Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Biology Contribution

Lung Cancer and Heart Disease Risks Associated With Low-Dose Pulmonary Radiotherapy to COVID-19 Patients With Different Background Risks

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Purpose: The respiratory disease COVID-19 reached global pandemic status in 2020. Excessive inflammation is believed to result in the most severe symptoms and death from this disease. Because treatment options for patients with severe COVID-19 related pulmonary symptoms remain limited, whole-lung low-dose radiation therapy is being evaluated as an anti-inflammatory modality. However, there is concern about the long-term risks associated with low-dose pulmonary irradiation. To help quantify the benefit-risk balance of low-dose radiation therapy for COVID-19, we estimated radiation-induced lifetime risks of both lung cancer and heart disease (major coronary events) for patients of different sexes, treated at ages 50 to 85, with and without other relevant risk factors (cigarette smoking and baseline heart disease risk).

Methods and Materials: These estimates were generated by combining state-of-the-art radiation risk models for lung cancer and for heart disease together with background lung cancer and heart disease risks and age/sex-dependent survival probabilities for the U.S. population.

Results: Estimated absolute radiation-induced risks were generally higher for lung cancer compared with major coronary events. The highest estimated lifetime radiation-induced lung cancer risks were approximately 6% for female smokers treated between ages 50 and 60. The highest estimated radiation-induced heart disease risks were approximately 3% for males or females with high heart disease risk factors and treated between ages 50 and 60.

Conclusions: The estimated summed lifetime risk of lung cancer and major coronary events reached up to 9% in patients with high baseline risk factors. Predicted lung cancer and heart disease risks were lowest in older nonsmoking patients and patients with few cardiac risk factors. These long-term risk estimates, along with consideration of possible acute reactions, should be useful in assessing the benefit-risk balance for low-dose radiation therapy to treat severe COVID-19 pulmonary symptoms, and suggest that background risk factors, particularly smoking, should be taken into account in such assessments.

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Introduction

Severe acute respiratory syndrome coronavirus 2 rapidly spread throughout the world in 2020 and reached global pandemic status. By January 5, 2021, 83 million confirmed cases and 1.8 million deaths due to COVID-19 caused by this virus have been reported through the World Health Organization.[1] The United States is one of the most seriously affected countries, with over 20.7 million COVID-19 cases and over 350,000 deaths, as reported by the Centers for Disease Control and Prevention on January 5, 2021.[2]

The mechanisms involved in how severe acute respiratory syndrome coronavirus 2 causes severe disease are being actively studied. Current evidence suggests that the most serious symptoms and death from COVID-19 result from an ineffective immune response in some patients, where a proinflammatory feedback loop is created.[3] This process leads to accumulation of immune cells in the lungs and the overproduction of proinflammatory cytokines (cytokine storm), which damages the lungs and multiple other organs.[3,4]

Because treatment options for patients with severe COVID-19 remain limited, and effective vaccination for preventing the spread of this disease is only starting to become available in limited amounts, whole-lung low-dose irradiation is being considered as a treatment modality.[5-13] Although ionizing radiation is a well-known mutagenic, carcinogenic, and cytotoxic agent, it is successfully harnessed to aid human health, for example in cancer radiation therapy, where it kills malignant cells. The role of ionizing radiation in modulating immune function and inflammation can also be seen as a "double edged sword": radiation, especially at high doses, can induce inflammation, but evidence suggests that at lower doses (typically below those used for cancer radiation therapy), it can have the opposite anti-inflammatory effect.[14] Despite incomplete understanding of its anti-inflammatory mechanisms, radiation has a history of effective use to treat nonneoplastic conditions (*eg*, degenerative bone diseases) where inflammation is involved.[4,14,15] Such ability of radiation at relatively low doses to disrupt persistent inflammation created the rationale for using it to treat severe COVID-19. Multiple clinical trials of lung irradiation for COVID-19, most of which use doses of 0.5 to 1.5 Gy to treat patients aged 50 to 85, are ongoing in 2020, with initial encouraging reports regarding its effectiveness (reviewed by Prasanna et al[9]). Mean lung doses delivered by such treatments are estimated to be similar to the nominal prescribed doses[16] and lie within the dose range that was historically used to treat pneumonia.[17]

As with all radiation-based modalities, it is important to understand potential radiation-associated risks, to assess the benefit-risk balance. Because the methodology of radiation treatment for COVID-19 is new, measurement of potential long-term risks of this modality is not yet possible. However, the detrimental effects of ionizing radiation have been studied for decades. Large amounts of data and theoretical knowledge have accumulated over this time, allowing quantitative estimates of potential risks of radiation treatment to be calculated.

