Ultrasonography survey and thyroid cancer in the Fukushima Prefecture

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Abstract

Thyroid cancer is one of the major health concerns after the accident in the Fukushima Dai-ichi nuclear power station (NPS). Ultrasonography surveys are being performed for persons residing in the Fukushima Prefecture at the time of the accident with an age of up to 18 years. We assess the expected thyroid cancer prevalence in the Fukushima Prefecture based on an ultrasonography survey of Ukrainians, who were exposed at age of up to 18 years to ^{131}I released during the Chernobyl NPS accident, and on differences in equipment and study protocol in the two surveys. Radiation risk of thyroid cancer incidence among survivors of the atomic bombings of Hiroshima and Nagasaki in the Life Span Study and preliminary estimates of thyroid dose due to the Fukushima accident were further inputs to predict baseline and radiation-related thyroid cancer risks. We estimate a prevalence of thyroid cancer of 0.027% (95% CI: 0.010%; 0.050%) for the first screening campaign in the Fukushima Prefecture. Compared to the incidence rate in Japan in 2007, the ultrasonography survey is predicted to increase baseline thyroid cancer incidence by a factor of 7.4 (95% CI: 0.95; 17.3). Under the condition of continued screening, thyroid cancer during the first fifty years after the accident is predicted to be detected for about 2% of the screened population. The prediction of radiation-related thyroid cancer in the most exposed fraction (a few ten thousand persons) of the screened population of the Fukushima Prefecture has a large uncertainty with best estimates of the average risk of 0.1% to 0.3%, depending on average dose.

Keywords:
Fukushima, Radiation, Thyroid cancer, Ultrasonography

Introduction

Large amounts of radionuclides were released from the Fukushima Dai-ichi nuclear power station (NPS) in the aftermath of the 2011 Great East Japan earthquake, tsunami and reactor accident. Thanks to prompt actions of Japanese authorities, radiation exposures of the

population were generally low. However, average thyroid doses of young children in some settlements were reported to be of the order or even exceeding 100 mSv (WHO 2013). These dose estimates are based on environmental and food measurements (WHO 2012). However, measurements of incorporated ^{131}I indicate that thyroid doses in the population were lower than the WHO estimate (Kamada et al. 2012; Tokonami et al. 2012; Kim et al. 2013; Matsuda et al. 2013).

There is concern about thyroid cancer induced by the accident at the Fukushima Dai-ichi NPS. The concern is triggered by the massive increase of thyroid cancer among those, who were highly exposed during childhood due to the Chernobyl accident (Kazakov et al. 1992; UNSCEAR 2011). In order to monitor thyroid cancer, periodic thyroid ultrasonography surveys have been introduced for all young inhabitants of the Fukushima Prefecture up to age of 18 years at the time of the accident (Fukushima Medical University 2013a).

Thyroid cancer is a rare disease, although thyroid cancer incidence has increased worldwide during the previous decades. The increase might be related to improved diagnostics. No evidence for an influence of iodine supplementation could be demonstrated (Bloomberg et al. 2012). Ultrasonography has a large potential of detecting so-called occult carcinoma that do not become clinically relevant during lifetime (Welch and Black 2010; Moynihan et al. 2012). The existence of such carcinoma has been demonstrated by autopsies with prevalence values ranging from 1.5% in Greece (Delides et al. 1987) to 36% in Finland (Harach et al. 1985). Different definitions of prevalence are given in the literature. We use here '*proportion of a population that has a disease at a specific point in* time' (Rothmann and Greenland 1998).

Autopsies of 2372 of otherwise cancer-free survivors of the atomic bombings of Hiroshima and Nagasaki revealed 106 papillary thyroid microcarcinoma, mostly of the sclerosing variant (Hayashi et al. 2010). This corresponds to a prevalence of 4.5%. These results apply mainly to adults. No conclusive autopsy data on occult thyroid cancer in

children are available. The number of occult carcinomas detected by ultrasonography depends on the equipment and study protocol used. Several other factors like the age-gender structure of the cohort and the country-specific or even group-specific thyroid cancer frequency influence prevalence (first screening) and incidence rate (subsequent screenings) in ultrasonography surveys.

As of 31 July 2013, ultrasonography has been performed for 41 296 children, adolescents and young adults living on 11 Mar 2011 in thirteen municipalities of the Fukushima Prefecture that were targeted for screening before April 2012 (Fukushima Medical University 2013a). Secondary examination was required for 214 persons with thyroid nodules larger than 5 mm or cysts larger than 20 mm. These examinations were completed for 165 persons allowing a first estimation of thyroid cancer prevalence in the young population. Cytology of fine needle aspiration (FNA) biopsies revealed 14 cases of suspected malignancy. Surgery has been performed for 10 of them; 9 were identified as papillary carcinoma, one as a benign tumour. The 13 cases of confirmed (9) or still suspected (4) thyroid cancer correspond to a prevalence of 13/41 296 = 0.031%. The prevalence is expected to increase because of possible thyroid cancer cases among the 49 persons, for whom secondary examination was required but not completed at 31 July 2013.

In a second group of municipalities that were targeted for screening between April 2012 and March 2013, 135 586 people were screened and 30 cases of suspected thyroid cancer were detected by cytology of FNA biopsies. Only 45% of required secondary examinations had not been finished at 31 July 2013, thus the prevalence in these municipalities is expected to increase beyond the present values of 0.022%.

Ultrasonography has been performed for the UkrAm cohort consisting of Ukrainians, who were up to age of 18 years on 26 Apr 1986, the date of the Chernobyl accident (Tronko et al. 2006). Concerning sex-age distribution of the cohort at the time of the accident and baseline incidence rate (National Cancer Register of Ukraine 2013), the cohort is comparable

to the study group in the Fukushima Prefecture. However, the first screening was performed from 1998 to 2000, not until twelve years after exposure. The study protocol selected nodules smaller than 10 mm for secondary examination only, if further criteria were fulfilled. Thus this protocol leads under otherwise same conditions to a smaller prevalence than the study protocol in the Fukushima Prefecture. Nevertheless, prevalence of confirmed thyroid cancer cases not related to the exposure from the Chernobyl accident was higher than what is expected for the Fukushima Prefecture, because cohort members at the time of the first screening were older, in average by about 12 years.

