Electronic Supplementary Material

Ultrasonography surveys and thyroid cancer after the Fukushima accident

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1. Data for calculating prevalence

Age- and gender-structure for children and adolescents in Fukushima prefecture have been taken from the data of Fukushima Medical University (2013), and for non-contaminated areas in prefectures Aomori, Yamanashi and Nagasaki from the recent study Taniguchi et al 2013). The numerical values are shown in table S1.

Table S 1. Age- and gender-distribution of children and young adults subjected to ultrosonographic screening in Fukushima (Fukushima Medical University 2013) and Aomori, Yamanashi, Nagasaki (Taniguchi et al 2013) prefectures.

Age (year)	Fukushima (November 2011 – March 2012)		Fukushima (April 2012 – March 2013)		Aomori, Yamanashi, and Nagasaki (November 2012 – January 2013)	
	male	female	male	female	male	female
0–5	5386	5249	19164	18072	96[a]	93[a]
6–10	5757	5492	20587	19245	621	654
11–15	6019	5990	20381	20006	1005	990
16–18	3139	3270	7899	8720	353	553

[a] ages from 3 to 5 years

The cohort in the UkrAm study in the first screening (2-year-screening was performed in 1998–2000) encountered 6471 males and 6656 females with age distribution spanning from 12 to 33 years (Tronko et al 2006). Thyroid cancer incidence in Ukraine during this time has been taken from National Cancer Registry of Ukraine (Fedorenko et al. 2002). Using these data, thyroid cancer incidence rate weighted with age- and sex-distribution specific to the first screening in the UkrAm cohort results in the following value: $\lambda_{Ukraine,U1}=1.756\times10^{-5}$.

Thyroid cancer incidence in Japan in 2007 has been taken as reported by Japan National Cancer Center (2012). Using age- and sex-distributions for children and young adults in Fukushima prefecture shown in Table S1, one gets average incidence rates $\lambda_{Japan,Fp}$ $=0.267\times10^{-5}$ (screening in 2011–2012) and 0.332×10^{-5} (screening in 2012–2013). For the cohort of children and adolescents from prefectures Aomori, Yamanashi and Nagasaki the incidence rate, weighted according to distributions shown in Table S1, equals to 0.317×10^{-5}.

2. Re-analysis of thyroid cancer incidence in the LSS cohort

2.1 Data set and the cohort

The analysis is based on the LSS cohort data for cancer incidence in 1958–1998 contained in the file lssinc07ahs.csv, which has been downloaded from the RERF website (http://www.rerf.or.jp). It comprises 105,427 subjects and 471 cases of incidental thyroid cancer recorded in 2,764,725 person years (PYRs). The crude data is summarized in Table A18 of Preston et al. (2007). The person-year weighted means are 23 years for age at exposure, 53 years for attained age, 60 years for age of cases and 105 mGy for the weighted dose to the thyroid. In the dose calculation, the neutron-related component was weighted with a relative biological effectiveness (RBE) of ten.

2.2 Baseline model

The baseline incidence rate $\lambda_0(s, a, e, c, AHS, NIC)$ depends on explanatory variables of sex s, attained age a, age at exposure e, city (Hiroshima: c=1; Nagasaki c=2), status of AHS participation (no: AHS=0; yes: AHS=1) and of having been in the city at the time of the bombing (for distance from hypocenter <10 km: NIC=0; otherwise: NIC=1). The baseline incidence rate factorizes

$$\lambda_{0,LSS}\left(s,a,e,c,AHS,NIC\right)\times10^4=\lambda_{0,fit}\left(s,a,e\right)F_{scr}\left(a,e,AHS\right)g\left(c,NIC\right)$$

into a fit function common for all cohort members:

$$\lambda_{0,fit}\left(s,a,e\right)=\exp\left(\beta_{0,s}+\beta_{a_1,s}\ln\frac{a}{60}+\beta_{a_2,s}\ln^2\frac{a}{60}+\beta_{e_1,s}\frac{e-20}{10}+\beta_{e_2,s}\left(\frac{e-20}{60}\right)^2\right)$$

and an adjustment factor accounting for screening effect for members AHS:

