Supporting Information

Research article

Additional risk of diabetes exceeds the increased risk of cancer caused by radiation exposure after the Fukushima disaster

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S1 Methods

Estimation of additional doses

The additional effective dose from external exposure was separated into two phases: the first 4 months (March 11–July 11, 2011) and thereafter. The effective dose for the first 4 months was determined from average values (excluding radiation workers) in the Soso district (0.8 mSv) [1]. The external exposure from July 12, 2011 and thereafter was estimated using the assumed ambient dose equivalents of 1.08 μSv/h before decontamination on July 1, 2012 and 0.55 μSv/h after decontamination, which were calculated from the average of values from outside 109 residences in contaminated areas of Minamisoma [2]. Temporal changes in effective doses before and after the decontamination were estimated only from physical decay [3] and the radiocesium composition after the accident in 2011 (radiocesium composition, 134Cs:137Cs = 1:1; contribution to additional effective dose, 134Cs:137Cs = 0.73:0.27 on August 23, 2011 [4]). We did not consider weathering effects and can therefore regard the doses as conservative. The additional effective dose from external exposure (D_{ee}) was estimated as:

\[
D_{ee} = a_f \times D_{eef} + \int (ADR \times k - BGR)dt \times RF \times C_{age}
\]

where \(a_f\) = 1 during the first 4 months and 0 thereafter, \(D_{eef}\) is the additional effective dose from external exposure during the first 4 months, ADR is the ambient dose equivalent rate, \(k\) converts the ADR to an effective dose (0.6 [5]), BGR is the background rate (0.03 μSv/h [5]), RF is the reduction factor, and \(C_{age}\) is the correction factor for children (<16 y: \(C_{age} = -0.0144 \times \text{age} + 1.27\); ≥16 y: \(C_{age} = 1\) [5]). The RF was set at 0.45, or the average of 0.3 among children [6] and 0.6 in the whole population in a conservative scenario [7]; this value agreed with the value of 0.46 estimated from shielding factors and actual indoor occupancy factors [8].

Doses from inhalation were considered only in the first year, as in a previous study [7]. These doses were reported to be negligible during the second year [9]. Doses were estimated as:

\[
D_{ih} = A_{Cs-137} \times I_i \times \sum_m(A_m/A_{Cs-137})/V_{bm} \times d_{mi}
\]

where \(D_{ih}\) is the additional effective dose from inhalation for age group \(i\) [mSv], \(I_i\) is the breathing rate of age group \(i\) [m^3 s^{-1}], \(m\) is the radionuclide (131I, 132I, 132Te, 134Cs, 137Cs), \(A_{Cs-137}\) or \(A_m\) is the surface activity density of 137Cs or radionuclide \(m\) on the ground [Bq m^{-2}], \(V_{bm}\) is the bulk deposition velocity of radionuclide \(m\) [m s^{-1}], and \(d_{mi}\) is the effective dose inhalation coefficient for radionuclide \(m\) and age group \(i\) [mSv Bq^{-1}]. The median of the values measured in Minamisoma [10] was used for \(A_{Cs-137}\) to maintain consistency with the external exposure estimates.

Doses from ingestion were assumed to be similar to those in Fukushima City (~50 km from the Fukushima Daiichi NPS) [11]. The doses from ingestion during the first year included 131I, 134Cs and 137Cs, whereas those during the second year and thereafter were
calculated from the doses of $^{134}$Cs and $^{137}$Cs in March 2012 and from physical decay. The doses from ingestion in Minamisoma and Soma might have been slightly higher than those in Fukushima but were minor relative to the external exposure and inhalation \[11,12\]. Therefore, this difference would not influence the results.

**LLE due to radiation-induced cancer**

Ages of 0, 5, 10, 20, 30, 40, 50, 60, 70, and 80 years at the time of the disaster were used to represent ages 0, 1–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, respectively. We used the mortality risk models for all solid cancers \[13\] and leukemia \[14,15\], which were based on the recent Life Span Study cohort of Hiroshima and Nagasaki atomic bomb survivors. A previous study \[13\] showed that a linear–quadratic dose–response model yielded a better fit in the range of <2 Gy, whereas a linear non-threshold model provided a better fit without range limitation. Therefore, we used the linear–quadratic dose–response model.

