Hiroshima, Nagasaki, Hanford, and Fukushima

Critical Review on Radio Epidemiology Studies

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Agenda

- Research Purpose
- Brief Introduction to LSS studies
- Limitations of LSS studies
- Re-analysis of LSS 14 data
  - Limiting samples to lower dose
  - Model selection
  - Effect of Aggregation
- Re-analysis of Nuclear worker data
- Possible warning for Fukushima?
- Summary and Conclusion

Research Purpose

- Critically examine methodology of LSS reports that seems to be a standard approach in Radio-epidemiology
- Re-analyze LSS 14 data to confirm problems of their analysis.
- Re-analyze Nuclear worker data in US facilities with which previous studies failed to detect effect of radiation with individual level data
- Review studies on radiation and thyroid anomalies.
- Analyze relationship between exposure dose (UNSCEAR estimates) and thyroid nodules using Fukushima thyroid screening data.

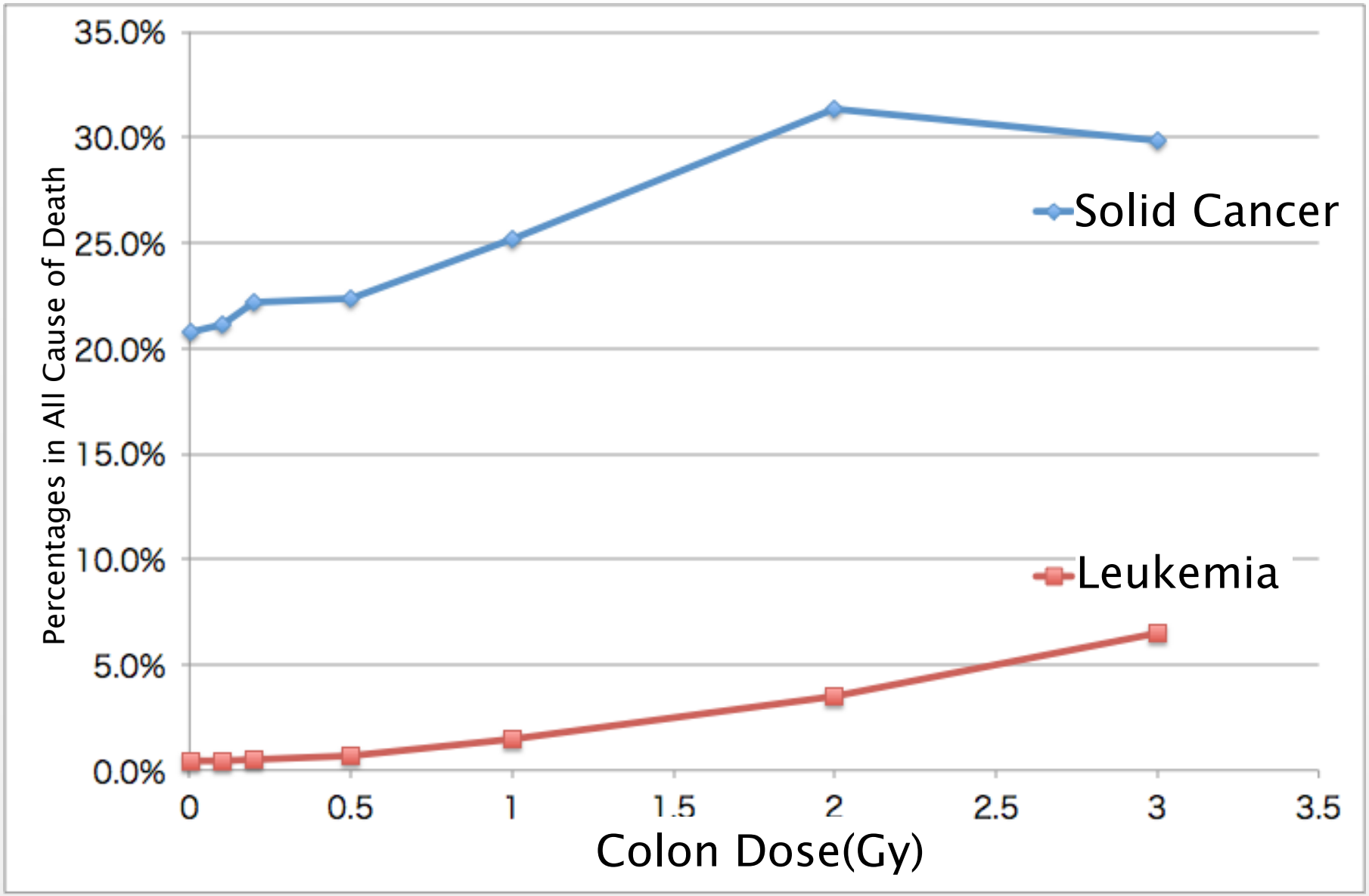
Introduction to A-Bomb Survivor Data Analysis

- Since 1950, Radiation Effects Research Foundation (formerly Atomic Bomb Casualty Commission) has investigated effects of radiation on health with a cohort of a-bomb survivors that consists of some 94,000 directly exposed to the bombings and 27,000 who entered the city just after the bombings.
- Life Span Study (LSS)
  - Almost every five or ten years, the RERF has published reports that examine relationships between radiation exposure and cancer mortality, cancer incidents, non-cancer mortality, etc.
- This study critically examines the Report 13 (Preston et al. 2003) and the Report 14 (Ozasa et al. 2012), then re-analyze newest and publicly available LSS14 data.

Brief Introduction to LSS studies
Summary of LSS14 Data (Ozasa et al. 2012)

Colon Dose (Gy)	Subjects	City		Sex		Age at Ex-posure	Mortality		
		Hiroshima	Nagasaki	Male	Female		Total	Solid cancer	Leukemia
~0.005	38,509	56.3%	43.7%	41.4%	58.6%	22.3	22,270 (100%)	4,621 (20.7%)	99 (0.4%)
~0.1	29,961	75.9%	24.1%	41.2%	58.8%	22.1	17,292 (100%)	3,653 (21.1%)	78 (0.5%)
~0.2	5,974	84.3%	15.7%	39.9%	60.1%	23.2	3,557 (100%)	789 (22.2%)	18 (0.5%)
~0.5	6,356	79.7%	20.3%	39.0%	61.0%	23.4	3,898 (100%)	870 (22.3%)	27 (0.7%)
~1.0	3,424	69.3%	30.7%	41.3%	58.7%	23.1	2,061 (100%)	519 (25.2%)	30 (1.5%)
~2.0	1,763	65.3%	34.7%	46.1%	53.9%	22.2	1,127 (100%)	353 (31.3%)	39 (3.5%)
2.0+	624	69.7%	30.3%	48.6%	51.4%	20.1	415 (100%)	124 (29.9%)	27 (6.5%)
Total	86,611	67.5%	32.5%	41.2%	58.8%	22.4	50,620 (100%)	10,929 (21.6%)	318 (0.6%)