Repeated ultrasonography has also been performed for the UkrAm cohort (Brenner et al. 2011). Comparison with the baseline thyroid cancer incidence rate in Ukraine allows an assessment of the impact of the screening on reported incidence rates. The effect of increased surveillance of the thyroid was also analysed for Belarusian and Ukrainian population groups (Jacob et al. 2006a; Likhtarov et al. 2006). Based on these three studies, we estimate in the present paper the baseline (not related to the radiation exposure due to the accident at the Fukushima Dai-ichi NPS) thyroid cancer incidence rate in the Fukushima Prefecture under the conditions of on-going surveys.

Long-term thyroid cancer risk due to exposure to external radiation has been analysed in a number of studies (Ron et al. 1995; Furukawa et al. 2013; Veiga et al. 2012). However, higher thyroid doses among inhabitants of the Fukushima Prefecture were mainly caused by incorporation of radioiodine (WHO 2012). For young age at exposure and the first twenty years after the Chernobyl accident, an increased risk has been demonstrated (Tronko et al. 2006; Brenner et al. 2011; Cardis et al. 2012; Kopecky et al. 2006; Jacob et al. 2006b). However, the risk information is less complete than for external exposures. We derive in this study radiation risks from data for the atomic bomb survivors, and check the consistency with results obtained in studies of people exposed to ^{131}I from the Chernobyl nuclear power plant. Excess rates in the Fukushima Prefecture are predicted by applying to the LSS risk function a

screening factor that is based on experiences in the UkrAm cohort and differences in the study protocol of the ultrasonography surveys.

Materials and Methods

Study groups, screening intervals and thyroid dose

The Fukushima Health Management Survey includes ultrasonography of the thyroid of all residents of the Fukushima Prefecture aged up to 18 years at 11 March 2011 (Fukushima Medical University 2013a). Based on post-Chernobyl studies we calculated thyroid cancer prevalence for two campaigns of the first screening, October 2011 to March 2012, and April 2012 to March 2013 (see Supporting Information for sex-age distributions). Prevalence is also calculated for the sex-age distribution in the ultrasonography survey of children and adolescents in the three non-contaminated prefectures of Aomori, Yamanashi und Nagasaki (Taniguchi et al. 2013).

According to WHO (2013), we assume in one scenario an average thyroid dose of 50 mSv for the most exposed fraction (a few ten thousand persons) of the surveyed population in the Fukushima Prefecture. Since measurements of the iodine content indicate lower doses (Kamada et al. 2012; Kim et al. 2013; Matsuda et al. 2013; Tokonami et al. 2012), we assume in a second scenario an average thyroid dose of 20 mSv. Individual thyroid doses could have been considerably larger or smaller. For a linear dose response, however, excess incidence rate is determined by the average dose and not by other parameters of the dose distribution.

Thyroid cancer prevalence detected by ultrasonography

The UkrAm cohort consists of 13,127 Ukrainians, who were up to age of 18 years on 26 April 1986, the date of the Chernobyl accident (Tronko et al. 2006). During the time of the first screening in the UkrAm cohort, the age-standardized thyroid cancer incidence rate in Ukraine was 1.2 and 4.9 cases per 10^5 person-years for males and females, respectively (National Cancer Registry of Ukraine 2013). These rates are comparable to those in Japan in 2007 (2.2 and 7.9 cases per 10^5 person-years). The first round of ultrasonography in the

UkrAm cohort was performed 12 to 14 years after the accident. Forty five pathologically confirmed thyroid cancer cases were detected. Tronko et al. estimated that 11.2 (95%CI: 3.2; 22.5) of these cases would have been detected in the absence of the exposure due to the Chernobyl accident. This corresponds to a prevalence, P_{UA}, of about 0.09 (95%CI: 0.02; 0.17) %.

We estimated the prevalence for the population in Fukushima Prefecture, P_{Fp}, by taking into account differences in study protocols and sex-age structures of the screened populations:

$$P_{Fp} = f_{sp}\, P_{UA}\, \lambda_{Japan,Fp} / \lambda_{Ukraine,U1}, \quad (1)$$

where $\lambda_{Japan,Fp}$ and $\lambda_{Ukraine,U1}$ are the average incidence rates in a hypothetical group of Japanese (National Cancer Center 2012) with the sex-age structure of the surveyed Fukushima population and of a hypothetical group of Ukrainians (Fedorenko et al. 2002) with the sex-age structure of the UkrAm cohort during the first survey, respectively. The factor f_{sp} accounts for differences in the study protocols in the UkrAm study and the Fukushima survey. The ratio of the numbers of all tumors larger than 5 mm (study protocol in the Fukushima Prefecture) and larger than 10 mm (UkrAm cohort) under otherwise the same conditions is the maximum of f_{sp} , because also some nodules in the size range from 5 to 10 mm were selected in the UkrAm for further investigation and turned out to be cancer (O'Kane et al. 2010).

No direct information is available to determine f_{sp} for tumours. As a surrogate, we use the corresponding ratio for nodules. This choice is supported by the thyroid screening study in Hong Kong (Yuen et al. 2011), in which the ratio for nodules larger than 5 mm and larger than 10 mm is 2.4 (398/169). For tumours the ratio is 2.2 (11/5), nearly equal to that for nodules. The screenings from October 2011 to March 2013 in the Fukushima Prefecture detected 1125 nodules larger than 5 mm and 354 nodules larger than 10 mm (Fukushima Medical University 2013b). Correspondingly, the upper boundary of f_{sp} is estimated to 1125/354=3.2. The lower boundary is assumed to correspond to no additional cases according

to differences in the study protocol, 1.0. The factor f_{sp} is assumed to have a symmetrical triangular distribution between these two boundaries.