Organ (colon and bone marrow) doses were calculated from the additional effective doses and from the ratio of the organ dose to effective dose \[16\]. The excess relative risk (ERR) model for the mortality risk of all solid cancers was:

$$\text{ERR} (D, e, a, g) = (\alpha \times D + \beta \times D^2) \times (1 + t \times g) \times \exp[g_e \times (e - 30) + g_a \times \ln(a/70)]$$  

where $D$ is the organ dose (Sv), $e$ is the age at exposure, $a$ is the age attained, $g$ is sex, $\alpha = 0.22, \beta = 0.18, t = 0.29, g = -1$ for men and 1 for women, $g_e = -0.034$, and $g_a = -0.89$.

The ERR model for the mortality risk model of leukemia was:

$$\text{ERR} (D, a) = (\alpha \times D + \beta \times D^2) \times \exp[\gamma \times \ln(a/50)]$$

where $\alpha = 1.612, \beta = 1.551$, and $\gamma = -1.634$.

The minimum latency periods were set at 5 years for all solid cancers and 2 years for leukemia. The mortality rates for all solid cancers and leukemia were determined from the age- and sex-stratified all-cause mortality in Japan \[17\]. Based on these estimated additional age-specific mortality rates, the LARs of mortality and LLEs were calculated from the survival probabilities of Japanese men and women \[18\] (S5 and S6 Tables).

**LLE due to diabetes**

The ages of 40, 50, 60, and 70 years in 2011 were used to represent the age groups 40–49, 50–59, 60–69 and 70–79 years, respectively. Assuming that the prevalence of diabetes would not improve and that the time-changes in diabetes prevalence consequent to the increased mortality rates would be negligible, the additional incidence of diabetes AD was estimated as:

$$\text{AD}(x, t) = P_{ad}(x, t) - P_{bl}(x, t) - (P_{ad}(x, t-1) - P_{bl}(x, t-1))$$

where $x$ is the age, $t$ is the time stage (1: March 11, 2011–March 10, 2015; 2: March 11, 2015–March 10, 2021; 3: March 11, 2021–_), $P_{ad}$ is the diabetes prevalence ratio after the disaster, $P_{bl}$ is the diabetes prevalence ratio at baseline (same as before the disaster), and $P_{ad}(x,$
where $P(x, 0) = 0$.

The cohort study [19] from which data in this study were obtained was initiated in 1990 and ended in 2010 (median follow-up: 17.8 years). The ages of participants ranged from 40 to 69 years, and a total of 99 584 participants (men: 46 017; women: 53 567) were included. We excluded participants with any of the following conditions at baseline: cardiovascular disease, chronic liver disease, kidney disease, any cancer, or a body mass index (BMI) of <14 or >40. Here, a history of diabetes (i.e., physician diagnosis at any point) or the current use of anti-diabetes drugs was used to indicate diabetes.

The adjusted HR for all-cause mortality related to diabetes depended on the period of diagnosis: among men, before baseline = 1.59, between baseline and the 5-year survey = 1.20, between the 5- and 10-year surveys = 1.22; among women, before baseline = 2.00, between baseline and the 5-year survey = 1.55, and between the 5- and 10-year surveys = 1.45. Because the median follow-up period was 17.8 years, we classified HRs into ≤15 years and >15 years after the incidence of diabetes. In summary, the following HRs were used: for men, ≤15 years after the incidence of diabetes, 1.20 and >15 years after, 1.59; for women, ≤15 years after the incidence of diabetes, 1.45 and >15 years after, 2.00. However, these values may lead to an underestimation of risk (see details in “Sources of uncertainty”).

Additional diabetes-induced mortality rates ($C_e$) were estimated as:

$$C_e(x) = M(x) \times R(x) \times (HR - 1) \quad (6)$$

where $M(x)$ is the all-cause mortality rate and $R(x)$ is the ratio of all-cause mortality among those without diabetes to the total, calculated as:

$$R(x) = (1 - P(x))/(1 - P(x) + P(x) \times HR) \quad (7)$$

where $P(x)$ is the prevalence of diabetes.