Relationships between Exposure and Mortality



Publicly Available Data

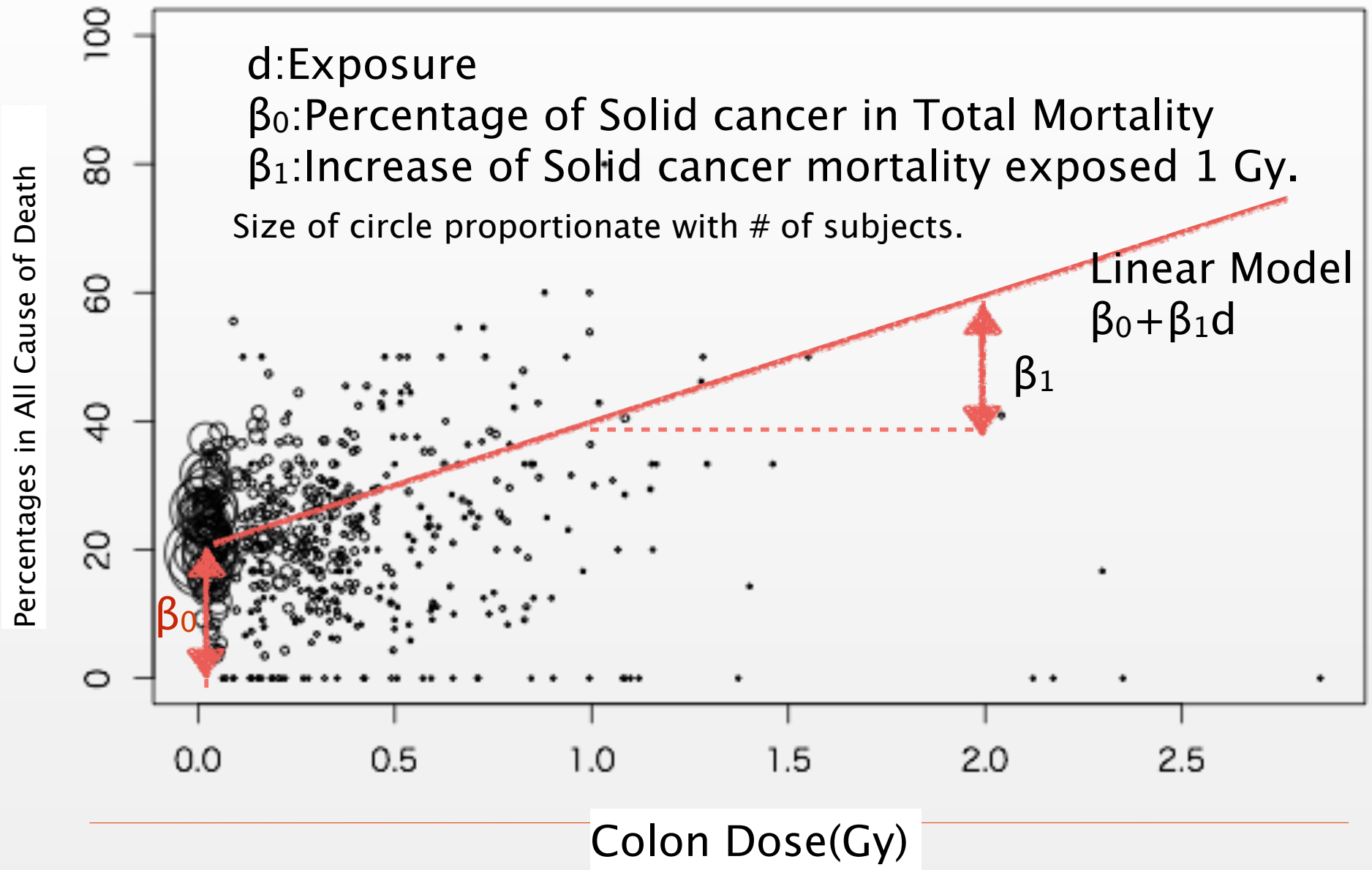
- Individual-level data is Tabulated by
  - Dose
    - 22 categories
  - city
  - sex
  - Age at exposure
  - Attained age

city	sex	gd3	ahs	agexca	agecat	ctime	doseca	subjec	pyr	agex	age	colon1	st	death	solid	esoph	sto
1	1	1	0	1	2	1	1	259	594.8	1.656	8.404	2.641	2.	0	0	0	
1	1	1	0	1	2	1	2	726	1701	1.712	8.432	10.54	1(	0	0	0	
1	1	1	0	1	2	1	3	277	571.2	1.862	8.505	29.09	2!	1	0	0	
1	1	1	0	1	2	1	4	151	335.2	1.786	8.466	49.08	5(	1	0	0	
1	1	1	0	1	2	1	5	109	252.3	1.726	8.44	70.32	7:	0	0	0	
1	1	1	0	1	2	1	6	79	177.8	1.712	8.432	90.46	9:	0	0	0	
1	1	1	0	1	2	1	7	98	209.6	1.807	8.474	112.1	1'	1	0	0	
1	1	1	0	1	2	1	8	61	135.1	1.87	8.511	137.8	1-	0	0	0	
1	1	1	0	1	2	1	9	64	142	1.7	8.415	163.2	1(	1	0	0	
1	1	1	0	1	2	1	10	63	131	1.94	8.546	187.4	1!	0	0	0	
1	1	1	0	1	2	1	11	63	161.8	1.506	8.329	222.3	2:	0	0	0	
1	1	1	0	1	2	1	12	60	118.4	2.026	8.56	271.9	2(	2	0	0	
1	1	1	0	1	2	1	13	118	258.2	1.777	8.459	393	4'	1	0	0	
1	1	1	0	1	2	1	14	59	144.9	1.659	8.405	592.8	6'	1	0	0	
1	1	1	0	1	2	1	15	4	8.594	2.052	8.602	811.3	8'	0	0	0	
1	1	1	0	1	2	1	16	3	3.782	3.063	9.108	1060	1	0	0	0	

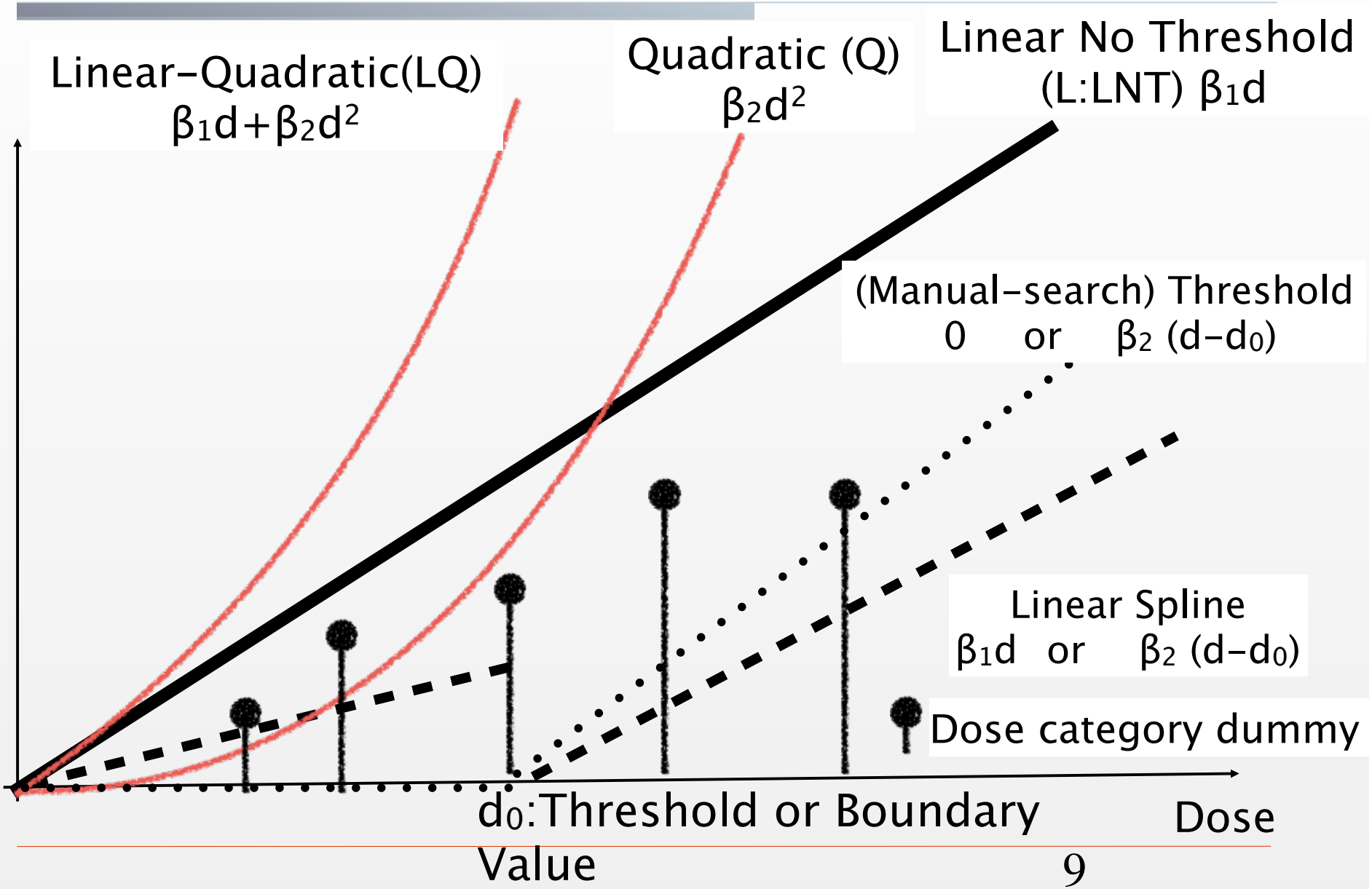
- These variables must be included in the analysis of effect of radiation on health.

RERF Downloadable Data
Life Span Study Report 14. Cancer and noncancer disease mortality data, 1950–2003
http://www.rerf.or.jp/library/dl/index.html

Exposure and Solid Cancer Mortality



Various Dose-Response Functions



Excessive Relative Risk Model

Mortality rate after exposure (d)

=Baseline or background mortality rate at zero dose

×[1+Characteristics of survivors × f(d)]

Excessive Relative Risk

f(d): Dose-response function

Characteristics of survivors

$=(1+\gamma_1 Sex)\times\exp\{\gamma_2(Age\ at\ exposure-30)+\gamma_3 \log(Attained\ age/70)\}$

- Assumptions of the Model
  - Exposure could raise mortality (Excessive Relative Risk)
  - Relationship between exposure and increase in mortality rate is given dose-response model.
  - Dose-response is modified by survivors 'sex, age at exposure, and attained age.
  - Mortality at 70 years old of those who were exposed at 30 years old is used as reference for estimation.