Impact of ultrasonography and thyroid surveillance on thyroid cancer incidence rate

The impact of the second to fourth screenings on the incidence rate in the UkrAm cohort can be calculated as the ratio of the baseline incidence rate in the cohort (Brenner et al. 2011) and the incidence rate in Ukraine in the period 2001 to 2007 for a hypothetical population with the same sex-age distribution (National Cancer Registry of Ukraine 2013). The baseline incidence rate in the cohort can be estimated by the ratio of the excess absolute rate per unit dose, EAR_{UA}, and the excess relative risk per unit dose, ERR_{UA}. Brenner et al. (2011) estimated the EAR_{UA} to 22.1 (95% CI: 0.04; 5.78) cases per 10^5 person-years, and the ERR_{UA} to 1.91 (95% CI: 0.43; 6.34). These numbers indicate a best estimate of the baseline incidence rate in the UkrAm cohort during the second to fourth screening of 11.6 cases per 10^5 person-years. The incidence rate in Ukraine with the same sex-age structure as in the UkrAm cohort during the second to fourth screening, $\lambda_{Ukraine,U2\text{-}4}$, is 3.3 cases per 10^5 person-years (National Cancer Center of Ukraine 2013). The screening factor in the UkrAm, f_{UA}, is calculated by

$$f_{UA} = EAR_{UA} / (ERR_{UA} * \lambda_{Ukraine,U2\text{-}4}). \quad (2)$$

EAR_{UA} and ERR_{UA} are correlated, and the coefficient of determination (square of correlation coefficient) has been assumed to be uniformly distributed from 0.7 to 1.0.

Thus the distribution of the screening factor in the Fukushima Prefecture, F_{scr}, is a product of the screening factor in the UkrAm cohort, f_{UA}, and the factor taking into account differences in the study protocol, f_{sp}.

Thyroid cancer risk in LSS

Recently, thyroid cancer risk in the cohort of survivors of the atomic bombings of Hiroshima and Nagasaki has been analysed by Furukawa et al. (2013) in the frame of the so-called Life Span Study, (LSS). Their analysis excluded microcarcinoma (tumours smaller

than 10 mm). However, tumours smaller than 10 mm are expected to contribute significantly to thyroid cancer prevalence and incidence rate in the Fukushima Prefecture under the conditions of ultrasonography surveys. An earlier analysis of thyroid cancer in the LSS by Preston et al. (2007) included microcarcinoma, but did not give separate risk results for LSS members participating or not participating in screening under the Adult Health Study (AHS). AHS participants are medically examined every second year. In order to take into account both effects of carcinoma of size smaller than 10 mm and of increased thyroid surveillance in the AHS, we re-analysed the LSS data. In an excess relative risk model, standard dependences on age-at-exposure, *e*, and attained age, *a*, were applied, and for LSS members participating in the AHS baseline thyroid cancer incidence rate was modified by a time-dependent screening factor $F_{AHS}(a,e)$, having different values before and after 1970:

$$F_{AHS}(a,e) = \begin{cases} \exp\left(\beta_{AHS,1}\right), & \text{if } a-e \geq 25 \text{ (member of AHS in 1970 and later)} \\ \exp\left(\beta_{AHS,1}+\beta_{AHS,2}\right), & \text{otherwise (member of AHS before 1970)} \end{cases} \quad (3)$$

These two time periods were chosen to differentiate the early period with many autopsies from the later period with fewer autopsies (Preston et al. 2007). More details on the risk models and their parameters are given in Electronic Supplementary Material.

Excess absolute rate in the Fukushima Prefecture

The standard approach of transferring risk estimates for thyroid cancer in the LSS to other populations is assuming a multiplicative interaction of radiation and other risk factors, i.e., the excess relative risk per unit dose (*ERR*) is assumed to be the same in the both populations (US Environmental Protection Agency 2011; National Research Council 2006). Thus, the excess absolute rate per unit dose in the population of interest, *EAR*, is obtained by multiplication of *ERR* with the country-specific incidence rate. For the present study, we apply three additional factors: F_{scr} (see above), $F_L(a\text{-}e)$ that takes into account that radiation-induced cases are not expected before three years after the exposure (Heidenreich et al. 1999),

and F_{DREF} for the additional uncertainty of the risk function at low dose rate (Jacob et al. 2009). In summary, we calculate in the model of multiplicative interaction

$$EAR(s,e,a) = F_{scr}\, F_L(a\text{-}e)\, F_{DREF}\, ERR_{LSS}(s,e,a)\, \lambda_{Japan}(s,a), \quad (4)$$

where $ERR_{LSS}(e,a)$ is the excess relative risk per unit dose for LSS cohort members not participating in the AHS.

Baseline thyroid cancer incidence rate in Japan in 2007 is lower than 10^{-6} per year for males of age younger than 15 years, which is reported as zero (National Cancer Center 2012). Based on these data and according to eq. (4), no cases would be expected during the first fifteen years among males exposed as infants. In order to avoid this artefact, we assume an equal probability of any risk between results obtained with models of additive and multiplicative interactions (mixed transfer):

$$EAR(s,e,a) = F_{scr}\, F_L(a-e)\, F_{DREF}\ \ ERR_{LSS}(s,e,a)\, [f\, \lambda_{Japan}(s,a) + (1-f)\, \lambda_{LSS}(s,e,a)] \quad (5)$$

where f is uniformly distributed between 0 and 1. Similarly, WHO (2013) used weighted-average of multiplicative and additive risk transfer, assuming equal weights.

Attributable risk

We calculate the risk rate attributable to radiation exposure, *ARR*, by multiplication of $EAR(s,e,a)$ with thyroid dose, D, and taking into account cancer-free survival, $S(s,a)$, in Japan in 2007 (National Cancer Center 2012; Ministry of Health, Labour and Welfare of Japan 2013; see also Electronic Supplementary Material):

$$ARR(s,e,a,D) = EAR(s,e,a)\, D\, S(s,a)/S(s,e) \quad (6)$$

Attributable risks are obtained by integration over pre-defined periods after exposure:

$$AR(s,e,a,D) = \int_e^a ARR(s,e,t,D)\, dt \quad (7)$$

Lifetime attributable risk refers to an integration period from exposure over the whole lifetime.

Similarly, baseline risk is modelled as follows

$$BR(s,e,a) = \int_e^a \lambda_{Japan}(s,t)\,S(s,t)\,dt \,/\, S(s,e). \quad (8)$$

Risks for the study group are calculated by averaging over the sex-age distribution at the time of exposure.