$$F_{scr}\left(a,e,AHS\right)=\exp\left(\beta_{AHS}\left(a-e\right)AHS\right),$$

where for non-zero factor AHS:

$$\beta_{AHS}(a-e)=\begin{cases}\beta_{AHS,1}, & a-e\geq 25 \text{ (AHS in 1970 and later);}\\ \beta_{AHS,1}+\beta_{AHS,2}, & a-e<25 \text{ (AHS before 1970).}\end{cases}$$

and a factor accounting for residential status (city and 'not-in-the-city' factor – NIC):

$$g(c,NIC)=\exp\left(\beta_c(c-1)+\beta_{NIC}NIC\right).$$

The baseline model of Preston et al (2007) is nested to the baseline model of the present analysis. In the further calculations, *city*- and *NIC*-status have been averaged out with weights defined from the number of cancer cases observed in each of the sub-groups of the LSS cohort.

2.3 Dose response

For the dose response an ERR model was chosen using the form

$$ERR(s,e,a)=\alpha_d\ D\exp\left(\alpha_s s+\alpha_a\ln\frac{a}{60}+\alpha_e\frac{e-20}{10}\right)$$

where *α*... are parameters, *D* is the weighted thyroid dose and parameter *s* equals to +1 for females and to −1 for males.

The original ERR model of Preston et al (2007) used 22 parameters with a deviance of 3037.97 (Akaike Information Criterion *AIC*=3081.97). The present model consumed 17 parameters and yielded a deviance of 3037.65 (*AIC*=3069.65). Maximum likelihood estimates (MLE) and confidence intervals are given in Table S2. Estimates of the ERR at 1 Gy from Preston et al (2007) and the present study differ by less than ten percent. The confidence intervals are quite symmetrical. Table S3 gives standard deviations and the correlation matrix of the parameters.

Table S2. MLE estimates and confidence intervals (CIs) for the parameters of the ERR model from the present analysis. CIs are calculated from the likelihood profile.

Name	Unit	MLE estimate and confidence intervals
$\beta_{0,m}$	–	−0.39 (−0.62; −0.17)[a]
$\beta_{0,f}$	–	0.53 (0.36; 0.70)[a]
β_{city}	–	−0.22 (−0.33; −0.11)[a]
β_{AHS}	–	0.21 (0.08; 0.33)[a]
$\beta_{AHS,1970}$	–	0.33 (0.22; 0.44)[a]
β_{NIC}	–	−0.47 (−0.61; −0.34)[a]
$\beta_{a1,m}$	–	1.9 (1.3; 2.5)[a]
$\beta_{a1,f}$	–	2.0 (1.5; 2.4)[a]
$\beta_{a2,f}$	–	−0.75 (−1.30; −0.24)[a]
$\beta_{e1,m}$	yr^{-1}	0.091 (n.a.; 0.19)[a]
$\beta_{e1,f}$	yr^{-1}	−0.24 (−0.33; −0.16)[a]
$\beta_{e2,f}$	yr^{-2}	0.080 (0.060; 0.098)[a]
α_d	Gy^{-1}	1.07 (0.71; 1.51)[a] (95% 0.44; 2.04)[b]
α_e	–	−0.59 (−0.89; −0.32)[a] (95% −1.20; −0.08)[b]
α_a	yr^{-1}	−1.03 (−1.89; −0.16)[a] (95% −2.74; 0.70)[b]

α_s	–	0.11 (−0.16; 0.42)[a] (95% −0.52; 0.77)[b]

[a] 68% confidence interval

[b] 95% confidence interval

Table S3. Maximum likelihood estimates (MLE), standard deviations and covariance matrix of parameters of the ERR model for thyroid cancer incidence in the LSS.