Results of Estimation
(Solid Cancer Mortality, Linear Model)

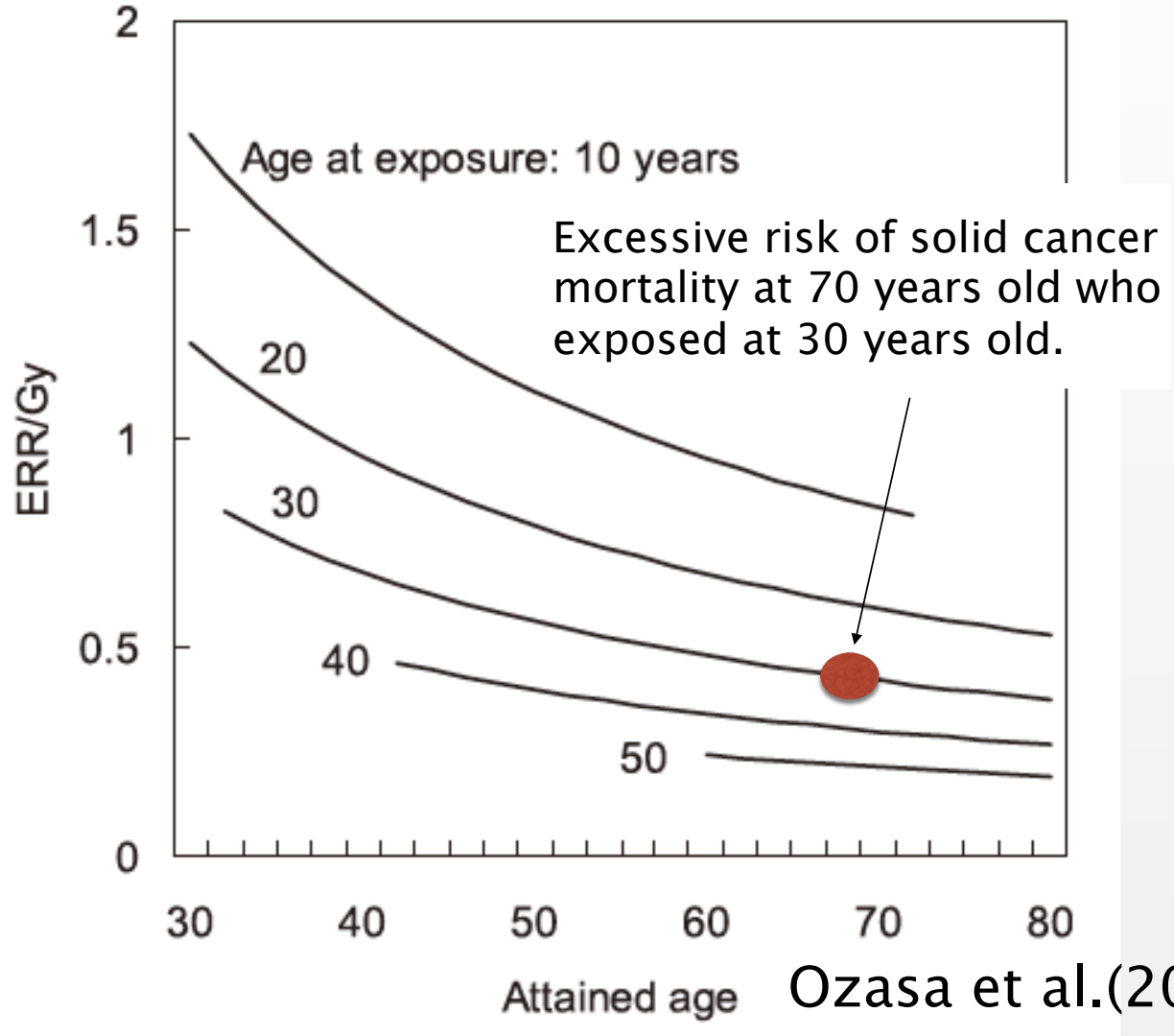
	Estimates	Std. Error	t-value	P-value		95% Confidence Interval
Colon Dose (Gy)	0.42	0.05	8.40	<0.001	***	(0.32, 0.52)
Age at Exposure	-0.35	0.08	-4.25	<0.001	***	(-0.51,-0.19)
Attained age	-0.86	0.42	-2.03	0.04	**	(-1.69,-0.03)
Sex(Male-1,Female=1)	0.34	0.09	3.92	<0.001	***	(0.17, 0.51)
N	53782					
Deviance	18299.0					

Significance Level ***: 1% **:5% *:10%

Age at Exposure and ERR

$\exp\{\gamma_2(\text{Age at exposure}-30)+\gamma_3\log(\text{Attained age}/70)\}$

- Children are sensitive to solid cancer mortality
  - Care for children is important.



Ozasa et al.(2012)

Limitations in LSS Studies

- Through our critical review of the Life Span Survey (LSS) Report 13 (Preston et al., 2013) and Report 14 (Ozasa et al. 2012), the limitations were identified.
- They are summarized the next table (Hamaoka 2015b).

- Focuses of our analysis.
  - Limiting samples to lower dose ranges
  - Incomplete model selection
  - Aggregation of individual level data

Limitations in LSS13 and LSS14(Hamaoka 2015b)

Limitations			LSS 13 1950–1997 (Preston et al. 2003)	LSS 14 1950–2003 (Ozasa et al. 2012)
Data Management	Aggregation of individual data	Loss of statistical power	✓	✓
Model Formulation	Multicolinearlity in LQ	Unstable esitimates	✓	✓
	Does not estimate threshold itself	Statistical significance can not be tested.	✓	✓
Model estimation	Limiting samples to lower dose range	Loss of statistical power	✓	
	Additional analysis that compare L, Q, and LQ model limiting samples to less than 2Gy.			✓
	Pooled analysis with Hiroshima and Nagasaki	Neglecting differences	✓	✓
Model Selection	All of estimates are not displayed, such as modification terms, that helps model diagnosis and model improvement.	Insufficient model diagnosis	✓	✓
	Incomplete model selection	Confusing results	✓	✓

Limiting Samples to Lower Dose (Preston et al. 2003)

- LSS Report 13 shows estimation using a linear model and restricting to the low dose range yields significant coefficients beyond the 0-125 mSv range.
- This is an inappropriate conclusion neglecting a decrease in the sample size that cause loss of statistical power.
- All data should be used so as not to lose statistical power.

Dose Range (Sv)	ERR/Sv	t-value	P-value	
0–0.05	0.93	1.09	0.150	
0–0.1	0.64	1.16	0.300	
0–0.125	0.74	1.95	0.025	**
0–0.15	0.56	1.75	0.045	**
0–0.2	0.76	2.62	0.003	***
0–0.5	0.44	3.67	<0.001	***
0–1	0.47	4.70	<0.001	***
0–2	0.54	7.71	<0.001	***
0–4	0.47	9.40	<0.001	***

Preston et al.(2003)

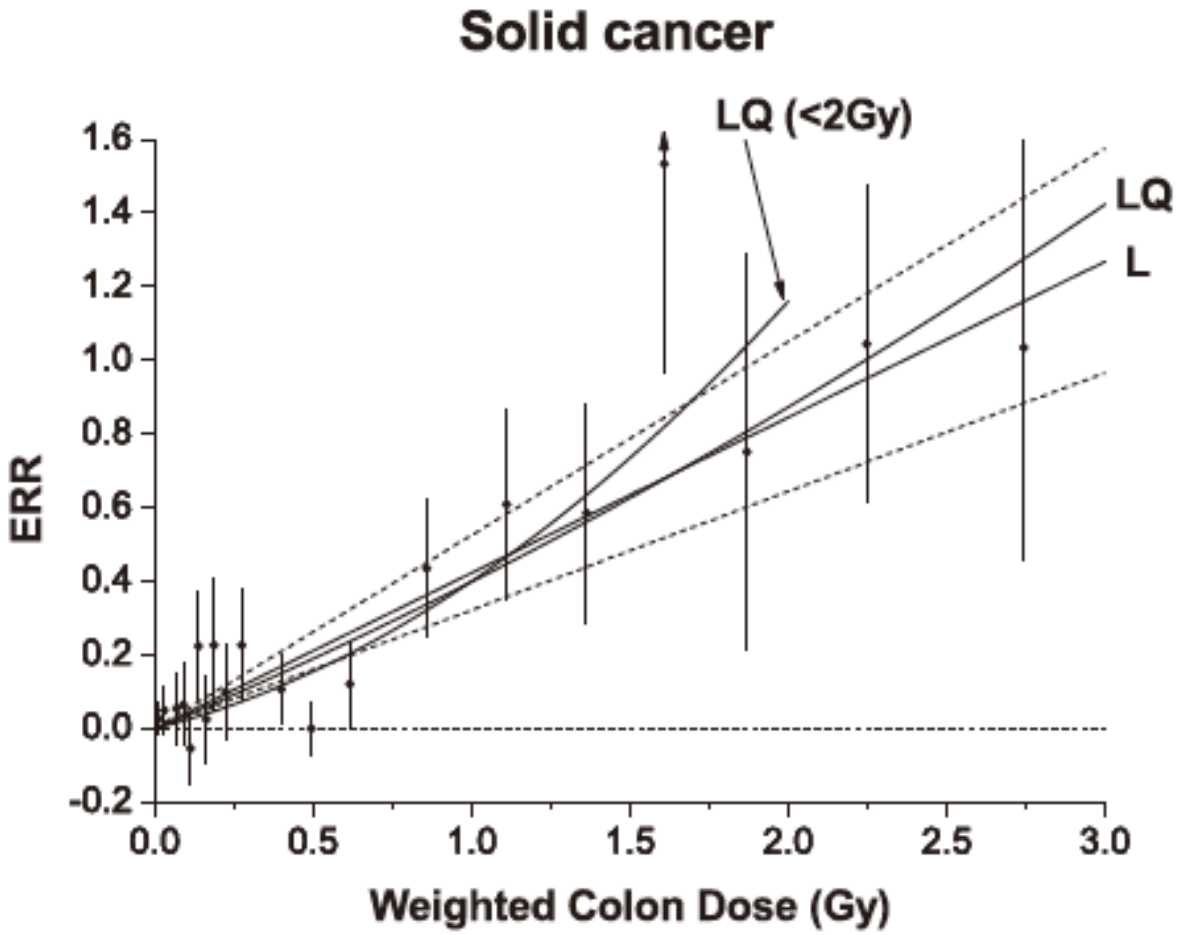
UNSCEAR Follows This Inappropriate Analysis

