ProZes (Kocher et al. 2008; Ulanowski et al. 2016).

The multipath models for PTC and lung adenocarcinoma feature two distinct molecular pathways of which only one pathway was associated with radiation exposure (Kaiser et al. 2016, 2020; Castelletti et al. 2019). This dichotomy entails additive pathway-specific hazard functions and can be exploited to improve the accuracy of POC determination. The conventional POC^{con} is given by the ratio $h_r^{(1)}/h^{tot}$ with $h_r^{(1)}$ and h^{tot} denoting the radiation-induced hazard in the first pathway and the total hazard, respectively. It does not fully account for the pathway-specific incidence, only in addition to the sporadic hazard $h_0^{(1)}$. The total hazard consists of three components $h^{tot} = h_r^{(1)} + h_0^{(1)} + h^{(2)}$. The hazard $h^{(2)}$ in the second pathway is not radiation-dependent and can be omitted in the POC definition.

Now we introduce the pathway-specific $\mathrm{POC}^{(1)} = h_r^{(1)}/(h_r^{(1)} + h_0^{(1)}) > \mathrm{POC}^{con}$.

Compared to POC^{con} by harnessing molecular profiles $POC^{(1)}$ yields a better approximation of a sharp step function, which provides precise evidence for the radiogenic origin of PTC. As a starting point Kaiser et al. (2020) have discussed a practical application of risk assessment for PTC incidence after the Fukushima accident.

Dose and dose rate effectiveness factor

Based on broad radiobiological knowledge an upward curvature for the risk response at moderate-to-high doses and high dose rates is often assumed for low-LET radiation. Even if a linear dose response yielded the best fit with a descriptive model at moderate-to-high doses and high dose rates, a dose and dose rate effectiveness factor (DDREF) is applied to appropriately modify the response at low doses and dose rates. At present the best estimate for a DDREF is still uncertain and may even include the value of one (Rühm et al. 2015).

For purposes of radiation protection the DDREF issue merits a revision with BBCR models. The assumption of upward curvature can be tested with biologically-based dose responses. In BBCR models linear responses on the biological level (i.e. for mutation rates) do not necessarily produce linear responses on the epidemiological risk level. To date, the actual shape of organ-specific risk responses over a wider dose range has not been investigated. A systematic response evaluation with published organ-specific BBCR models would help to assess the validity of the upward-curvature assumption and the application of DDREFs.

Future research

Guidance for experiments

Facilitated by growing availability of omics technologies the search of radiation-induced signals in molecular data was often conducted without pertinent hypotheses. Although such search has merits of its own it proved quite costly due to the high number of negative and false positive results. BBCR models offer interfaces for data from a variety of sources including molecular profiles. Based on this integrating property they are able to generate hypotheses on the prevalence of such profiles in cancer tissue of cohort

participants. For example, a BBCR model for PTC incidence in the LSS provides a detailed prediction of radiation marker prevalence stratified by attained age, age at exposure and thyroid dose (Kaiser et al. 2020). The BBCR model for lung adenocarcinoma in the LSS predicts a dose response for molecular damage in receptor-mutant genes, most notably EGFR (Castelletti et al. 2019). For colon cancer in the LSS the BBCR model yields a detailed prediction of the number of cases burdened with either microsatellite instability or chromosomal instability (Kaiser et al. 2014). Hence, with BBCR models clearly defined hypotheses are formulated to guide molecular measurements which can validate or falsify model concepts.

Intermediate stages

Experiments and measurements are performed either shortly after radiation exposure or in the event of a clinically relevant tumor. Carcinogenesis from early oncogenic mutations to full-blown cancer takes several decades but subclinical information on disease development during this long period is scarce (Luebeck et al. 2013). Nevertheless, data on the intermediate stages of carcinogenesis are urgently needed for more complete model parametrization. For example, measurements on adenoma as preneoplastic lesions for colon cancer could help to estimate model parameters pertaining to clonal expansion (Luebeck et al. 2019). The BBCR model for colon cancer predicts an influence of radiation on clonal growth which could be checked with data of adenoma prevalence in LSS participants (Kaiser et al. 2014). The potential benefits of evaluating routinely generated data from colonoscopies or from CT scans to obtain information on model parameters pertaining to intermediate stages of disease development should be investigated. Such data would shed light into the prolonged *time tunnel* of carcinogenesis from early mutations to tumor growth.