Here we focused on quantifying long-term risks of radiation-induced lung carcinogenesis and heart disease for patients exposed to whole-lung irradiation at doses proposed for COVID-19 treatment. Such estimates of radiation-induced lifetime risks of lung cancer and heart disease are needed to facilitate the important task of quantifying the benefit-risk balance of radiation treatment for COVID-19. To complement existing literature on this subject,[5-13] which is still limited in scope due to the novelty of COVID-19, here we estimated radiation-induced lifetime risks of lung cancer and heart disease (major coronary events) for patients of different 'sexes and ages (≥50), focusing on risk factors (cigarette smoking, baseline heart disease risk) that can potentially interact with radiation. This focus on baseline risk factors allows the identification of those patient populations that are likely to suffer the highest radiation-induced long-term risks. Ultimately, lung cancer and heart disease risks should of course be considered in the context of other potential adverse effects of irradiation for COVID-19, including acute reactions and noncancer delayed effects (*eg*, the contribution of several elements of the lung microenvironment to posttreatment effects). The role of the COVID infection itself in causing long-term organ damage, such as heart disease,[18,19] vascular damage, and coagulopathy,[20,21] should also be taken into account. In addition, there is considerable overlap in the inflammatory syndromes caused by COVID-19 and radiation injury,[22] although notable differences between these syndromes also exist; for example, radiation pneumonitis is usually unilateral and occurs within 3 months after exposure, whereas COVID-19 can induce bilateral damage and occur at any time.[23,24]

Our risk estimates were generated by combining state-of-the-art radiation dose response models for lung cancer and heart disease with background lung cancer and heart disease risks and age-/sex-dependent survival probabilities for the U.S. population. We believe that the results of these calculations can be useful for clinicians by adding to the currently limited information on potential long-term consequences of COVID-19 treatment by radiation.

Methods and Materials

The main goal of this study was to estimate lifetime risks of lung cancer and heart disease induced by whole-lung irradiation for severe COVID-19. We used the following approaches to calculate such estimates for patients of different ages and sexes and with different baseline risk factors.

Lung cancer risks

To estimate excess absolute risks (EAR) of lung cancer associated with lung irradiation, we gathered the following information: (1) patient survival probabilities as function of age, sex, and smoking status; (2) background lung cancer risks as function of age, sex, and smoking; and (3) effects

of radiation and smoking (and interactions of both factors) on lung cancer risks, as a function of age and sex. A detailed description of the lung cancer risk calculations is provided in the Appendix EA.

Heart disease risks

Whole-lung irradiation for COVID-19 can potentially expose the heart and nearby major blood vessels to ionizing radiation, thereby creating the possibility for radiation-induced heart disease. To estimate lifetime EAR for heart disease, we used the same conceptual approach as described previously for lung cancer. It relied on the following information: (1) effects of ionizing radiation on heart disease risks; (2) background heart disease risks as function of age, sex, and other risk factors; and (3) survival probabilities as a function of age and sex.

Heart disease was defined as the sum of several types of major coronary events, such as myocardial infarction, coronary revascularization, or death from ischemic heart disease, following the definitions used in an important study of radiation effects on the heart by Darby et al.[25] This study suggested that the radiation effect is multiplicative, with a constant excess relative risk per Gy of 0.074.[25] More complex models with age-dependent excess relative risk per Gy are also available,[26] but we did not use them here because they are limited to myocardial infarctions, whereas Darby et al[25] considered several relevant heart disease endpoints. A detailed description of the heart disease risk calculations is provided in Appendix EB.

Results

The estimated lifetime EARs of lung cancer due to low-dose radiation therapy for COVID-19 treatment are summarized in Figures 1 and 2 and in Table 1 for smoking and nonsmoking patients of different sexes, treatment ages, and treatment doses. The risks decreased with age at exposure over the investigated range of 50 to 85, in large part due to decreasing life expectancy. The highest risk estimates were produced for smokers, especially for female smokers. This pattern is based on the findings of lung cancer epidemiologic modeling in Japanese atomic bomb survivors, which suggested complex and sex-dependent interactions between radiation and smoking.[27,28] In younger female smokers (aged 50-60), our estimates suggest that lung cancer risks due to COVID-19 irradiation can exceed 4% at 1 Gy, with linear scaling as function of dose (Table 1). Even for an age at exposure of 85, the lung cancer EAR for female smokers is estimated to be >2%/Gy (Table 1). In contrast, in male nonsmokers, the estimated risks are <1%/Gy for all ages in exposure groups (Table 1).