- UNSCEAR2006 Report
  - They conducted the same analysis for cancer mortality and cancer incident with a model taking uncertainty in dose estimates into account. They found the lowest dose ranges that obtained significant coefficients of radiation were 0-200 mSv for solid cancer mortality, and 0-250 mSv for solid cancer incidents.

- UNSCEAR 2011 Report (Summary of UNSCEAR 2006)
  - ”Statistically significant elevations in risk are observed at doses of 100 to 200 mGy and above. UNSCEAR(2011, parag. 25)“

Incomplete Model Selection
Results of LSS14 (L, Q, LQ, Dose category dummy)

- Model fit was compared among nested L,Q and LQ models with log-likelihood test. Then, L model was selected as the best model.
- However, fit of dose-category dummy model is not discussed.
- Some researcher insists “hormesis effect”, because dose-category dummy model has negative estimates at the lower dose range.



Ozasa et al.(2012)

Results of LSS14 (Linear Spline Model)

- Inappropriate analysis: limiting samples to lower dose was not conducted in LSS Report 14, Linear spline model that allows a change in slopes at pre-determined boundary values was applied for the analysis.

- Linear spline (L1L2)
  $\beta_1 d$ $(d<d_0)$
  $\beta_2 (d-d')$ $(d \geqq d_0)$

- The figure exhibit estimates and their 95% confidence interval. Ozasa et al. 2012 explains that "The lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy with an estimated ERR/Gy of 0.56"
  - based on this results threshold at 0.Gy is insisted by a researcher.

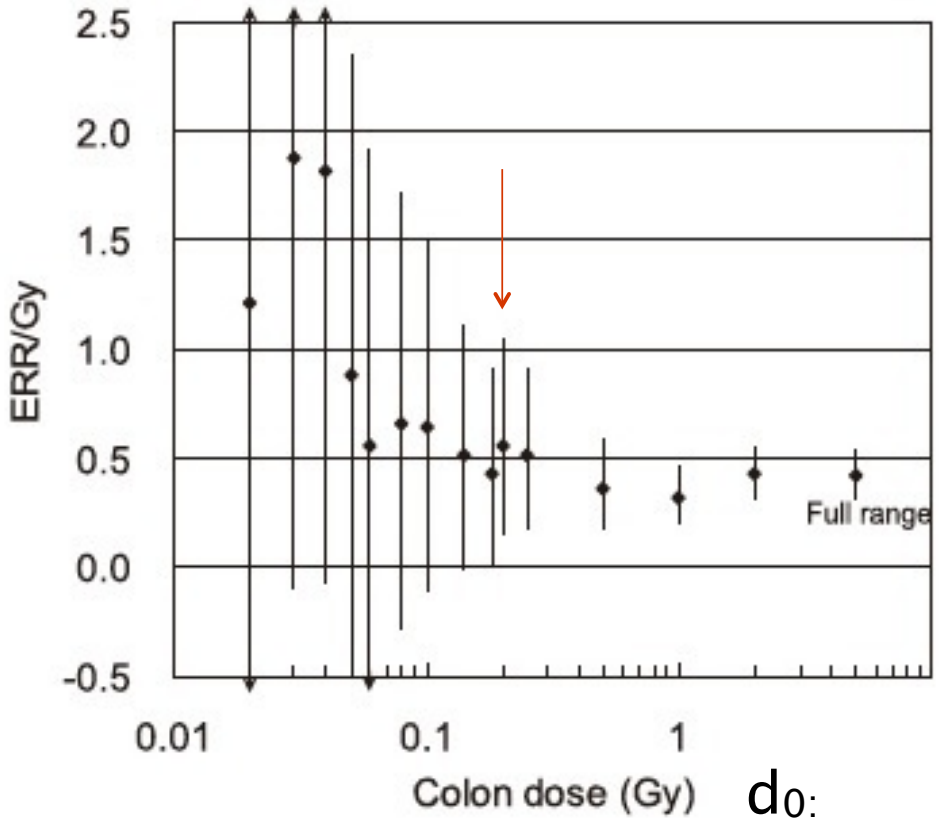


FIG. 5. Excess relative risk per Gy (ERR/Gy) for all solid cancer for selected dose ranges. The figure shows the ERR/Gy and 95% CI for a dose range from zero to a given dose based on the linear model for the full data that allowed for different ERRs below and above the given dose and taking radiation effect modifiers as common to the two dose ranges. The increased ERR/Gy in the low-dose levels less than 0.1 Gy corresponds to the estimates of ERR higher than the expected linear line in Fig. 4.

Ozasa et al.(2012)

Estimated Dose-Response Function and Method of Model Selection

LSS14 (Ozasa et al. 2012)

- Model 1 L:LNT $\beta_1 d$
- Model 2 Linear-quadratic(LQ) $\beta_1 d+\beta_2 d^2$
- Model 3 Quadratic(Q) $\beta_2 d^2$
  - Model 1-3 were estimated for all dose range and limiting dose range less than 2G.
- Model 4 (Manual search) Threshold (d_0=10,20,30mGy,,)

  0 $(d<d_0)$

  β_2 (d-d') $(d\geqq d_0)$
- Model 5 Dose category dummy
  - 15 categories
- Model 6 (Manual search) Linear spline (L1L2)(d_0=10,20,30mGy,,)

  $\beta_1 d$ $(d<d_0)$

  β_2 (d-d') $(d\geqq d_0)$

Present study

- Model 7 Kinked at 2 Gy Model

  L1, L1Q1, or Q1 (d< 2Gy)

  L2, L2Q2, or Q2 (d≧2Gy)
- Model 8 (Statistically estimated) Threshold

  0 $(d<\tau)$

  β_2 (d-τ) $(d\geqq\tau)$

Log-likelihood Ratio test

Maximum likelihood

?

Maximum likelihood

Sugiyama et al.(2014) "Skin cancer incident" AIC

Present study AIC, BIC

Confusing Results

- Abstract of LSS14 (Ozasa et al.2012)
  - The sex-averaged excess relative risk per Gy was 0.42 [95% confidence interval(CI): 0.32, 0.53] for all solid cancer at age 70 years after exposure at age 30 based on a linear model. Supporting LNT

    Implicates threshold at 0.2Gy?
  - The estimated lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy, and a formal dose-threshold analysis indicated no threshold; i.e., zero dose was the best estimate of the threshold. Supporting LNT
  - (Underline by Hamaoka)

Re-Estimation

- Data
  - Full samples in LSS 14 on Solid cancer mortality
- Estimation
  - Model 1-7
    - AMFIT of Epicure (Preston et al.)
      - Maximizes partial likelihood
  - Model 8
    - optim of R
      - Maximize full likelihood
      - Model 1 (Linear) was also estimated with R optim to compare model fit.

Model Selection

- "Information criterions" that can compare fits of non-nested models.
  - Akaike's Information Criterion
    - AIC=deviance+ 2k
  - Bayesian Information Criterion
    - BIC =deviance+ k*log(N)
  - Here,
    - k: # of free parameters
    - N: Sample size
  - Deviance ~ (Observation - Prediction by a model) →Smaller is the better
  - k indicates "complexity of model" →Simpler model is the better.
    - Smaller AIC(BIC) is better model.
  - AIC and BIC
    - LSS14 data consist of N= 53782 records, thus log(N)~10.9 is larger than 2. BIC penalize more on model complexity.
    - BIC prefers simpler model than AIC.