Parameter	MLE	Std.dev	Covariance matrix							
			$\beta_{0,m}$	$\beta_{0,f}$	β_{city}	$\beta_{\text{ahs},1}$	$\beta_{\text{ahs},2}$	β_{NIC}	$\beta_{a_1,m}$	$\beta_{a_1,f}$
$\beta_{0,m}$	-3.9E-01	2.3E-01	5.2E-02	2.3E-02	-3.1E-03	-1.9E-02	5.7E-03	-2.2E-03	5.5E-02	1.7E-02
$\beta_{0,f}$	5.3E-01	1.7E-01	2.3E-02	2.9E-02	-3.0E-03	-1.8E-02	5.2E-03	-2.5E-03	1.6E-02	1.8E-02
β_{city}	-2.2E-01	1.1E-01	-3.1E-03	-3.0E-03	1.2E-02	-2.2E-04	9.2E-05	9.5E-04	4.3E-04	5.9E-04
$\beta_{\text{ahs},1}$	2.1E-01	1.3E-01	-1.9E-02	-1.8E-02	-2.2E-04	1.6E-02	-5.5E-03	-1.5E-03	-1.2E-02	-1.4E-02
$\beta_{\text{ahs},2}$	3.3E-01	1.1E-01	5.7E-03	5.2E-03	9.2E-05	-5.5E-03	1.2E-02	-8.0E-05	2.6E-02	3.1E-02
β_{NIC}	-4.7E-01	1.3E-01	-2.2E-03	-2.5E-03	9.5E-04	-1.5E-03	-8.0E-05	1.8E-02	-2.6E-04	6.2E-04
$\beta_{a_1,m}$	1.9E+00	5.9E-01	5.5E-02	1.6E-02	4.3E-04	-1.2E-02	2.6E-02	-2.6E-04	3.5E-01	7.9E-02
$\beta_{a_1,f}$	2.0E+00	4.4E-01	1.7E-02	1.8E-02	5.9E-04	-1.4E-02	3.1E-02	6.2E-04	7.9E-02	1.9E-01
$\beta_{a_2,f}$	-7.5E-01	5.3E-01	-1.1E-03	-6.9E-03	3.4E-04	-4.6E-03	1.3E-02	-5.4E-05	-1.3E-02	1.1E-01
$\beta_{e_1,m}$	9.1E-02	1.0E-01	-1.4E-02	-2.5E-03	1.8E-04	2.1E-03	-4.8E-03	1.2E-04	-4.5E-02	-1.4E-02
$\beta_{e_1,f}$	-2.4E-01	8.3E-02	-2.5E-03	-2.9E-03	2.3E-04	1.5E-03	-4.5E-03	5.9E-05	-1.3E-02	-2.4E-02
$\beta_{e2,f}$	8.0E-02	1.9E-02	-4.0E-05	-4.5E-04	-6.8E-06	1.8E-04	-1.7E-04	5.5E-05	2.4E-04	-1.3E-05
α_d	1.1E+00	4.0E-01	-2.7E-03	8.4E-03	1.1E-03	-1.8E-02	2.3E-03	1.1E-02	2.1E-03	7.6E-04
α_e	-5.9E-01	2.8E-01	1.1E-02	5.9E-03	-3.2E-05	-4.3E-03	-5.0E-03	3.2E-03	9.0E-03	9.8E-03
α_a	-1.0E+00	8.4E-01	-2.1E-02	-1.8E-02	2.0E-04	-2.8E-03	1.3E-02	-3.3E-04	-1.1E-01	-4.4E-02
α_g	1.1E-01	2.8E-01	2.0E-02	-2.4E-03	1.6E-04	-1.5E-03	-5.2E-04	9.4E-04	-2.5E-02	6.7E-03

Table S3 (cont'd). Maximum likelihood estimates (MLE), standard deviations and covariance matrix of parameters of the ERR model for thyroid cancer incidence in the LSS.