The estimated lifetime EARs of heart disease (major coronary events) due to irradiation for COVID-19 are summarized in Figures 3 and 4 and in Table 2 for patients of different sexes, ages at exposure, and baseline heart disease risk factors. Because current evidence suggests a multiplicative radiation effect on heart disease,[25] the highest radiation-induced risks (>2%/Gy) were produced for males and females with high baseline risk factors, such as high serum total cholesterol level, low high-density lipoprotein level, elevated systolic blood pressure, high C-reactive protein level, smoking, and family history of myocardial infarction before age 60. The risks were generally <1%/Gy in low baseline risk patients of both sexes (Table 2). As for lung cancer, heart disease EARs decreased with age at exposure, mainly due to decreasing life expectancy.

These findings suggest that the combined lifetime risks of radiation-induced lung cancer and major coronary events associated with irradiation for COVID-19 can exceed 5% in some patient subsets, such as relatively young (<60 years old) smokers with high baseline heart disease risk factors. Older patients with no smoking history and low-medium baseline heart disease risk factors are predicted to have much lower radiation-induced lung cancer and heart disease risks.

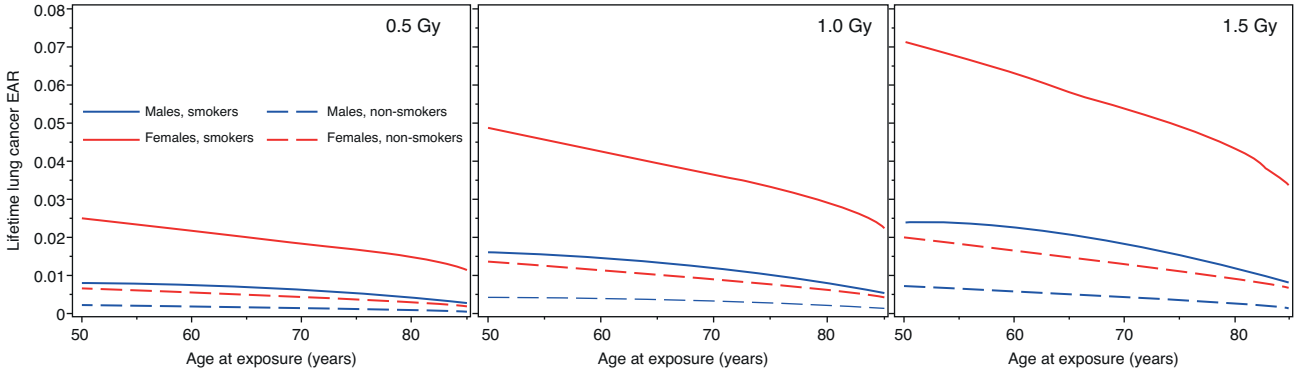

Fig. 1. Estimated excess absolute risks for lung cancer at different radiation doses in male and female smokers and nonsmokers, as function of age at exposure. EAR = estimated excess absolute risks.