Results

Thyroid cancer prevalence

Our estimate of prevalence of pathologically-confirmed thyroid cancer cases among the screened population of the municipalities in the Fukushima Prefecture targeted for the survey for the period Oct 2011 to Mar 2012 is 0.027 (95%CI: 0.010; 0.050)% (Table 1). The large uncertainty of our estimation is mainly caused by the uncertainties of the prevalence of baseline cases in the UkrAm cohort, P_{UA} and of the impact of differences of the study protocol, expressed by the factor, f_{sp}.

Prevalence for the municipalities of the Fukushima Prefecture targeted for later periods is predicted to be higher, because the screening has been performed later, thus mean age in the cohort and, correspondingly, average baseline rate are higher (see Table 1).

Screening factors due to ultrasonography surveys

Thyroid cancer incidence in the UkrAm cohort during the second to fourth screening is estimated to be higher than the national incidence rate in Ukraine by a factor, f_{UA}, of 3.6, with a 95% confidence range from 0.5 to 7.9 (Fig. 1).

Thyroid cancer incidence in the Fukushima Prefecture under the condition of continued ultrasonography surveys is estimated to be increased compared to the incidence rate in 2007 by a factor of 7.4, with a 95% confidence range from 0.95 to 17.3. Because of differences in the study protocol, the screening factor is the Fukushima Prefecture is larger and has a wider confidence interval than the screening factor in the UkrAm cohort.

Thyroid cancer incidence risk in the LSS

Compared to present day ultrasonography of the thyroid, the impact of screening and autopsies on thyroid cancer incidence among AHS participants was relatively small. For the period before 1970 with a relatively high rate of autopsies, we find a screening factor of 1.72 (95%CI: 1.17; 2.55), and for the period afterwards of 1.23 (95%CI: 0.96; 1.59).

ERR in the LSS decreases with age at exposure and age attained (see Fig. 2). EAR decreases with age at exposure as well. However, it increases with time since exposure.

Attributable risk rate

In the mixed transfer model, the risk rate attributable to radiation exposure increases for young ages at exposure after the minimal latency period of three years for a few years steeply with time since exposure (Fig. 3). It continues to increase with a smaller slope for the next fifty years. For an exposure of females at age of 1 year with a thyroid dose of 100 mSv, the attributable risk rate is predicted to increase from about 0.2 cases per 10^4 person-years at an attained age of 10 years to 6 cases per 10^4 person-years at age 50.

For exposure at older age, the increase is less steep. The attributable risk rate reaches a maximum at attained age of about 60 years, and decreases subsequently due to the decrease of the survival function.

In general, best estimates of the attributable risk rate for females are larger than for males. The ratio is maximal for attained age of about 40 years with a value of 5.5 for age at exposure of 1 year. The difference is, however, not significant due to the large uncertainty of the estimates. Main sources of uncertainty are the risk function derived from the LSS, the screening factor, and extrapolation of the risk function to low dose rates (in the order of decreasing importance).

With the exception of young attained age, the multiplicative transfer, eq. (4), gives results very similar to the mixed transfer. For boys below attained age of 15 years and girls below age of 10, the multiplicative transfer results in no excess cases, whereas the mixed transfer gives non-zero results.

Attributable risk

The dominant part of the attributable risk accumulates over several decades (Table 2). The contribution of the first ten years to the risk over fifty years decreases with increasing age at exposure. The long latency is especially expressed for females: for age at exposure of 1 year, less than 1% of the attributable risk cumulated during fifty years after exposure (for 100 mSv: 1.4%) is contributed by the first ten years (0.013%).

For the same thyroid dose, the attributable risk accumulating over several decades after exposure decreases with increasing age at exposure. However, the effect is relatively modest (about a factor of two for ages at exposure of 1 and 18 years).

Under the condition of continued screening, baseline thyroid cancer risk during the first fifty years after exposure in the screened population of the Fukushima Prefecture is predicted to 2.2 (95% CI: 0.27; 5.3)% (Table 3). For an average thyroid dose of 20 mSv, the risk related to the radiation exposure amounts to 0.13 (95% CI: 0.005; 0.40)%. Less than 5% of the radiation-related risk accumulates during the first ten years after the exposure.

Discussion

Thyroid cancer prevalence

The first ultrasonography survey in the Fukushima Prefecture is intended to be finished at 31 Mar 2014, about three years after the accident at Fukushima Dai-ichi NPS. After the Chernobyl accident, an excess of thyroid cancer cases was not observed before three years after exposure (Heidenreich et al. 1999). Thus, the prevalent cases in the Fukushima Prefecture are not assumed to be related to radiation exposure.

As of July 31, 2013, surgery of the thyroid has been performed for 10 persons out of 41296, who lived at the time of the accident in 13 municipalities that were targeted for ultrasonography survey before April 2012 (Fukushima Medical University 2013a). Nine of the cases were papillary carcinoma, one turned out to be a benign nodule. This corresponds to

a prevalence of confirmed cases of 9/41 296 = 0.022%. This number is a lower boundary for the prevalence because

- four persons having suspected malignancy according cytology of FNA biopsies had not been operated before July 31, 2013;
- only 165 out of 214, for whom secondary examination was required, have concluded or even started such an examination.

Thus, the results obtained so far by the survey are in agreement with our calculations (Table 1).

Screening factors in post-Chernobyl studies

In a population-based study of Likhtarov et al. (2006), population groups with ultrasonography frequency of more than 1.8% and less than 0.7% have been compared. They estimated thyroid cancer incidence rate in the former group to be larger by a factor of 3.3 than in the latter.

For Ukrainian oblasts with high thyroid exposures due to the Chernobyl accident and for most oblasts in Belarus, baseline thyroid cancer incidence in 1999 compared to 1988 was assessed to be higher by a factor of about three (Jacob et al. 2006a). This effect was attributed to an increased surveillance of the thyroid.

The present result of the screening factor in the UkrAm cohort of 3.6 (95%CI: 0.5; 7.9) is consistent with the assessment of the two population based studies mentioned above.