Comparison of Estimated Models (Hamaoka 2015b, e)

Model			Threshold/ boundary	L1	Estimates Q1	L1 or L2	Q or Q2	Note	Information Criterion AIC	BIC
1	L			L1=L2		0.423***			18307.0	18317.9
2	LQ			L1=L2		0.361***	0.038	Multi-colinear	18308.2	18321.8
3	Q			L1=L2			0.218***		18330.7	18341.6
4	Manual Threshold	0+L2	1	0 (Fixed)		0.423***			18307.0	18317.9
		0+L2	5	0		0.423***			18306.8	18317.7
		0+L2	10	0		0.422***			18306.9	18317.9
		0+L2	20	0		0.420***			18307.2	18318.1
		0+L2	50	0		0.416***			18308.2	18319.2
		0+L2	100	0		0.412***			18309.4	18320.3
5	Category dummy								18318.1	18380.9
6	Linear Spline	L1+L2	1	20.430		0.426***			18308.9	18322.5
		L1+L2	5	-22.160**		0.420***		Not Converged	18305.2	18318.9
		L1+L2	10	-2.146		0.420***			18308.8	18322.4
		L1+L2	20	1.209		0.427***			18308.8	18322.5
		L1+L2	50	0.884		0.427***			18308.5	18322.2
		L1+L2	100	0.645		0.426***			18308.7	18322.3
7	Kink at 2Gy	L1+L2		0.398***		0.433***			18308.8	18322.4
		L1Q1+L2Q2		0.626	-0.089	0.211**	0.181**	Multi-colinear	18306.6	18325.7
		L1Q+L2		0.213**	0.181**	0.385***		Multi-colinear	18304.8	18321.2
		Q1+Q2			0.135***		0.330***		18309.2	18322.8
8	Threshold		-23.15 (z=-0.087)			0.417***		R-optim (Full likelihood)	33286.9	33781.6
1	L					0.414***			33285.0	33759.8

Note) Significance Level ***:1% **:5% *:10% Red letters indicate smallest AIC and BIC.

Aggregation/Tabulation of Individual Level Data

- Individual level data is tabulated by dose, sex, city, age at exposure, and attained age group.
  - Dose category: 22 intervals
    - (0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.15, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5 , 3 +)
- Two limitations
  - Arbitrary categorization (the number of intervals and upper and lower bound)
    - For LSS data, among 86,611 subjects, 38,509 are classified to the lowest dose category.
  - Aggregation of individual-level data cause loss of information

Table Aggregation Cause Loss of Information

	Data	Variance
Raw data	1,2,3,4,5,6,7,8,9,10	Var(x)=9.17
Categorized data	1~5 x 5 samples 6~10 x 5 samples	Var(x)=6.94

Loss of Statistical Power

- Small variance leads to loss of statistical power
  - Significance of parameters of Poisson regression are tested with t-value (Cameron and Trivedi 1998, Ch.3).
  - Smaller variance leads to a smaller t-value, which tends to fail to reject the null hypothesis H0: β=0.

$$t = \hat{\beta} / s.e(\hat{\beta}) = \hat{\beta}\sqrt{\exp(d'\hat{\beta})Var(d)}$$

- Restricting dose range and sample reduces sample size and range of dose, both of them lead to smaller t-value that is the loss of statistical power.

Effect of Aggregation

- In LSS 14, dose is categorized into 22 intervals.
  - (~0.005, ~0.02, ~0.04, ~0.06, ~0.08, ~0.1, ~0.125, ~0.15, ~0.175, ~0.2, ~0.25, ~0.3, ~0.5, ~0.75, ~1.0, ~1.25, ~1.5, ~1.75, ~2.0, ~2.5 , ~3.0, 3.0Gy~)
  - # of record= 53782

- Aggregate them into 12 and 6 intervals.
  - 12 intervals (~0.02, ~0.06, ~0.1, ~0.15, ~0.2, ~0.3, ~0.75, ~1.25, ~1.75, ~2.5 , 2.5Gy~)
    - # of record= 33973
  - 6 intervals (~0.06, ~0.15, ~0.3, ~1.25, ~2.5 , 2.5Gy~)
    - # of record= 22257
- For these data the following models are estimated.
  - Linear model $\beta_1 d$
  - Statistically estimated-Threshold model

$$\begin{cases} 0 & (d<\tau) \\ \beta_2 (d-\tau) & (d\geqq\tau) \end{cases}$$

- Estimation
  - Maximize log-likelihood with optim library of R

Effect of Aggregation

a) Linear Model

	22 Categories				11 Categories				6 Categories			
	Estimate	s.e.	t-value		Estimate	s.e.	t-value		Estimate	s.e.	t-value	
Dose : Slope (/Gy)	0.413	0.051	8.07	***	0.408	0.052	7.84	***	0.391	0.053	7.34	***
Sex (male=-1, female=1)	0.340	0.088	3.88	***	0.331	0.089	3.72	***	0.340	0.092	3.70	***
Age at exposure (30 yrs old)	-0.334	0.084	-4.00	***	-0.347	0.086	-4.04	***	-0.364	0.092	-3.97	***
Attained age (70 yrs. old)	-0.949	0.382	-2.49	**	-0.878	0.390	-2.25	**	-0.823	0.407	-2.02	**
N		53782				33973				22257		
AIC		33285				26520				21115		
BIC		33760				26973				21548		

b) Statistically estimated-threshold model

	22 Categories				11 Categories				6 Categories			
	Estimate	s.e.	t-value		Estimate	s.e.	t-value		Estimate	s.e.	t-value	
Dose : Slope (/Gy)	0.417	0.071	5.86	***	0.408	0.074	5.55	***	0.385	0.073	5.25	***
Dose : Threshold	-0.023	0.264	-0.09		0.003	0.304	0.01		0.037	0.356	0.10	
Sex (male=-1, female=1)	0.345	0.105	3.29	***	0.330	0.108	3.07	***	0.332	0.114	2.91	***
Age at exposure (30 yrs old)	-0.338	0.096	-3.53	***	-0.346	0.100	-3.46	***	-0.358	0.107	-3.34	***
Attained age (70 yrs. old)	-0.985	0.562	-1.75	*	-0.874	0.577	-1.52		-0.774	0.619	-1.25	
N		53782				33973				22257		
AIC		33287				26522				21117		
BIC		33782				26994				21568		

- Standard error of estimates increases and t-value decreases with aggregation as we expected.
- For Linear-threshold model, threshold shifts upward as aggregation proceeds.
- Based on this result, if individual level model was applied, lower threshold will be obtained.
- For each aggregation level, fit of Linear model is better than Linear-threshold model.
- Based on these results, liner (no threshold) model is a empirically supported model for LSS14 data.
- To detect effect of low dose, we must avoid aggregation.

Re-analysis of US Nuclear worker

- Although RERF does not provide individual data for external researchers, U.S. Department of Energy publishes individual level data of nuclear workers.

- US Nuclear worker individual-level data at 3 sites analyzed by Gilbert et al. (1993) is re-analyzed.
  - Hanford: Nuclear
  - Oak Ridge National Laboratory
  - Rocky Flats: Weapons Plant

Descriptive Statistics of Population

		Total Population			Population for Analysis*		
		Hanford	Oak Ridge	Rocky Flats	Hanford	Oak Ridge	Rocky Flats
Total		44,156	8,318	7,616	33,973	6,743	6,788
Sex	Male	31,488	8,318	7,616	25,705	6,743	6,788
	Female	12,668	0	0	8,268	0	0
Follow-up period	Start	1944	1943	1952	1944	1944	1952
	End	1989	1984	1987	1989	1984	1987
Cumulative dose (mSv)	Mean	23.5	17.3	32.2	25.4	21.1	35.6
	Median	3.0	1.4	7.4	3.7	3.5	9.7
	Max	1477.0	1144.0	726.0	1477.0	1144.0	726.0
Cause of death							
ALL		9771	1433	794	7012	1208	719
Cancer		2390	352	214	1732	316	194
	Solid cancer	2133	302	186	1540	271	171
	Leukemia	87	28	10	62	26	10
	Other cancer	170	22	18	130	19	13
Non-cancer		6145	891	479	4446	741	437
External		911	172	100	618	137	87
Unknown		325	18	1	216	14	1

- *)Following Gilbert et al.(1993), we limited analysis to workers of at least 6 months who were monitored for external radiation. We also excluded seriously exposed three workers.
- Our population is larger than Gilbert et al. (1993) because of additional follow-up years.