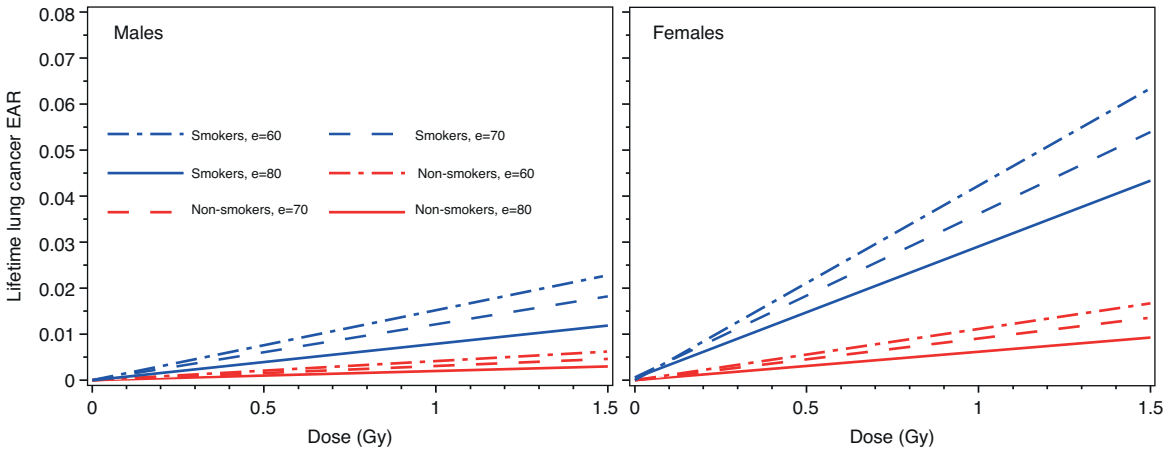

Fig. 2. Estimated excess absolute risks for lung cancer at different ages at exposure (e) in male and female smokers and nonsmokers, as function of radiation dose. EAR = estimated excess absolute risks.

Discussion

A quantitative comparison of benefits and risks for any new disease treatment modality is an important part of evidence-based medicine, which assists clinicians in making informed decisions about this treatment. Importantly, the benefit-risk balance can be different for different patients. Here we performed estimation of lifetime lung cancer and heart disease risks associated with the new technique of whole-lung irradiation for severe COVID-19. The goal was

Table 1 Estimated EAR (%) for lung cancer at different radiation doses in male and female smokers and nonsmokers

		Males						Females					
		Nonsmokers			Smokers			Nonsmokers			Smokers		
Dose (Gy)	Age at exposure (y)	Mean	Range		Mean	Range		Mean	Range		Mean	Range	
0.5	50	0.23	0.16	0.42	0.82	0.58	1.46	0.69	0.37	1.18	2.47	1.36	4.11
0.5	55	0.22	0.15	0.40	0.80	0.56	1.42	0.62	0.34	1.07	2.34	1.29	3.88
0.5	60	0.20	0.14	0.36	0.76	0.54	1.35	0.56	0.30	0.95	2.17	1.19	3.60
0.5	65	0.18	0.12	0.32	0.70	0.49	1.24	0.50	0.27	0.85	2.00	1.10	3.32
0.5	70	0.15	0.10	0.27	0.61	0.43	1.09	0.44	0.24	0.75	1.85	1.02	3.05
0.5	75	0.12	0.08	0.22	0.51	0.36	0.90	0.38	0.20	0.65	1.69	0.93	2.79
0.5	80	0.09	0.06	0.17	0.39	0.27	0.70	0.31	0.17	0.53	1.48	0.81	2.45
0.5	85	0.06	0.04	0.12	0.28	0.20	0.50	0.22	0.12	0.37	1.15	0.63	1.91
1.0	50	0.46	0.32	0.84	1.63	1.15	2.88	1.37	0.74	2.34	4.86	2.69	7.97
1.0	55	0.43	0.30	0.79	1.59	1.12	2.81	1.24	0.67	2.12	4.59	2.54	7.53
1.0	60	0.40	0.28	0.72	1.51	1.07	2.68	1.11	0.60	1.90	4.27	2.37	6.99
1.0	65	0.35	0.24	0.64	1.39	0.98	2.46	0.99	0.53	1.69	3.94	2.19	6.45
1.0	70	0.30	0.21	0.54	1.22	0.86	2.16	0.88	0.47	1.50	3.64	2.02	5.95
1.0	75	0.24	0.17	0.44	1.01	0.71	1.79	0.76	0.41	1.30	3.33	1.84	5.45
1.0	80	0.18	0.13	0.33	0.78	0.55	1.39	0.61	0.33	1.05	2.92	1.62	4.80
1.0	85	0.13	0.09	0.23	0.56	0.39	1.00	0.43	0.23	0.75	2.27	1.25	3.76
1.5	50	0.69	0.48	1.26	2.43	1.71	4.28	2.05	1.11	3.48	7.16	3.99	11.60
1.5	55	0.65	0.45	1.18	2.37	1.67	4.18	1.85	1.00	3.16	6.77	3.78	10.97
1.5	60	0.59	0.41	1.08	2.26	1.59	3.98	1.66	0.90	2.83	6.30	3.51	10.20
1.5	65	0.53	0.37	0.96	2.08	1.47	3.66	1.48	0.80	2.53	5.82	3.25	9.43
1.5	70	0.45	0.31	0.81	1.82	1.28	3.21	1.31	0.71	2.24	5.37	3.00	8.70
1.5	75	0.36	0.25	0.66	1.51	1.06	2.67	1.14	0.61	1.94	4.92	2.74	7.98
1.5	80	0.27	0.19	0.50	1.17	0.82	2.07	0.92	0.50	1.58	4.33	2.41	7.06
1.5	85	0.19	0.13	0.35	0.83	0.58	1.49	0.65	0.35	1.12	3.37	1.86	5.56