Thyroid cancer risk in LSS vs. post-Chernobyl studies

The excess relative risk for thyroid cancer after exposure during childhood with a thyroid dose of 1 Sv in the LSS compares generally well to study results of populations exposed to ^{131}I after the Chernobyl accident (Fig. 4). For times after exposure shorter than 13 years, i.e. before the collection of incidence data in the LSS started, it cannot be excluded that excess relative risks after exposure at young age are larger than the extrapolation of the LSS function. This would have, however, negligible implications for our results on attributable

risk, because the baseline risk in Japan in 2007 for age below 20 years is very small, and because there is a good agreement of the excess absolute rate results (see below).

The excess absolute rate depends on the screening conditions. It is relatively small for the LSS members not participating in the AHS (Fig. 4). Applying the full screening factor, F_{scr}, leads to an EAR estimate that tends to be higher than what was observed in the UkrAm cohort. This is plausible, because the study protocol in the Fukushima Prefecture is expected to lead to a higher screening effect than in the UkrAm cohort. Indeed, if the screening factor for the UkrAm cohort f_{UA} is applied to EAR_{LSS}, then good agreement with the excess absolute rate per unit dose in the UkrAm cohort is obtained.

Overall, these comparisons do not give any evidence against the application of the LSS risk function and the screening factor F_{scr} to populations screened in the Fukushima Prefecture.

Attributable risk rate

In our approach with a mixed transfer of excess risk estimates from the LSS to the population in the Fukushima Prefecture, the attributable risk rate increases steeply after a minimal latency period of three years. According to the multiplicative transfer, however, excess cases do not appear before attained age of 15 for males and age attained 10 for females. The latter approach is not in accordance with experiences after the Chernobyl accident, where many excess cases were observed before attained age of 10 years (UNSCEAR 2011).

Attributable risk

According to our results in Table 2 for an age of exposure of 1 year, about 15% of the attributable risk accumulated over twenty years is contributed by the first ten years. For an age of exposure of 10 years, we obtain a contribution of 30%. These predictions compare well to thyroid cancer incidence after the Chernobyl accident. In Belarus, where most of the observed thyroid cancer incidence was attributed to radiation exposure (Jacet et al. 2006a),

29% of thyroid cancer cases during the first twenty years occurred during the first ten years for the age-at-exposure group of 0-4 years, and 35% for the age-at-exposure group of 5–9 years (UNSCEAR 2011).

Another check of consistency with post-Chernobyl experiences relates to age-at-exposure dependence. According to our prediction, the attributable risk accumulated over the first twenty years is about the same for ages at exposure of 1 and 10 years, if the thyroid dose is the same. In Belarus, the number of cases was higher for the age-at-exposure group of 0-4 years than for the age-at-exposure group of 5–9 years by a factor of 1.7. Thyroid doses differed by a similar factor (Jacob et al. 2006a).

Finally, we predict the excess rate during the first twenty years after exposure among females to be higher than among males by a factor of 2–3. Again, in Belarus the risk was higher by a factor of 2.6 (crude rate among females of 6.7 versus 2.6 per 10^4 person-years for males, according to UNSCEAR (2011)).

Whereas our predictions for the first twenty years after exposure have some support from studies of thyroid cancer after the Chernobyl accident, our longer-time predictions are more uncertain and may overestimate the risk. We have neglected a so-called *harvesting effect* that might appear after twenty years after exposure. Early detection may lead to lower numbers of detected cases at later campaigns of a survey. However, we are not aware of studies that give evidence of a harvesting effect of ultrasonography for thyroid cancer incidence.

For a period of 50 years after exposure at ages of up to 18 years, we predict that an average thyroid dose of 50 mSv would has a relative contribution of about 15%to the total thyroid cancer risk. This is in accordance with the results of WHO (2013), because of the close similarity of the approaches concerning relative risks. Concerning the total thyroid cancer risk, however, our results are higher by a factor of about seven, because WHO did not consider in its calculations the impact of the ultrasonography survey.

Conclusion

We expect that the ultrasonography survey of residents of Fukushima Prefecture will increase thyroid cancer incidence compared to thyroid cancer incidence in 2007 in Japan drastically. The estimated increase has a large uncertainty with a best estimate of a factor of about seven. Based on the assumption of an average thyroid dose of 20 mSv of the most exposed in the surveyed population, we estimated that in the early period about 10%, and in longer times about 5% of the reported incidence will be attributable to radiation exposure. Thus, the fraction of thyroid cancer cases attributable to radiation exposure will be small, although there are regional differences due to varying dose. Our assessment has large uncertainties caused by uncertainties in the thyroid cancer risk function for the LSS, the impact of the ultrasonography survey, and the transfer of the risk function to low-dose exposures to ^{131}I. Independent of these uncertainties, the order of magnitude of the predicted thyroid cancer prevalence and incidence rate may help to be prepared for a relatively large number of thyroid cancer cases that are to be expected. It should be taken into account that most of the cases would not have become clinically relevant without the ultrasonography survey.

Acknowledgement

The study has been partially supported by EC-funded project EpiRadBio under contract 269553 and by German Federal Office for Radiation Protection (BfS) under contracts 3607S04570 and 3612S70030.

This report makes use of data obtained from the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. RERF is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter through the National Academy of Sciences. The data include

information obtained from the Hiroshima City, Hiroshima Prefecture, Nagasaki City, and Nagasaki Prefecture Tumor Registries and the Hiroshima and Nagasaki Tissue Registries. The conclusions in this report are those of the authors and do not necessarily reflect the scientific judgment of RERF or its funding agencies.

Authors thank Dr. Kyoji Furukawa from RERF (Hiroshima, Japan) for many useful discussions and for sharing the most recent information.

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Table 1 Expected prevalence of confirmed thyroid cancer among screened population groups targeted for Fukushima Health Management Survey before April 2012, for the period from April 2012 to March 2013, and in the non-contaminated prefectures of Aomori, Yamanashi and Nagasaki (Taniguchi et al. 2013).