Individual Level Model (Amamiya 1985)

- The *Binomial Logit* model for the specific mortality

$$P(Death\ by\ the\ specific\ cause\ ) = \frac{1}{1 + exp(-\beta x_i)}$$

- The *Multinomial Logit* model to estimate mortality due to one of several causes of death.

$$P(Death\ by\ the\ cause\ i\ among\ m\ causes) = \frac{exp(\beta x_i)}{\sum_{j=1}^{m} exp(\beta x_j)}$$

- Hazard model for the length of time before death due to the specific cause.

$$P(Death\ by\ the\ specific\ cause\ at\ t | Survived\ until\ t) = h_0(t) exp(\beta x_i)$$

Results of Estimation (Hamaoka 2015c, d)

- Gilbert et al. (1993) analyzed the tabulated data and failed to detect a significant relationship between cumulative doses and mortality.
- With the individual level data modeling, positive and significant coefficients of dose are obtained.

	Gilbert et al(1993)		Re-Analysis		
	Trend statistics	ERR	Binomial Logit	Multinomial Logit	Hazard(@)
ALL	-0.25		2.55**		
Cancer	-0.04	-0.0 (<0, 0.8)	2.22**		
(excluding leukemia)		0.0 (<0, 0.8)	2.37**		
			1.88*	1.70*	0.091 *
Solid cancer					
Leukemia		-1.0 (<0, 2.2)	-0.38	-0.40	
			2.02*	2.22**	
Other cancer					
Non-cancer			1.78*	2.50**	
	-0.08				
External			-0.14	-0.29	
	-1.85*				
Unknown	-1.46		2.48**	2.50**	

@:For hazard model log of dose: (log(1+dose)) was employed for the analysis.

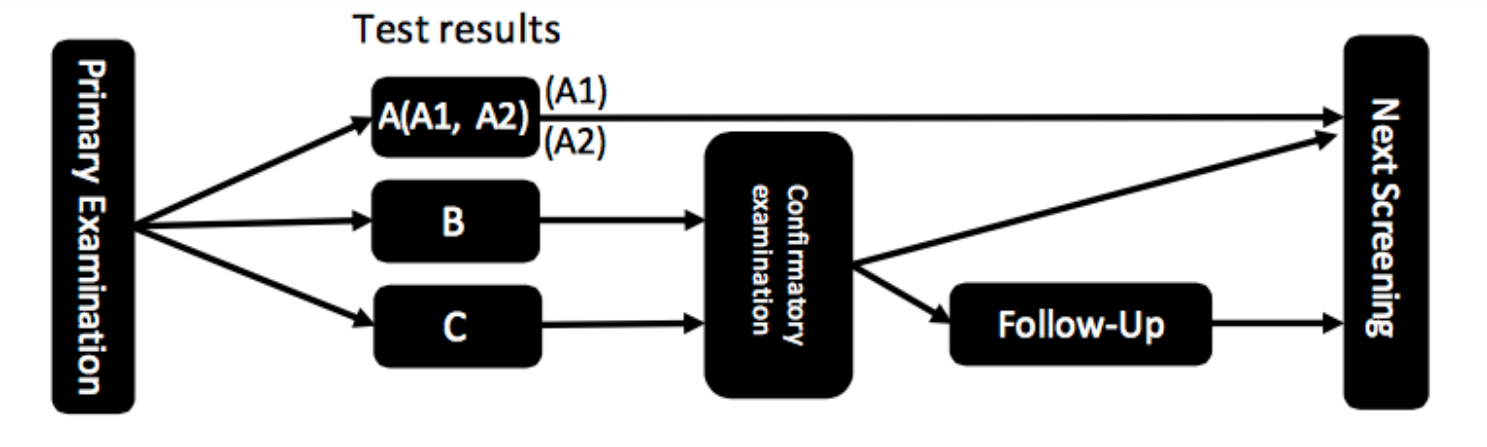
Results

- Through Logit models and hazard model, statistically significant effect of radiation dose on cancer mortality was detected.
- For the same data, the Mantel–Haenzel score test and Poisson regression failed to detect this relationship (Gilbert et al. 1993).

- To detect effect of low dose, individual level modeling is effective.

Radiation and Thyroid Nodule
Fukushima Health Management Survey

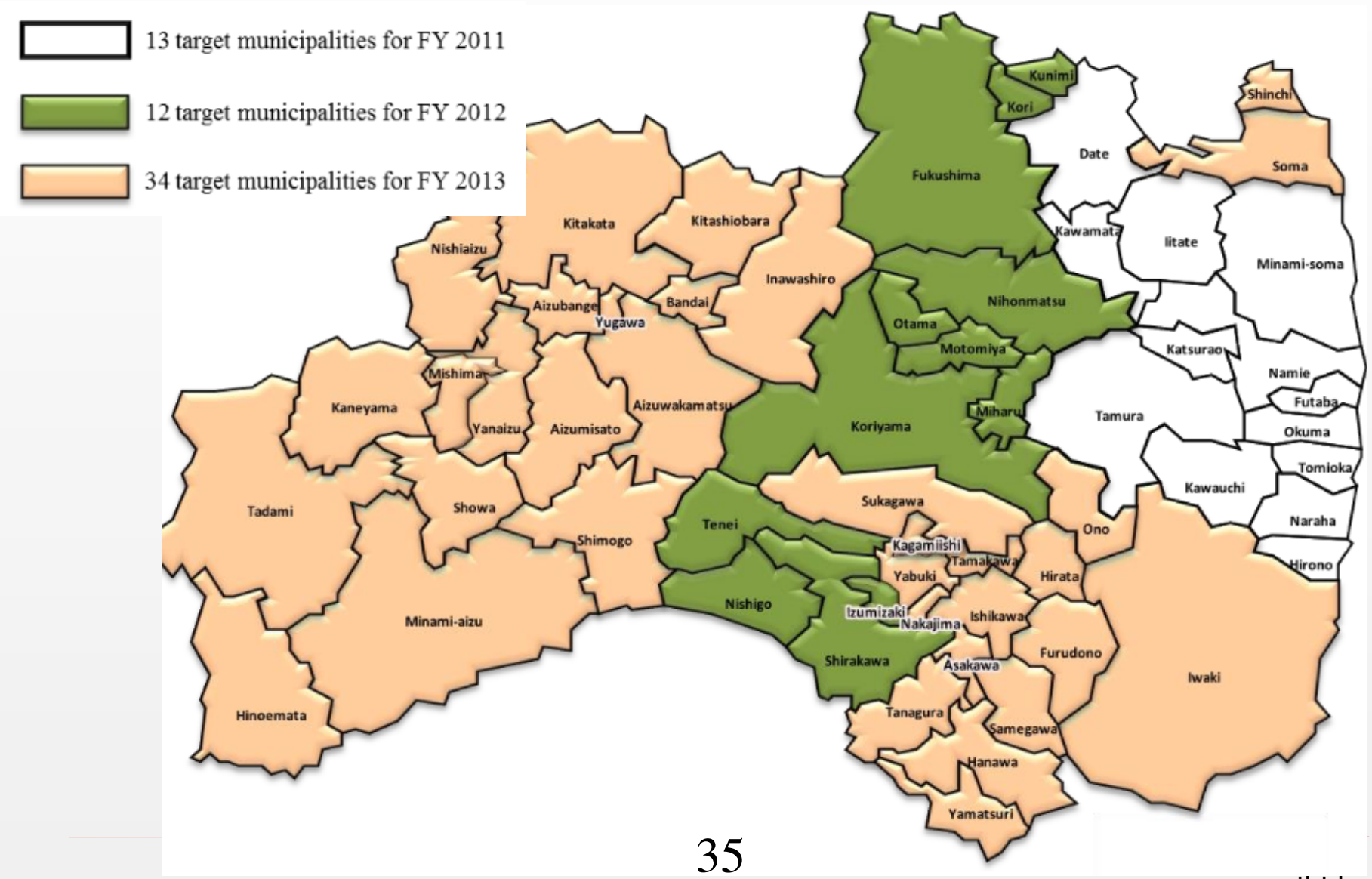
- Flow Chart of Thyroid Ultrasound Examination（Preliminary Baseline Screening)



- A
  - (A1) No nodules / cysts
  - (A2) Nodules <5.0 mm or cysts <20.0 mm
- B
  - Those with B test result are advised to take the Confirmatory Examination.
  - (B) Nodules >5.1 mm or cysts >20.1 mm
  - Some A2 test results may be re-classified as B results when clinically indicated.
- C
  - C test result are advised to take the Confirmatory Examination.
  - (C) Immediate need for confirmatory examination.

Interim Report of Thyroid Ultrasound Examination (Preliminary Baseline Screening)
Reported on 18 May 2015 http://fmu-global.jp/?wpdmdl=178

Subject Municipalities of Fukushima Thyroid Screening



ibid.