Abbreviation: EAR = excess absolute risks.
In this and the following table, range represents the span of minimum to maximum values over 300 Monte Carlo repeats, as described in Appendix EA.

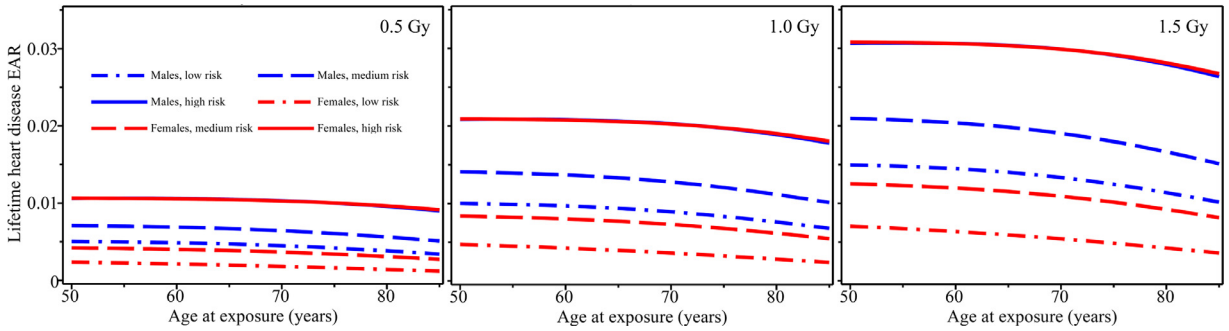

Fig. 3. Estimated excess absolute risks for heart disease at different radiation doses in males and females with low, medium, or high baseline risk factors, as function of age at exposure. EAR = estimated excess absolute risks.

to provide more information to quantify a benefit-risk assessment for this technique, particularly for patients with or without other risk factors.

Our analysis expands the so-far limited literature on the subject of log-term radiation-induced risks from radiation treatment of COVID-19.[5-13] Specifically, we focused on potential interactions between radiation and other risk factors (cigarette smoking, baseline heart disease risk). This approach of risk stratification allows those patient populations that are likely to be most at risk from radiation exposure for COVID-19 treatment to be identified.

By necessity, our risk estimation procedure involved multiple assumptions and limitations. Specifically, radiation responses were studied and modeled in large irradiated populations such as Japanese atomic bomb survivors or breast cancer radiation therapy patients, but here we applied them to the US population. Models based on very different data sets were therefore combined to generate the risk predictions, as described in the Methods and Materials section and Supplementary Materials (Appendices EA and EB). Uncertainties of the risk estimates were approximated by a simplified Monte Carlo procedure because detailed uncertainties of the component models were not fully known. An additional limitation involves potential underestimation of risk by not accounting for endothelial damage caused by radiation on top of COVID-19–related damage. Endothelial cells in microvessels are sensitive to radiation-induced damage,[29] and COVID-19 also initiates endothelial inflammation,[30] creating the possibility of synergistic interactions between damage induced by COVID-19 and radiation.

Due to these limitations, our radiation-induced lung cancer and heart disease predictions and uncertainties most likely represent order of magnitude estimates, rather than precise quantities. Radiation-induced breast cancer risk is another potential consequence of COVID-19 radiation therapy, but we did not focus on its estimation in this study because available evidence suggests that radiogenic breast cancer risk decreases steeply with age at exposure[31,32] and