Study group in Prefecture(s)	Period of screening	Weighted baseline rate in the group (PY^{-1})	Estimated prevalence (%) [a]
Fukushima (2011/2012)	Oct 2011 – Mar 2012	0.267×10^{-5}	0.027 (0.010; 0.050)
Fukushima (2012/2013)	Apr 2012 – Mar 2013	0.332×10^{-5}	0.034 (0.013; 0.061)
Aomori, Yamanashi and Nagasaki	Nov 2012 – Jan 2013	0.317×10^{-5}	0.032 (0.012; 0.057)

[a] arithmetic mean and 95% confidence interval

[b] no reported results of completed FNA

Table 2 Baseline and radiation-attributable thyroid cancer risk (mean value and 95% confidence interval) after an exposure with a hypothetical thyroid dose of 100 mSv for different time periods after exposure

Age at exposure (years)	Sex	Thyroid cancer	Thyroid cancer risk (%) for different periods after exposure with a thyroid dose of 100 mSv		
			10 years	20 years	50 years
1	male	baseline	0.0 (0.0; 0.0)	0.026 (0.003; 0.065)	0.52 (0.06; 1.2)
		attributable	0.014 ($<10^{-4}$; 0.090)	0.054 (0.002; 0.26)	0.30 (0.015; 1.2)
	female	baseline	0.0029 ($2 \cdot 10^{-4}$; 0.0088)	0.089 (0.012; 0.22)	2.3 (0.31; 5.5)
		attributable	0.013 ($3 \cdot 10^{-4}$; 0.069)	0.12 (0.007; 0.51)	1.4 (0.11; 4.6)
10	male	baseline	0.021 (0.003; 0.053)	0.11 (0.015; 0.27)	0.91 (0.12; 2.2)
		attributable	0.019 ($6 \cdot 10^{-4}$; 0.088)	0.059 (0.003; 0.24)	0.24 (0.013; 0.87)
	female	baseline	0.071 (0.008; 0.18)	0.33 (0.04; 0.80)	3.6 (0.44; 8.7)
		attributable	0.042 (0.002; 0.19)	0.16 (0.008; 0.59)	0.94 (0.058; 3.1)
18	male	baseline	0.080 (0.010; 0.20)	0.20 (0.026; 0.50)	1.2 (0.16; 3.0)
		attributable	0.018 ($7 \cdot 10^{-4}$; 0.077)	0.047 (0.002; 0.19)	0.18 (0.009; 0.64)
	female	baseline	0.22 (0.026; 0.52)	0.79 (0.091; 1.8)	4.7 (0.54; 11)
		attributable	0.044 (0.002; 0.17)	0.15 (0.007; 0.55)	0.63 (0.03; 2.0)

Table 3 Predicted thyroid cancer risk (mean and 95% confidence interval) in the Fukushima Prefecture: baseline and attributable to radiation exposure for thyroid doses of 50 mSv and 20 mSv assumed for the most exposed population groups.

Average thyroid dose (mSv)	Thyroid cancer	Thyroid cancer risk (%) for different periods after exposure:		
		10 years	20 years	50 years
–	baseline	0.055 (0.006; 0.14)	0.23 (0.027; 0.58)	2.2 (0.27; 5.3)
20	attributable	0.0057 (0.0002; 0.025)	0.021 (0.0007; 0.081)	0.13 (0.005; 0.40)
50	attributable	0.014 (0.0004; 0.063)	0.053 (0.002; 0.20)	0.32 (0.011; 1.0)