Parameter	Covariance matrix (cont'd)							
	$\beta_{a_2,f}$	$\beta_{e_1,m}$	$\beta_{e_1,f}$	$\beta_{e2,f}$	α_d	α_e	α_a	α_g
$\beta_{0,m}$	-1.1E-03	-1.4E-02	-2.5E-03	-4.0E-05	-2.7E-03	1.1E-02	-2.1E-02	2.0E-02
$\beta_{0,f}$	-6.9E-03	-2.5E-03	-2.9E-03	-4.5E-04	8.4E-03	5.9E-03	-1.8E-02	-2.4E-03
β_{city}	3.4E-04	1.8E-04	2.3E-04	-6.8E-06	1.1E-03	-3.2E-05	2.0E-04	1.6E-04
$\beta_{\text{ahs},1}$	-4.6E-03	2.1E-03	1.5E-03	1.8E-04	-1.8E-02	-4.3E-03	-2.8E-03	-1.5E-03
$\beta_{\text{ahs},2}$	1.3E-02	-4.8E-03	-4.5E-03	-1.7E-04	2.3E-03	-5.0E-03	1.3E-02	-5.2E-04
β_{NIC}	-5.4E-05	1.2E-04	5.9E-05	5.5E-05	1.1E-02	3.2E-03	-3.3E-04	9.4E-04
$\beta_{a_1,m}$	-1.3E-02	-4.5E-02	-1.3E-02	2.4E-04	2.1E-03	9.0E-03	-1.1E-01	-2.5E-02
$\beta_{a_1,f}$	1.1E-01	-1.4E-02	-2.4E-02	-1.3E-05	7.6E-04	9.8E-03	-4.4E-02	6.7E-03
$\beta_{a_2,f}$	2.8E-01	-9.0E-04	-2.9E-03	-2.8E-03	4.1E-02	-2.3E-02	1.9E-01	-8.4E-03
$\beta_{e_1,m}$	-9.0E-04	1.0E-02	2.6E-03	-9.4E-05	5.5E-03	-3.2E-03	1.3E-02	-4.1E-03
$\beta_{e_1,f}$	-2.9E-03	2.6E-03	6.9E-03	-9.6E-04	2.4E-03	-8.3E-03	1.8E-02	5.1E-04
$\beta_{e2,f}$	-2.8E-03	-9.4E-05	-9.6E-04	3.8E-04	-2.9E-04	2.2E-03	-4.2E-03	7.3E-05
α_d	4.1E-02	5.5E-03	2.4E-03	-2.9E-04	1.6E-01	1.2E-02	1.3E-01	-5.0E-02
α_e	-2.3E-02	-3.2E-03	-8.3E-03	2.2E-03	1.2E-02	7.7E-02	-1.4E-01	1.1E-02
α_a	1.9E-01	1.3E-02	1.8E-02	-4.2E-03	1.3E-01	-1.4E-01	7.0E-01	-2.2E-02
α_g	-8.4E-03	-4.1E-03	5.1E-04	7.3E-05	-5.0E-02	1.1E-02	-2.2E-02	8.1E-02

3. Excess absolute risk in study groups

3.1 Modifying factors

The onset of radiation-related excess in thyroid cancer incidence has been modelled as dimensionless function of time since exposure*:

$$F_L(t) = \left(1 + \exp\left(\frac{4-t}{0.218}\right)\right)^{-1}.$$

The uncertainty introduced by extrapolating the LSS-based risk function to low-dose-rate exposures, as they occurred mainly after the Fukushima accident, has been modelled by the corresponding modifying factor F_{DREF}, which has lognormal distribution with a mean value of 1.0 and a boundaries of the 95 % confidence interval at 0.4 and 2.1.