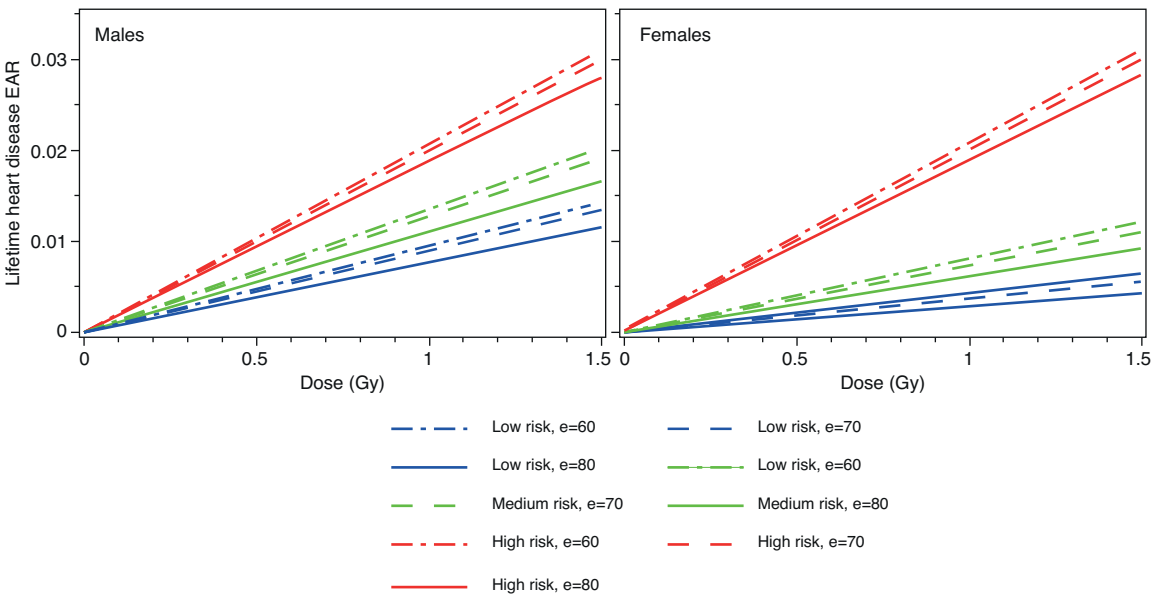

Fig. 4. Estimated excess absolute risks for heart disease at different ages at exposure (e) in males and females with low, medium, or high baseline risk factors, as function of radiation dose. EAR = estimated excess absolute risks.

Table 2 Estimated EAR (%) for heart disease at different radiation doses in patients with low, medium, or high baseline risk factors