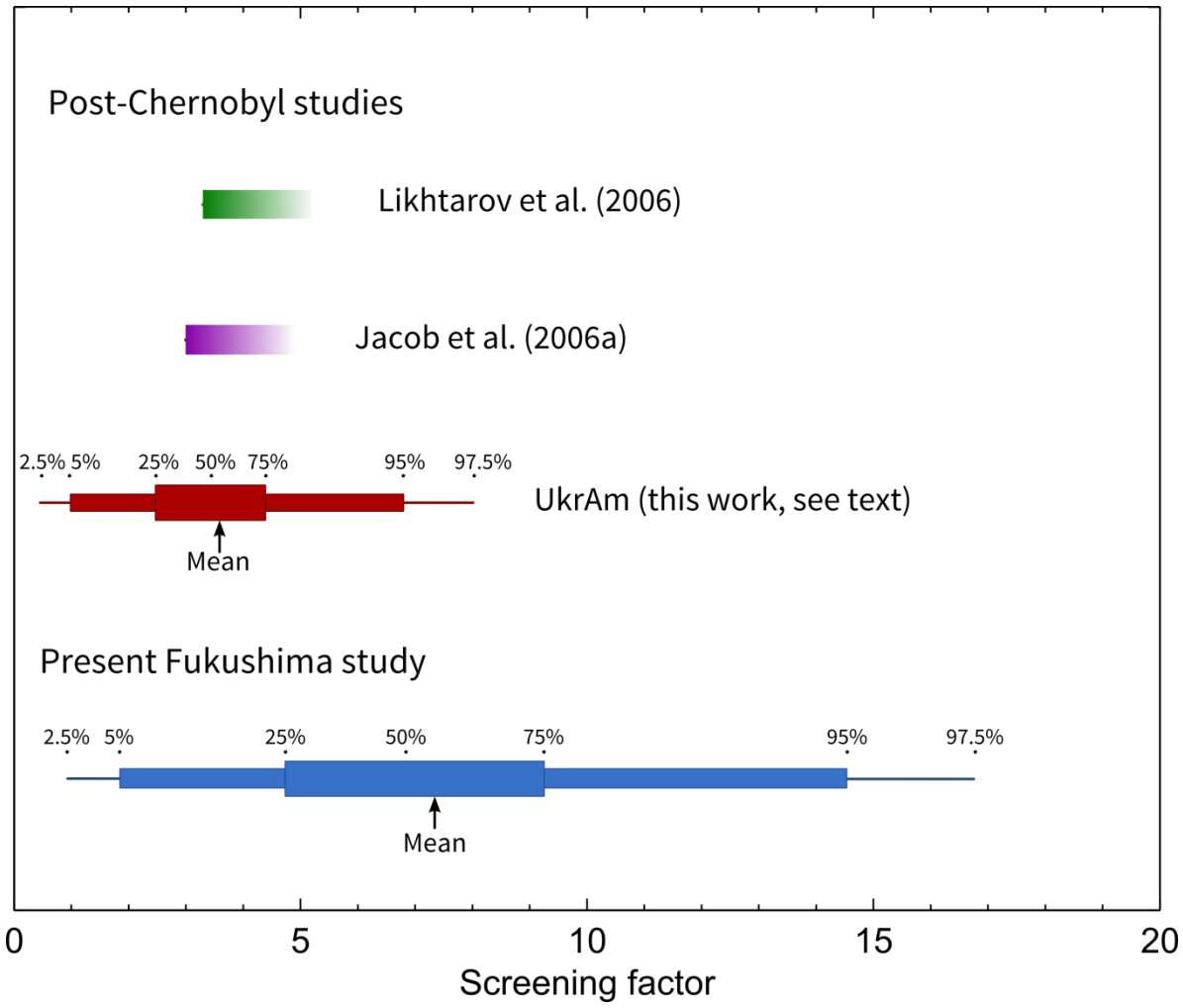


Fig. 1 Increase of thyroid cancer incidence rate due to ultrasonography screening. The upper two studies relate to populations without systematic screening, thus the estimates of the effect of 'grey' screening (left border of the boxes) are lower boundaries for the effect of a systematic screening. The screening factor for the Fukushima Prefecture, F_{scr}, is the product of the screening factor in the UkrAm cohort, f_{UA}, and a factor taking into account differences in the study protocol, f_{sp}.

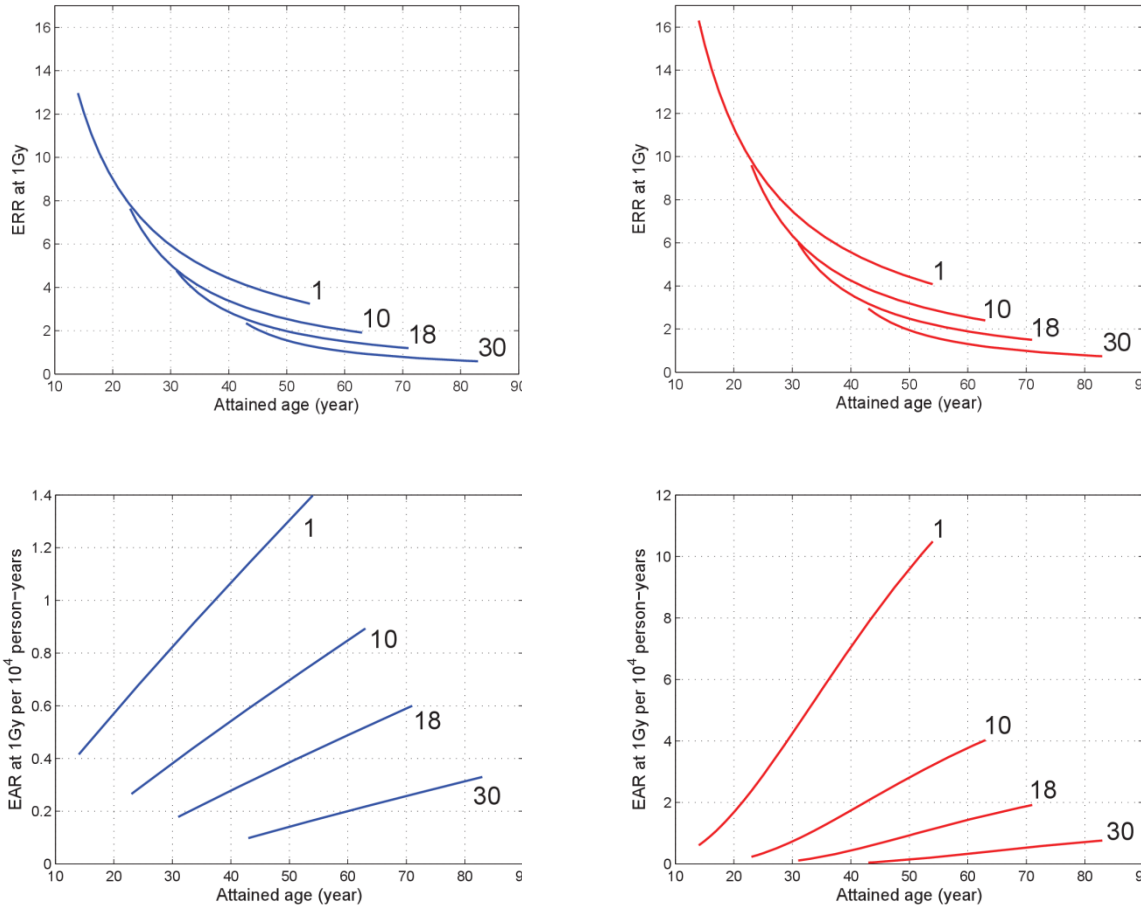


Fig. 2 Excess relative risk (upper panels) and excess absolute rate (lower panels) of male (left panels, blue curves) and female (right panels, red curves) LSS members not participating in the AHS of different ages at exposure (shown as numbers near the curves).