3.2 Ratio of baseline incidence rates in Japan in 2007 and in the LSS (non-participants in the AHS)

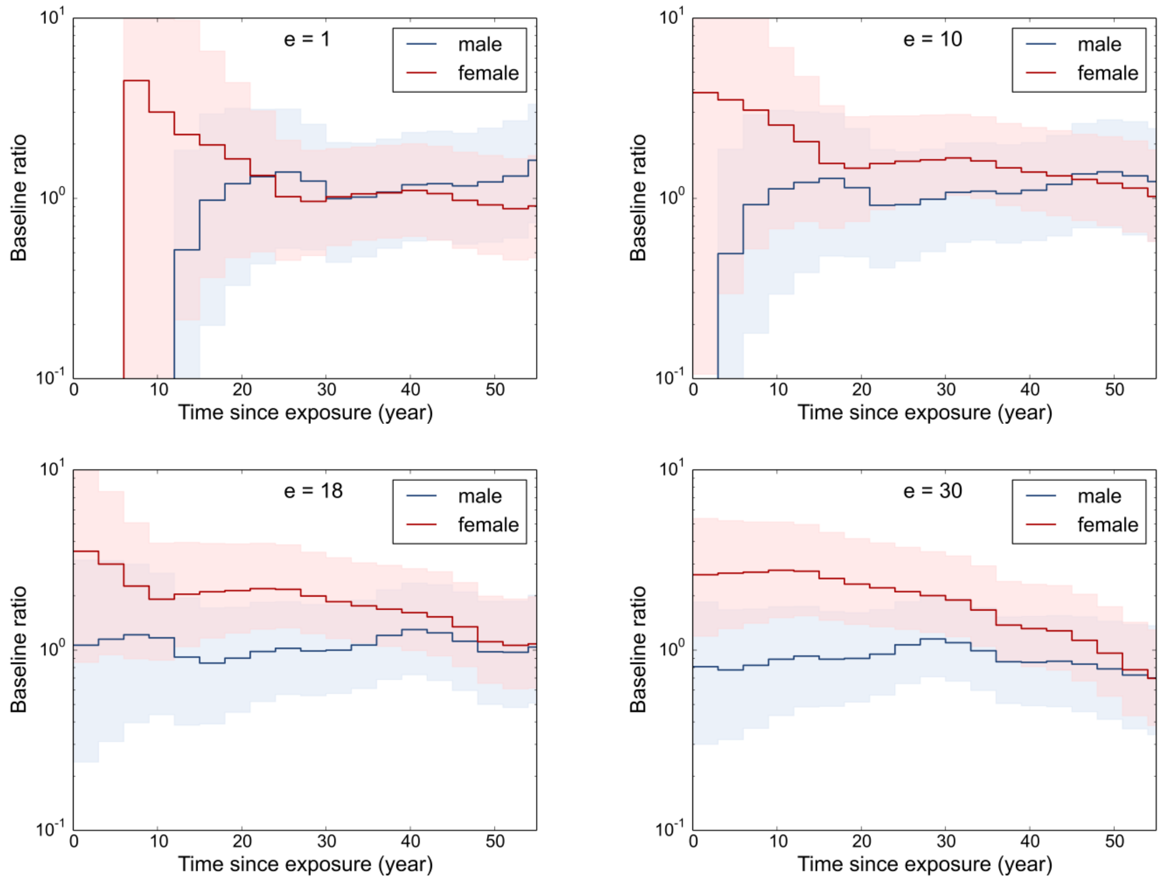

Fig. S2. Ratio of incidence rates for Japan in 2007 and baseline model for LSS members not participating in the AHS.

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* Authors thank Drs. Hoffman and Apostoaei (ORRISK, Oak Ridge, TN, USA) for the parameterization of the onset function.

3.3 Probability distributions of excess absolute risk

Probability distributions of risk estimates have been obtained by stochastic simulations. Parameter values have been sampled from:

- multivariable normal distribution using best estimates and covariances given in Table S3;
- uniform distribution of the transfer factor *f* ;
- uncertainty distributions of the modifying factors F_{scr} and F_{DREF} (see sub-section 3.1);
- Poisson distribution of the number of observed baseline cases in Japan in the corresponding 5-year age groups.

The risk models are then used to calculate risk estimates for given age at exposure *e*, attained age *a*, and a thyroid dose of 100 mGy. The procedure was repeated 10,000 times to obtain distributions of the risk estimates.

4. Cancer-free survival function for Japan in 2007

The survival function, $S(a)$, is related to the mortality rate $\mu(t)$ by:

$$S(a) = \exp\left(-\int_0^a \mu(t)\,dt\right).$$

Cancer-free survival function accounts only for those persons who had no prior cancer. This function is computed from all-cause mortality rate $\mu(t)$ modified by all-cancer incidence rate $\lambda_C(a)$ and all-cancer mortality rate $\mu_C(a)$ at age *a*, thus the cancer-free survival function is computed as follows:

$$S^*(a) = \exp\left(-\int_0^a \left(\mu(t) + \lambda_C(t) - \mu_C(t)\right)dt\right).$$

The survival function has been computed using all-cause mortality rate from Abridged Life Tables for Japan 2007 (Ministry of Health, Labour and Welfare of Japan 2013) and all-cancer incidence rate and all-cancer mortality rate from the data of Japan National Cancer Center (2012).