		Low risk			Medium risk			High-risk		
Dose (Gy)	Age at exposure (y)	Mean	Range		Mean	Range		Mean	Range	
		Males								
0.5	50	0.50	0.30	0.73	0.71	0.45	0.93	1.06	0.92	1.17
0.5	55	0.50	0.30	0.73	0.70	0.45	0.93	1.06	0.92	1.16
0.5	60	0.49	0.29	0.71	0.69	0.44	0.92	1.06	0.91	1.15
0.5	65	0.47	0.28	0.69	0.67	0.42	0.90	1.05	0.88	1.15
0.5	70	0.45	0.26	0.66	0.64	0.40	0.87	1.03	0.84	1.15
0.5	75	0.42	0.25	0.63	0.61	0.38	0.83	1.00	0.79	1.14
0.5	80	0.38	0.22	0.58	0.56	0.35	0.78	0.96	0.73	1.12
0.5	85	0.34	0.20	0.52	0.51	0.31	0.72	0.90	0.66	1.08
1.0	50	1.00	0.60	1.45	1.41	0.90	1.84	2.08	1.79	2.30
1.0	55	0.99	0.59	1.44	1.39	0.89	1.83	2.09	1.82	2.29
1.0	60	0.97	0.58	1.42	1.37	0.87	1.81	2.08	1.79	2.26
1.0	65	0.94	0.56	1.38	1.33	0.84	1.78	2.06	1.74	2.26
1.0	70	0.89	0.53	1.32	1.28	0.80	1.72	2.03	1.67	2.26
1.0	75	0.83	0.49	1.24	1.21	0.75	1.65	1.97	1.57	2.24
1.0	80	0.76	0.44	1.15	1.12	0.69	1.55	1.89	1.45	2.20
1.0	85	0.68	0.39	1.04	1.01	0.62	1.43	1.78	1.32	2.12
1.5	50	1.49	0.89	2.16	2.10	1.35	2.74	3.07	2.62	3.39
1.5	55	1.48	0.88	2.14	2.07	1.33	2.72	3.07	2.66	3.37
1.5	60	1.45	0.86	2.11	2.04	1.30	2.69	3.06	2.65	3.34
1.5	65	1.40	0.83	2.05	1.98	1.26	2.63	3.04	2.58	3.32
1.5	70	1.33	0.79	1.97	1.90	1.20	2.56	2.99	2.47	3.33
1.5	75	1.24	0.73	1.85	1.80	1.12	2.45	2.91	2.33	3.30
1.5	80	1.14	0.66	1.71	1.66	1.03	2.30	2.79	2.16	3.24
1.5	85	1.02	0.59	1.55	1.51	0.92	2.13	2.64	1.96	3.14
		Females								
0.5	50	0.24	0.17	0.37	0.42	0.32	0.63	1.06	0.91	1.17
0.5	55	0.22	0.17	0.36	0.41	0.31	0.62	1.06	0.91	1.17
0.5	60	0.21	0.16	0.34	0.40	0.30	0.61	1.06	0.92	1.17
0.5	65	0.20	0.15	0.31	0.39	0.29	0.58	1.05	0.92	1.16
0.5	70	0.18	0.13	0.29	0.37	0.28	0.56	1.03	0.92	1.14
0.5	75	0.16	0.12	0.26	0.34	0.25	0.52	1.00	0.89	1.12
0.5	80	0.14	0.10	0.23	0.31	0.23	0.47	0.96	0.84	1.10
0.5	85	0.12	0.09	0.19	0.27	0.20	0.42	0.91	0.79	1.08
1.0	50	0.47	0.35	0.74	0.84	0.63	1.26	2.09	1.78	2.31
1.0	55	0.45	0.33	0.71	0.82	0.62	1.23	2.09	1.79	2.30
1.0	60	0.42	0.31	0.67	0.80	0.60	1.20	2.08	1.80	2.29
1.0	65	0.39	0.29	0.63	0.77	0.58	1.16	2.06	1.81	2.28
1.0	70	0.36	0.27	0.57	0.73	0.55	1.11	2.02	1.81	2.24
1.0	75	0.32	0.24	0.51	0.68	0.51	1.03	1.97	1.76	2.19
1.0	80	0.28	0.21	0.45	0.62	0.46	0.94	1.90	1.67	2.17
1.0	85	0.24	0.17	0.38	0.54	0.41	0.84	1.80	1.56	2.12
1.5	50	0.71	0.52	1.11	1.25	0.95	1.88	3.08	2.60	3.40
1.5	55	0.67	0.50	1.06	1.23	0.93	1.84	3.08	2.62	3.39
1.5	60	0.64	0.47	1.00	1.20	0.90	1.80	3.06	2.64	3.38
1.5	65	0.59	0.43	0.94	1.15	0.87	1.74	3.04	2.65	3.36
1.5	70	0.54	0.40	0.86	1.09	0.82	1.65	2.99	2.67	3.31
1.5	75	0.48	0.35	0.77	1.01	0.76	1.54	2.92	2.60	3.24
1.5	80	0.42	0.31	0.67	0.92	0.69	1.41	2.81	2.47	3.19
1.5	85	0.36	0.26	0.57	0.81	0.61	1.25	2.67	2.31	3.13

Abbreviation: EAR = excess absolute risks.

is therefore likely to be small for the majority of patients with severe COVID-19.

Conclusions

Despite its limitations, we believe that our study can help to inform and guide clinicians in their decisions about the use of ionizing radiation to treat patients with severe COVID-19. Our results suggest that younger patients with high baseline risk factors for lung cancer and heart disease, such as cigarette smoking, have the highest predicted radiation-induced risks. In contrast, older patients with low baseline risk factors are predicted to have much lower radiation-induced risks. However, our estimates of lung cancer and heart disease risks should be considered in the context of other acute and late complications, including potential long-term detriment in lung function in COVID survivors and the likelihood of coexisting pulmonary issues (*eg*, chronic obstructive pulmonary disease) in a sizeable portion of the elderly population. Limitations in current understanding of the mechanisms of COVID-19−induced organ damage should also be considered. Overall, if the weight of evidence from the ongoing clinical trials supports the effectiveness of radiation for COVID-19 therapy, our long-term risk estimates suggest that such therapy may have the best benefit-risk balance for older patients with low baseline risk factors.

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