The $R(x)$ was calculated from the $P(x)$ in 2012 in Japan [20] and the HR (1.59 for men, 2.00 for women). The LARs of mortality and LLEs of a patient with diabetes were calculated using the $C_e(x)$ and the Japanese survival probability (S7 and S8 Tables). The LARs of mortality and LLEs due to diabetes in each scenario were then estimated from the additional incidence of diabetes and the LLEs of patients with diabetes during years 1–4 and 5–10 (S9 Table). In Scenario 2, we considered the premature incidence among men in their 40s and 50s to obtain the LLEs (or LARs of mortality) during years 1–4, and subtracted the LLEs (or LARs of mortality) estimated from the negative incidence of diabetes during years 5–10 (additional incidence: −3.7% for men in their 40s; −4.1% for men in their 50s) from the LLEs (or LARs of mortality) estimated from the incidence of diabetes during years 1–4.

**Costs and effectiveness of countermeasures**

The effects of restricted food distribution were estimated from the reduction in the effective dose from dietary sources in Fukushima City, the prefectural capital, during the first year after the disaster (March 21, 2011–March 20, 2012) as reported in a previous study [11],
rather than from the cities of Minamisoma and Soma. Because restricted food distribution was used for market regulation, Fukushima City was considered an appropriate target area. The life-years saved (LYS) were calculated from the reduction in dose for each sex and by age group (0, 5, 10, 20, 30, 40, 50, 60, 70, 80 years) using the above-described models (S11 Table). The LYS were then estimated for the whole population on March 1, 2011 [21]. The cost of the restricted food distribution comprised the costs of foods produced but discarded (CF) (i.e., opportunity losses) and of monitoring. The CF was estimated as:

\[ CF_j = \sum_{i,j,k} A_j \times B_{ij} \times C_{jk} \times X_{jk} \]  

(8)

where \( j \) is the food category (16 categories: rice, dairy products, milk, tea, turnips, spinach, heading leafy vegetables, broccoli and cauliflower, kiwifruit, chestnut, bamboo shoots, mushrooms, beef, and wild ayu, wild Japanese dace and wild landlocked masu salmon [11]), \( i \) is the age and sex group, \( k \) is the area where food distribution was restricted, \( A_j \) is the unit cost of food \( j \) (JPY/kg), \( B_{ij} \) is the daily consumption of food \( j \) per person \( i \) (kg/d), \( C_{jk} \) is the number of days food \( j \) distribution was restricted in area \( k \) (d), and \( X_{jk} \) is the arrival share (the fraction of food \( j \) on the market in Fukushima City that came from area \( k \)).

\( A_j \) was determined from previous reports [22-25]. The prices for shipping and selling on-cost (39.3%) were not included [22]. The median value of beef was used. The per-capita costs were calculated as 700 JPY (S12 Table). The total costs of monitoring foods and tap water were estimated from the unit cost of measurement (10 000 JPY) and the total number of measurements [26-29]. Food measurements were considered to be applicable for the whole Japanese population, and accordingly the total cost per person, 10 JPY, was estimated by dividing the total cost by the total number of people in Japan [30]. For tap water, we counted the number of monitoring tests in Fukushima City and divided the total cost by the total number of people in Fukushima City to yield 40 JPY. The final monitoring cost (50 JPY) was minor when compared with the opportunity loss for foods (700 JPY); in other words, uncertainty in the monitoring cost is unlikely to influence the results. The cost per life-years saved (CPLYS) of the restricted food distribution was 56 million JPY/year, comparable to those for vegetables from March to May 2011 (6.6–240 million JPY/year) and lower than those for rice in 2011 (310–1000 million JPY/year) [22].

The effect of decontamination was estimated under the assumption described in “Estimation of additional doses”, namely a reduction in the ambient dose equivalent from 1.08 to 0.55 μSv/h outside of residences on July 1, 2012 [2]. The doses were considered to decrease with physical decay. The LYS was calculated based on the estimated effective doses from external exposure (eq. 1) (S13 Table). The costs of decontamination in Minamisoma and Soma were taken from the literature [31-33]. For Minamisoma, the costs were the median values in scenarios wherein areas with effective doses of >1 mSv/year were decontaminated (details were provided by the author of the sources [31,32]). For Soma, the costs were
estimated from unit prices and the actual number of decontamination events planned to March 2016.