5. Parameters of risk function from Jacob et al (2006a)

Cancer baseline rate and EAR are characterized as functions of attained age *a*, age at exposure *e*, and thyroid dose *d*:

$$\lambda_0 = \exp\left(\beta_0 + \beta_c F_c + \beta_s F_s + \beta_a \ln\frac{a}{20} + \beta_e\left(e-10\right)\right),$$

$$EAR = \left(\alpha_{d_1} d + \alpha_{d_2} d^2\right)\exp\left(\alpha_c F_c + \alpha_s F_s + \alpha_a \ln\frac{a}{20} + \alpha_e\left(e-10\right)\right)$$

where country- and gender-dependent factors are:

$$F_c = \begin{cases} -0.5, & \text{Ukraine} \\ +0.5, & \text{Belarus} \end{cases} \quad \text{and} \quad F_s = \begin{cases} -0.5, & \text{male} \\ +0.5, & \text{female} \end{cases}$$

and values of model parameters and their covariance matrix are given in Table S4.

Table S4: Parameters of the EAR model for thyroid cancer according to Jacob et al (2006a): Maximum likelihood estimates (MLEs), standard deviations and covariance matrix (own calculation).

Parameter	MLE	Std.dev.	Covariance matrix									
			β_0	β_c	β_s	β_a	β_e	α_{d_1}	α_{d_2}	α_c	α_s	α_a
β_0	-1.12E+01	1.47E-01	2.15E-02	5.65E-03	-1.86E-02	-2.33E-02	-5.74E-04	-2.00E-06	1.09E-07	3.34E-03	-9.66E-04	-3.33E-03
β_c	-1.85E-01	1.36E-01	5.65E-03	1.84E-02	-9.99E-04	-2.44E-03	-2.77E-05	-5.07E-07	2.77E-08	-3.18E-03	-1.01E-03	-8.52E-04
β_s	1.78E+00	2.00E-01	-1.86E-02	-9.99E-04	4.00E-02	5.00E-03	8.28E-05	1.39E-06	-7.60E-08	-2.32E-03	-4.33E-03	1.51E-03
β_a	3.76E+00	4.73E-01	-2.33E-02	-2.44E-03	5.00E-03	2.24E-01	-8.14E-03	2.11E-06	-1.15E-07	-4.98E-03	3.83E-03	-1.41E-02
β_e	-5.79E-02	2.47E-02	-5.74E-04	-2.77E-05	8.28E-05	-8.14E-03	6.08E-04	3.20E-08	-1.75E-09	-2.13E-04	1.70E-04	1.19E-03
α_{d_1}	2.66E-04	2.40E-05	-2.00E-06	-5.07E-07	1.39E-06	2.11E-06	3.20E-08	5.76E-10	-3.14E-11	-8.34E-07	1.79E-07	6.41E-07
α_{d_2}	-1.45E-05	1.31E-06	1.09E-07	2.77E-08	-7.60E-08	-1.15E-07	-1.75E-09	-3.14E-11	1.72E-12	4.55E-08	-9.76E-09	-3.50E-08
α_c	3.08E-01	1.00E-01	3.34E-03	-3.18E-03	-2.32E-03	-4.98E-03	-2.13E-04	-8.34E-07	4.55E-08	1.01E-02	-5.02E-04	-1.06E-03
α_s	4.37E-01	9.21E-02	-9.66E-04	-1.01E-03	-4.33E-03	3.83E-03	1.70E-04	1.79E-07	-9.76E-09	-5.02E-04	8.49E-03	8.34E-04
α_a	1.05E+00	1.75E-01	-3.33E-03	-8.52E-04	1.51E-03	-1.41E-02	1.19E-03	6.41E-07	-3.50E-08	-1.06E-03	8.34E-04	3.05E-02
α_e	-1.06E-01	1.56E-02	-4.42E-04	-2.49E-04	4.56E-04	1.53E-03	-9.57E-05	1.94E-07	-1.06E-08	-5.42E-05	4.42E-05	-1.70E-03