Persistent radiation effects and radiation-associated inflammation

Radiation can modulate cancer initiation, progression, and transformation in multiple ways thereby leading to multiple cancer types. Interpreted in the AOP framework radiation is able to trigger multiple MIEs as hinted by Figure 1. The tumor cell killing effects of relatively high radiation doses against established cancers are well known

and are reviewed elsewhere (Schaue and McBride 2015). Widely studied in cellular and animal models as well as in human cohorts is acute and persistent genomic damage from radiation exposure such as double-stranded DNA breaks, indels, and balanced inversions, or gene fusions (Rothkamm and Löbrich 2002; Behjati et al. 2016; Efanov et al. 2018).

BBCR models have consistently shown evidence for chronic promoting effects in preneoplastic lesions not only for protracted but also for *acute* radiation exposure. Radiation-induced promotion of tumor-initiated cells in growing clones has been reported for both low-LET and high-LET radiation (Castelletti et al. 2019; Kaiser et al. 2012, 2014, 2020; Curtis et al. 2001; Heidenreich 2002; Heidenreich et al. 2001; Heidenreich and Paretzke 2008). Probably the net increase in growth is not caused by accelerated cell division but by reduced cell inactivation. These observations can be ascribed to radiation-induced changes in the microenvironment of tissue cells.

Confirming mechanistic model predictions, experimental evidence from a mouse model showed that radiation can favor the clonal expansion of mutated cells over normal adjacent ones because they are more resistant to oxidative stress (Fernandez-Antoran et al. 2019). The subclinical inflammatory status of eight inflammation-related cytokines and other plasma-related markers in LSS participants remained chronically elevated decades after exposure (Hayashi et al. 2012). How acute radiation exposures result in perpetual inflammation is obscure, but epigenetic changes, cytoplasmic chromatin, and radiation effects on non-epithelial cells that contribute to the tumor stroma are likely key factors in this phenomenon (Bald et al. 2014; Schaue and McBride 2015; Gandhi and Chandna 2017; Dou et al. 2017).

Other organs

Multipath models are tailored for specific organs, histology and molecular profiles. There is no *one-size-fits-all* BBCR model and new organ-specific models need novel conceptual designs based on observational and molecular data of high quality.

As a case in point the female breast is a very radiosensitive organ and risk projection for secondary malignancies after radiotherapy are of clinical relevance (Brenner et al. 2018). BBCR models have already been developed for the LSS and the Swedish

haemangioma cohort (Kaiser et al. 2012; Eidemüller et al. 2015). However, these models do not reflect the complexity of molecular profiles and their relation to morphological phenotypes (Koboldt et al. 2012; Heng et al. 2017). More comprehensive BBCR models for radiation-induced breast cancer need a better grasp on the complexity of the disease process.

Conclusion

Future risk assessment will not only on rely on statistical association but will be quantitatively informed with radiobiological insight. To implement this claim we propose to extract information from AOPs which can be used at first quantitatively to develop conceptual model designs. In a more advanced stage BBCR models might apply quantitative data provided by the AOP effectopedia, i.e. in the form of dose response relations for biological processes. Generally speaking, BBCR models could harness radiobiological knowledge of AOPs to estimate radiation risk, but practical methods still need to be worked out.

Adequate BBCR models are embedded in a high-dimensional data environment shown in Figure 2. Informed by these data BBCR models provide a finer stratification of the radiation risk for a more personalized risk assessment. They leave behind the *one-size-fits-all* approach of descriptive modeling with the downside of more involved and time-consuming model development. As a gain risk estimates based on mechanistic dose responses (KERs in the AOP framework) are based on both statistical association and biological plausibility. Descriptive models associate fewer epidemiological risk factors with broader outcome i.e. comprising all solid cancers. Their risk estimates are derived on more global terms and appeal to the demands of radiation protection.

Importantly, predictions from BBCR models can be validated against molecular measurements with standard omics procedures. Validated model results strengthen the link between molecular biology and epidemiology. However, availability of cancer tissue in good quality from patients with know radiation exposure constitutes a major bottleneck. A comprehensive survey of data archived from previous radiation studies could help to address this shortcoming, especially if data were easily accessible in

electronic form from well curated biobanks. Ambitious initiative is needed to recover stored tissue samples and make them available for molecular investigations. To conclude, application of advanced BBCR models informed by observational and molecular data will improve accuracy and reduce uncertainty of radiation risk estimates in future research.