Results of The First Round Fukushima Thyroid Examination (As of Feb. 2015)

1) Thyroid Screening

	Target Population (n)	Participants	Mean Age at Exposure (y)	A1	A2	B	C	Solid Nodule		Cyst	
				No Specific Finding	Nodule ≤5.0 mm or/and Cyst ≤20.0 mm	Nodule ≥5.1 mm or/and Cyst ≥20.1 mm	Needed Further Examination	≤5 mm	≥5.1 mm	≤20 mm	≥20.1 mm
2011	47,768	41,810 87.53%	9.4	26,373 63.10%	15,216 36.40%	221 0.53%	0 0.00%	232 0.55%	219 0.52%	15,140 36.21%	1 0.00%
2012	161,135	139,339 86.47%	9.0	76,183 54.70%	62,146 44.60%	987 0.71%	1 0.00%	730 0.52%	973 0.70%	62,259 44.68%	9 0.01%
2013	158,784	117,428 73.95%	8.6	50,460 43.00%	64,415 54.90%	1,042 0.89%	0 0.00%	718 0.61%	1,040 0.89%	64,704 55.10%	2 0.00%
Total	367,687	298,577 81.20%	8.9	153,016 51.20%	141,777 47.50%	2,250 0.75%	1 0.00%	1,680 0.56%	2,232 0.75%	142,103 47.59%	12 0.00%

2) Confirmatory Examination

	Target Participants (n)	Participants for Examination	Mean Age at Exposure (y)	Confirmed Results of Examination	Reclassified to	
					A1	A2
2011	221	199 90.00%	14.5	197 99.00%	12 6.10%	44 22.30%
2012	988	919 93.00%	15.0	899 97.80%	54 6.00%	246 27.40%
2013	1,042	949 91.10%	14.9	914 96.30%	51 5.60%	274 30.00%
Total	2,251	2,067 91.80%	14.8	2,010 97.20%	117 5.80%	564 28.10%

3) Total

Confirmed Results	A1	A2	Follow-up Advised	Cytology	Malignancy (Including Suspected)	Solid Nodules	
						≤5 mm	≥5.1 mm
41,786 99.90%	26,385 63.10%	15,260 36.50%	141 0.34%	91 0.22%	14 0.03%	276 0.66%	127 0.30%
139,228 99.90%	76,237 54.80%	62,392 44.80%	599 0.43%	262 0.19%	56 0.04%	976 0.70%	543 0.39%
115,789 98.60%	50,511 43.60%	64,689 55.90%	589 0.51%	170 0.15%	39 0.03%	992 0.86%	550 0.48%
296,803 99.40%	153,133 51.60%	142,341 48.00%	1,329 0.45%	523 0.18%	109 0.04%	2,244 0.76%	1,220 0.41%

ibid.

Interim report

Table 9. Proportion of B or C test results, and suspicious or malignant (Interim report) As of 31 March 2015

			13 municipalities[14]	Nakadori[15]	Hamadori[16]	Aizu[17]	Total
Participants			47,768	199,451	70,539	49,927	367,685
Number of participants of Primary Examination	A[10]		41,810	169,116	55,516	32,791	299,233
Mean age (SD) Total			10.4 (5.3)	10.7 (5.1)	11.2 (5.0)	11.1 (4.5)	-
Mean age (SD) Female			10.4 (5.3)	10.8 (5.2)	11.3 (5.1)	11.3 (4.6)	-
Mean age (SD) Male			10.3 (5.2)	10.6 (5.1)	11.0 (4.9)	10.9 (4.5)	-
Female (%)		%	49.6	49.3	49.9	49.7	49.5
B or C test results	B		221	1,230	505	323	2,279
Proportion of B or C test results	(B/A)	%	0.53	0.73	0.91	0.99	0.76
Number of participants of Confirmatory Examination	C[11]		197	1,106	448	283	2,034
Proportion of participants	(C/B)	%	89.1	89.9	88.7	87.6	89.2
Participants of FNAC	D[12]		94	296	97	48	535
Proportion of participants of Confirmatory Examination	(D/C)	%	47.7	26.8	21.7	17.0	26.3
Proportion of participants of Primary Examination	(D/A)	%	0.22	0.18	0.17	0.15	0.18
Number of suspicious or malignant	E[13]		14	63	23	11	111
Proportion	(E/D)	%	14.9	21.3	23.7	22.9	20.7
Proportion per 100,000	(E/A)		33.5	37.3	41.4	33.5	37.1
		%	(0.033)	(0.037)	(0.041)	(0.034)	(0.037)

ibid.

Limitations of This “Analysis”

- Does not adjust age at exposure and attained age (age at examination).
- No statistical test.
- 59 municipalities are aggregated into four regions without rationale.
- Focusing only on thyroid cancer

Studies on Radiation and Thyroid Nodules (Hamaoka 2015a,f)

Research		Subjects	Exposure			Diagnose				Percentages of Thyroid Anomalies [Total (Male/Fenale)] (%) Risk Parameter (P-value): Under line indicates significant coefficient			
			Year	Dose	Age	Year	N	Method	Age	Thyroid Nodule	Solid Nodule	Cancer	Cyst
A-bomb	Nagataki et al. (1994)	General Public	1945	0.488 Sv	18.7	1984-87	2,857	US	59.2	6.8 (4.0/9.8)	3.2 (1.5/4.7) EOR=?(p<0.01)	0.8 (0.3/1.1) EOR=?(p=0.09)	4.1 (2.5/5.0)
	Imaizumi et al. (2006)	General Public	1945	0.490Sv (Median=0.087Sv)	15	2000-2003	4,091	US	70	20.7 (12.3/24.8)	14.4 (8.0/17.6) EOR=2.01/Sv (p<0.001)	2.1 (0.8/2.8) EOR=1.95/Sv (p<0.001)	7.9 (4.7/9.5) EOR=0.89/Sv (p<0.001)
	Imaizumi et al. (2015)	General Public	1945	0.182Gy (Median=0.018Sv)	4.2	2007-2011	2,668	US	68.2	17.6 (12.6/21.8) EOR=1.65/Gy (p<0.001)	16.0 (11.2/20.0) EOR=1.72/Gy (p<0.001)	1.8 (0.7/2.6) EOR=4.4/Gy (p<0.001)	1.8 (1.5/2.1) EOR=1.11/Gy (p=0.01)
Chernobyl	Panasyuk et al. (1997)	Children (<18 yrs old)	1986-	-		1991-1996	120,605	US		4.85		0.52	-
	Inskip et al. (1997)	Worker	1986-91	10.8cGy	32	1995	1,984	Palpation	40.0	7.0 (7.0/-)			
								US		10.1 (10.1/-) ERR=-0.01/cGy (p>0.1)	3.93 (3.93/-)	0.25 (0.25/-)	0.55 (0.55/-)
Semi-palatinsk	Land et al. (2008)	General Public	1949–62	Ext. 0.04 Gy Int. 0.31 Gy	14	1998	2,994	US	56	30.6 (18.0/39.0) Ext. Dose EOR=2.26/Gy (p<0.05) Int. Dose EOR=0.60/Gy (p<0.05)	19.8 (11.3/25.5)	2.0 (0.6/2.9)	0.9 (0.8/1.1)
Medical	Schneider et al. (1993)	Patient	1939-62	58.6cGy (Min=45.8, max=71.5)	~16	1974-1990	2,634	Palpation	~44	-	39.6 (34.4/47.2) ERR=0.091/cGy (p<0.05)	11.7 (10.3/13.8) ERR=0.03/cGy (p<0.05)	
Fukushima	Fukushima Pref.(2015)	Children (<18 yrs old)	2011-	Range=11.5-58.0 mSv (*)	8.9	2011-2014/12	298,577	US	10.7	-	1.17 (0.76: <5mm, 0.41: >5.1mm)	0.04	47.5
	Sobue(2014)	Worker	2011	122mSv		2014	627 vs 1,437 Controls	US	43 vs 41	-	14.7 vs 12.0 (p=0.07)	0	40.4vs29.6 (p<0.001)
Aomori, Yamanashi, and Nagasaki	Hayashida et al. (2013)	Children (3-18yrs old, from 3 schools.)	-	-	-	2012	4,365	US	12.0	-	1.65 (0.64: <5mm, 1.01: >5mm)	0	56.9 (52.3: <5mm, 4.58: >5mm)