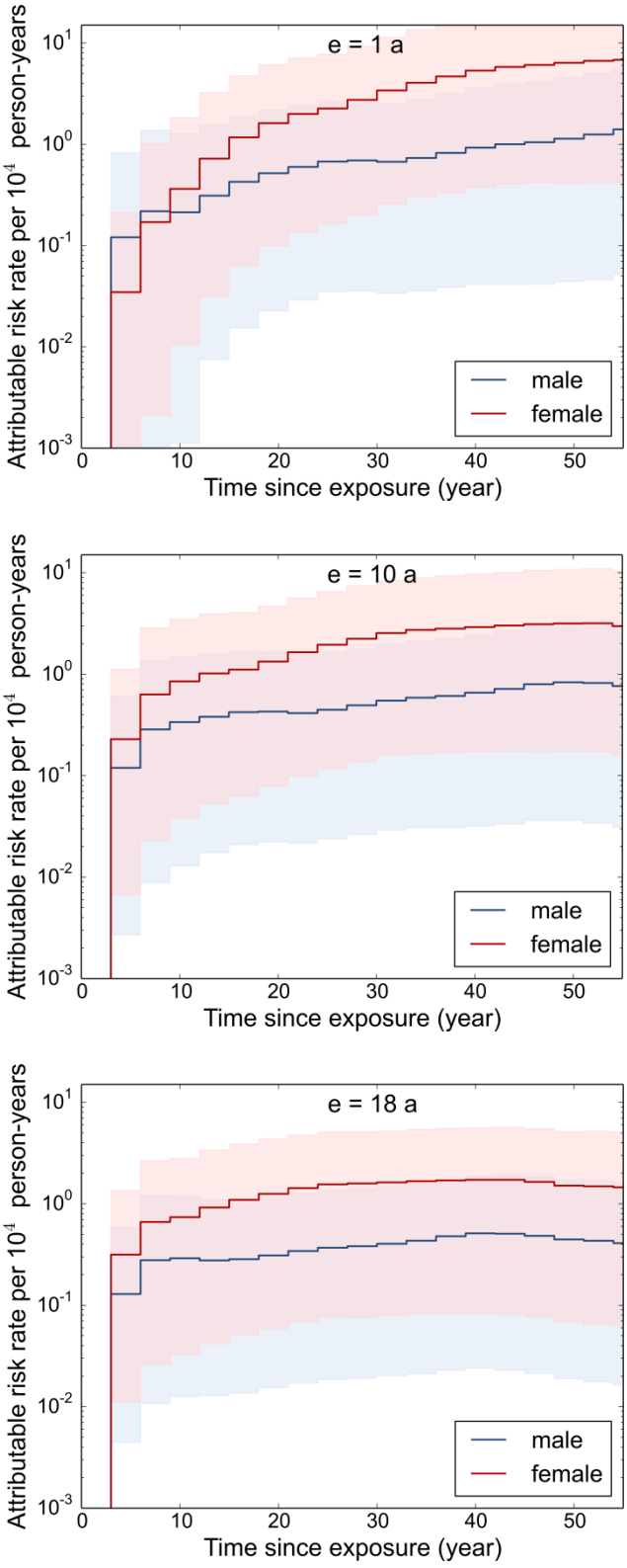


Fig. 3 Mixed transfer model for the attributable risk rate of thyroid cancer after exposure at age of 1, 10, and 18 years with a thyroid dose of 100 mGy. Mean values and 95% confidence intervals are shown.

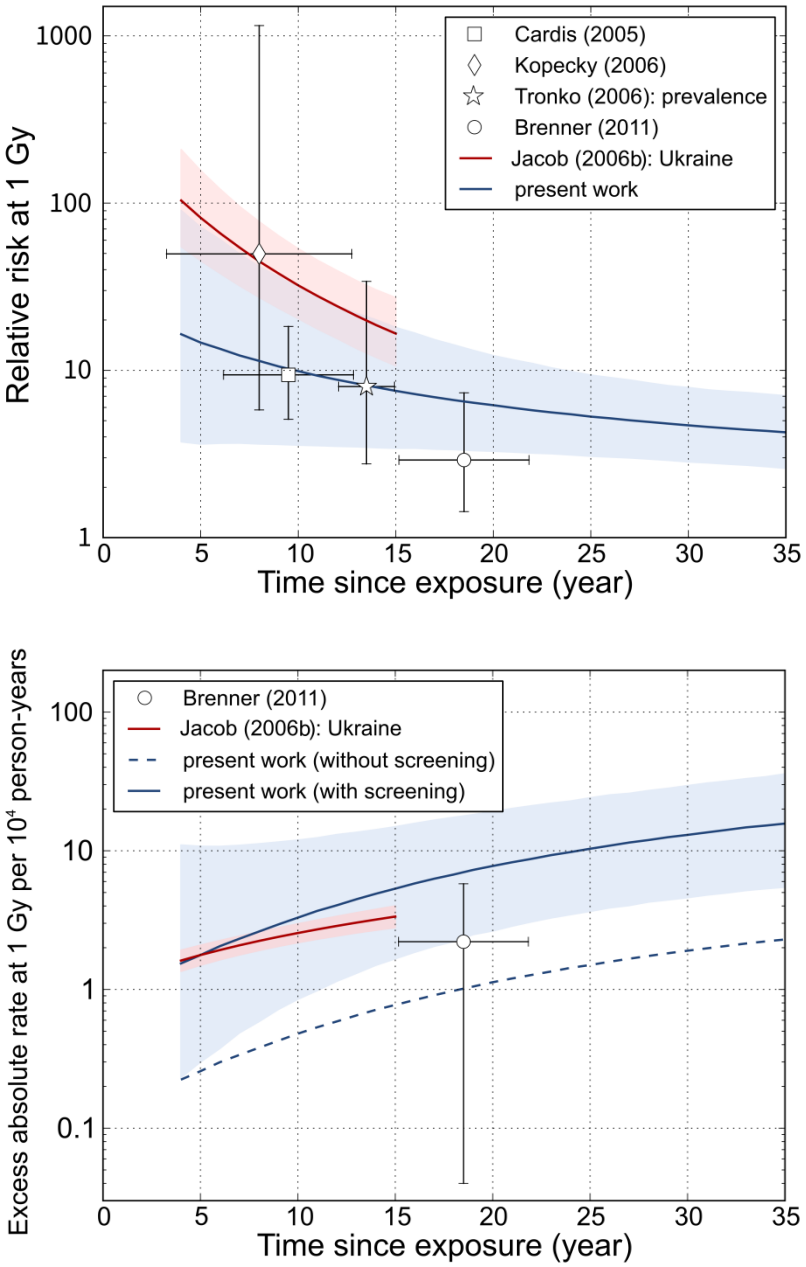


Fig. 4 Sex-averaged relative risk (upper panel) and excess absolute rate (lower panel) of thyroid cancer after an exposure at an age of 7 years (average age at exposure in post-Chernobyl cohort and case-control studies). Error bars and shaded areas indicate 95% confidence regions. Results for the LSS members not participating in the AHS are presented in blue, results from post-Chernobyl studies are presented in red and by symbols.