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Figures

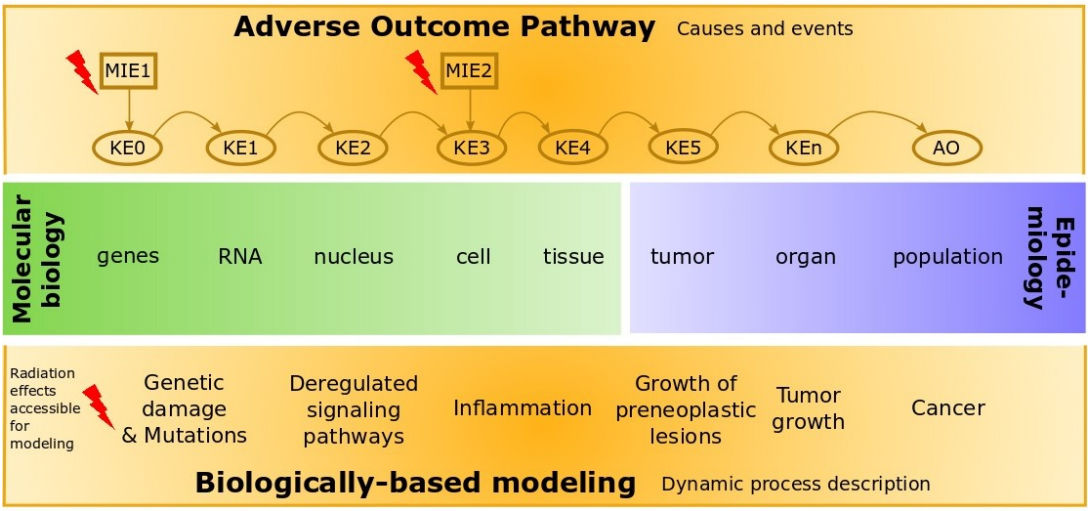

Figure 1. Juxtaposition of adverse outcome pathways (AOPs) and biologically-based modeling in radiation research. In the top row the generic AOP structure with molecular initial events (MIEs) and key events (KEs) is inspired by Figure 2 of Vinken et al. (2017); biological objects for experimental and observational investigation, which are typically addressed in BBCR models, are given in the center row; selected biological processes acting on these objects are cited in the bottom row; jagged arrow symbolizes a field of ionizing influencing biological processes.

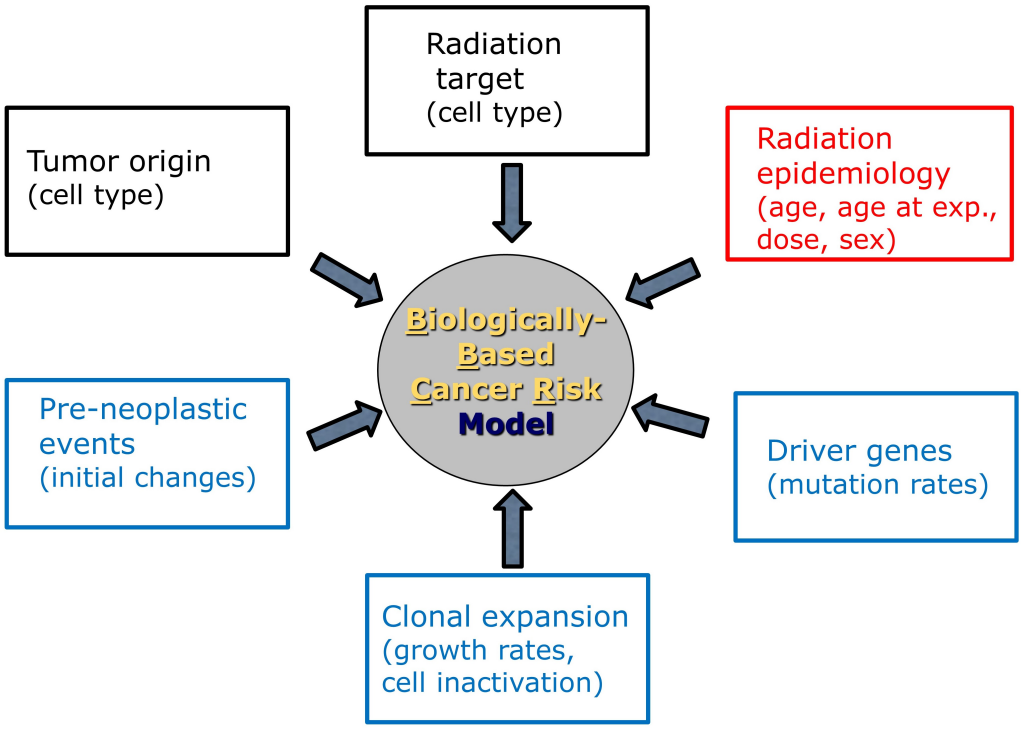

Figure 2. Determining factors of a Biologically-Based Cancer Risk (BBCR) model for radiation risk assessment. Classical covariables of descriptive models in red box, black boxes contain structural model elements, blue boxes display key events of an adverse outcome pathway (AOP).

Declaration of interest

The authors declare no conflict of interest.

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