The effects of whole-body counter tests and interventions were estimated from the results of a whole-body counter screening and counseling program conducted at Minamisoma Municipal General Hospital and Hirata Central Hospital (Hirata Village, ~40 km from Fukushima Daiichi NPS) [34]. Although whole-body counter screening was conducted in 2011, the effects of this screening were not clear because the dose reduction was attributed mainly to the physical and environmental decay of radiocesium in foods rather than to medical counseling. Therefore, we used the results obtained from March 11, 2012 to March 10, 2013. Of the 30,622 residents who participated in whole-body counter screening, 9 were found to have radiocesium levels exceeding 50 Bq/kg, and their effective doses from internal exposure to $^{134}$Cs and $^{137}$Cs ranged from 0.14 to 0.97 mSv/year. After counseling to reduce the intake of locally grown foods (generally, 30 d after the measurement), the 8 residents who remained in the study exhibited dynamic reductions in radiocesium levels (one resident dropped out from subsequent screenings) (S3 Figure). The $^{137}$Cs levels measured at the second and third screenings agreed well with estimates based on the biological half-life [35] and the assumption that radiocesium intake stopped 30 d after the whole-body counter screening. Therefore, we considered the effects of whole-body counter tests and interventions as the differences in the lifetime effective doses from internal exposure between the continuous intake of radiocesium from contaminated foods (0.14–0.97 mSv/year at the first measurement) and the average intake of foods in Fukushima Prefecture (0.0022 mSv/year, measured using food duplicate methods in March–May 2012 [36]). The ratio of $^{134}$Cs:$^{137}$Cs on March 11, 2011 was assumed to be 1:1, and radiocesium concentrations in foods were assumed to decrease by physical decay. The dose coefficient was taken from [37]. The LYS was similarly calculated using dose reduction (S14 Table). The costs for whole-body counter screening comprised instruments, consultation, travel, and time. One whole-body counter scanner cost 45.3 million JPY, and four scanners were installed at Minamisoma Municipal General Hospital and Hirata Central Hospital. The useful life span was set at 10 years, and the costs for 1 year were estimated. A discount rate was not considered. One measurement and consultation cost 5000 JPY. The travel costs for one measurement were estimated using the unit price of gasoline (120 JPY/L), travel distance (20 km for Minamisoma; 60 km for Hirata), and gasoline consumption rate (10 km/L). The time was calculated from the unit value (20 JPY/min) and the travel speed (30 km/h for Minamisoma; 50 km/h for Hirata). The total number of individuals was 30,622 (cumulative number: 9969 in Minamisoma and 20,668 in Hirata; some participated more than once).

As a countermeasure against diabetes, we considered health checkups and metformin therapy for diabetes, as metformin therapy was shown to be effective for overweight patients with Type 2 diabetes (>120% ideal body weight; body mass index (BMI) = 25.6 kg/m$^2$) in a
randomized controlled trial that used the outcome of all-cause mortality in the UK (median duration: 10.7 years) [38,39]. Although empagliflozin was recently reported to reduce mortality associated with cardiovascular causes among for patients with Type 2 diabetes [40], we did not consider the cost-effectiveness of this drug because of a lack of efficient practical applications. Although we needed to estimate the differences in LYS between therapy and no therapy, data were not available for the latter. Because metformin therapy for overweight patients increased the LYS per patient by 1.0 year when compared with other conventional therapies, we expected that it would also increase the LYS per patient by >1.0 year when compared with no therapy. The LYS for the whole population was estimated from the prevalence of diabetes among the overweight (BMI >25.6 kg/m²) in Minamisoma and Soma during the period of 2012–2014 (men: 5.6%; women: 3.5%). The costs comprised health checkups and the total costs associated with therapy and complications. The costs for health checkups applied to all participants, as all were screened for diabetes. The unit price of a health checkup is 8000 JPY/person, and we assumed that individuals would undergo 35 total health checkups (annually in the age range of 40–74 years). The total costs of metformin therapy and complications, 7883 GBP/patient (∼1.26 million JPY/patient on the basis of 160 JPY/GBP), were obtained from a UK study and were lower than those obtained for other conventional therapies (8165 GBP/patient ∼1.31 million JPY/patient) [39]. The cost of health checkups was greatly overestimated because these are not performed merely to identify overweight patients with diabetes. Overall, the CPLYSs for health checkups and metformin therapy for diabetes were overestimated by up to 7.4 million JPY/year.

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