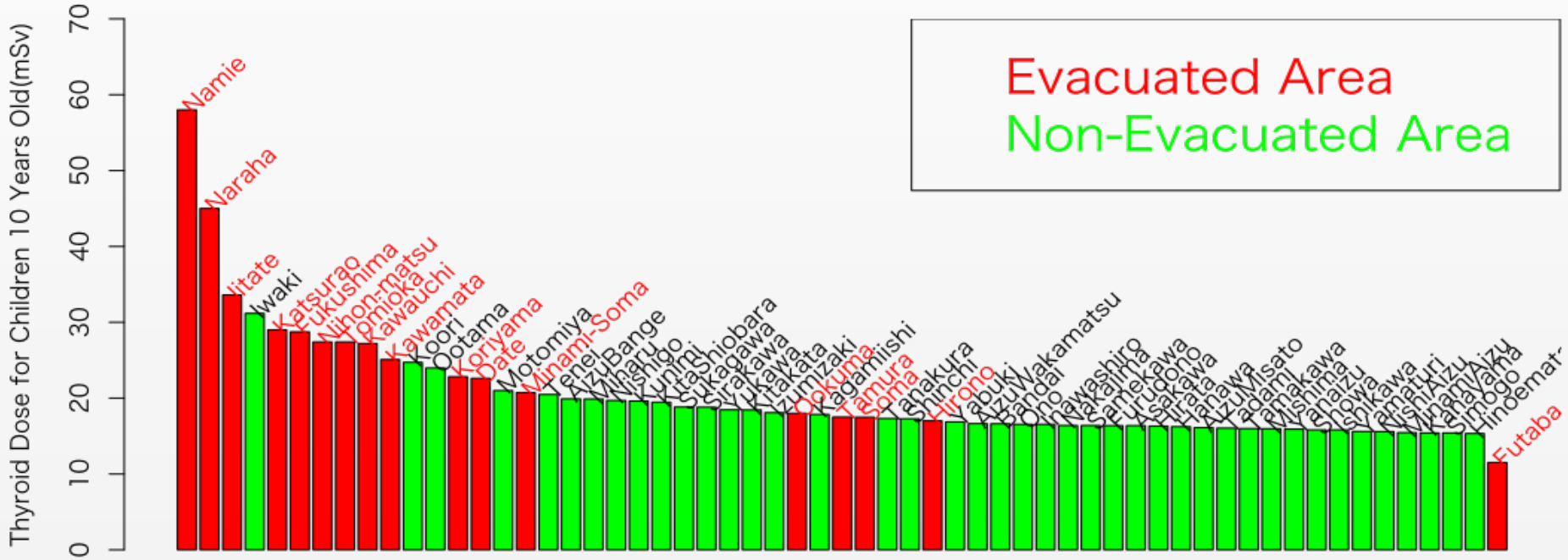
(*) Estimate for 10 yrs old (Municipality mean) (UNSCEAR 2013)

Follow-up Studies on Thyroid Nodules (Hamaoka 2015a,f)

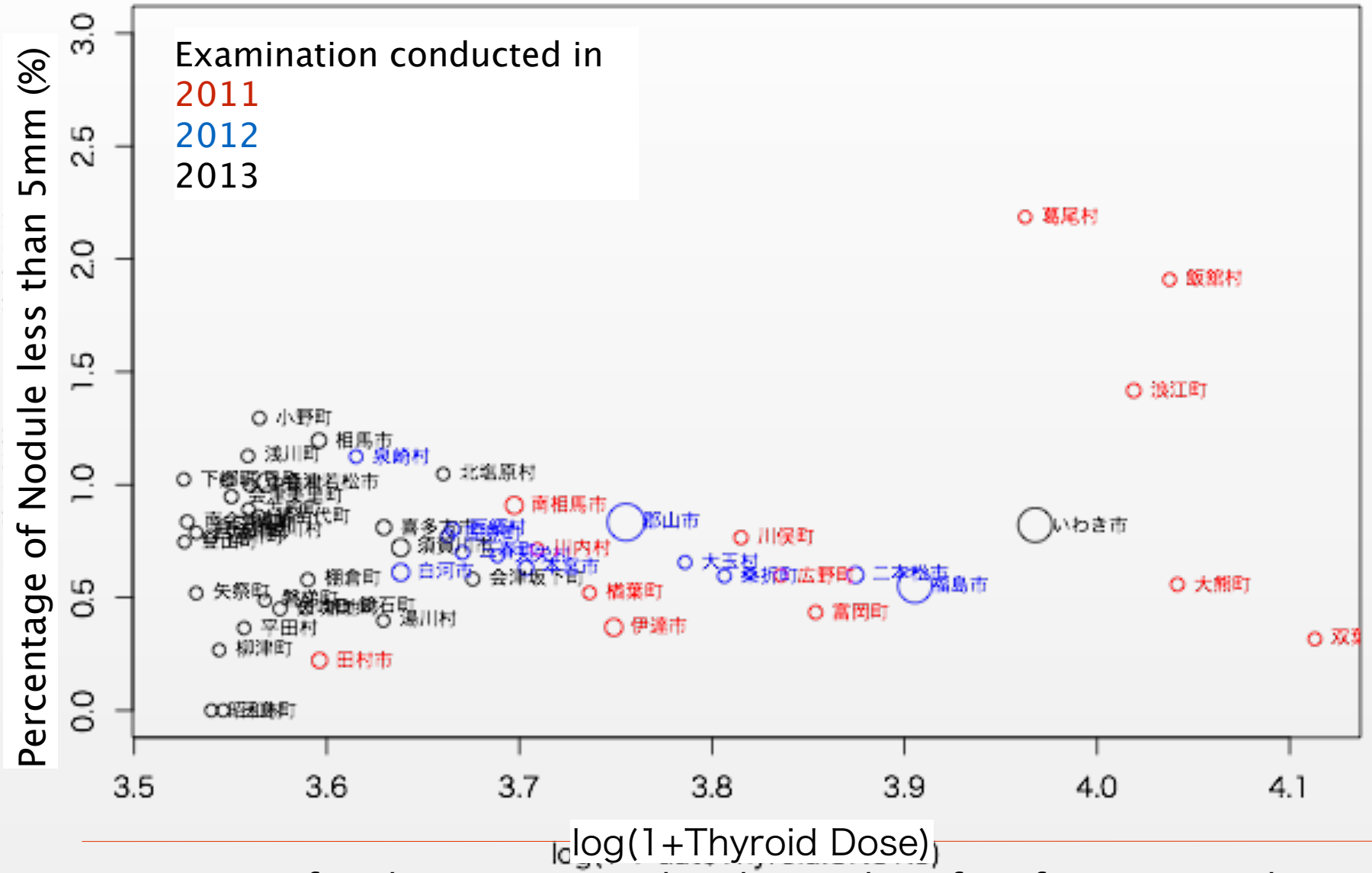
Research		Subjects	Exposure			Diagnose				Percentages of Thyroid Cancer (%) Risk Paremeter (P-value)
			Year	Dose	Age	Year	N	Method	Age	Cancer
A-bomb	Imaizumi et al. (2005)	General Public	1945	0.488 Sv	18.7	1984-87	2,637 (82 solid nodules, 121 cysts, and 2434 nodule-free controls)	US	59	Control Group 0.3 % Solid nodule Group 7.3% HR=23.6(p<0.05) Cyst Group 0.8 % HR=23.6(p>0.05)
Cherno-byl	Hayashi da et al. (2012)	Children	1986-	-	6.0	2009-20 10	160 cases/ 160 controls	US	29.0	Malignancy 1.9% vs 0% (p=0.08)。 Suspicious of malignancy (FNAB) 7.5% vs 0% (p<0.001) -

Source) ibid.

Thyroid Dose Estimates for 10 Years Old (UNSCEAR 2013)

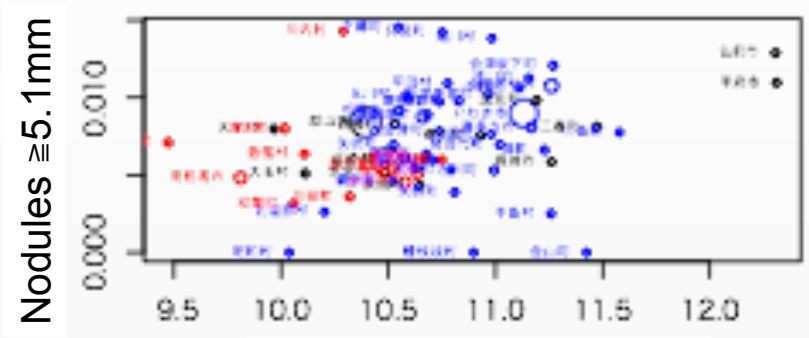


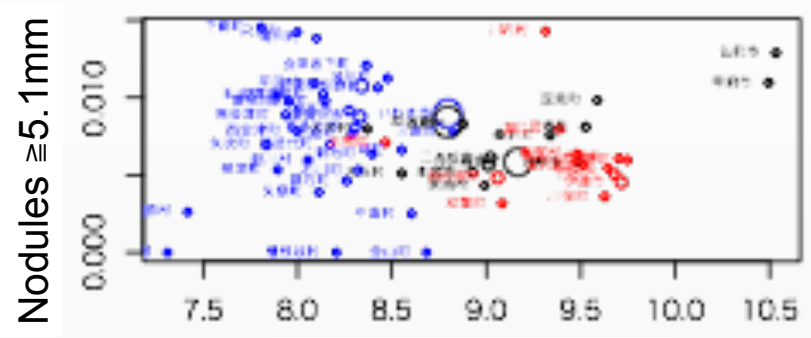
Thyroid Dose and Nodules (≤5mm) for Each Municipality

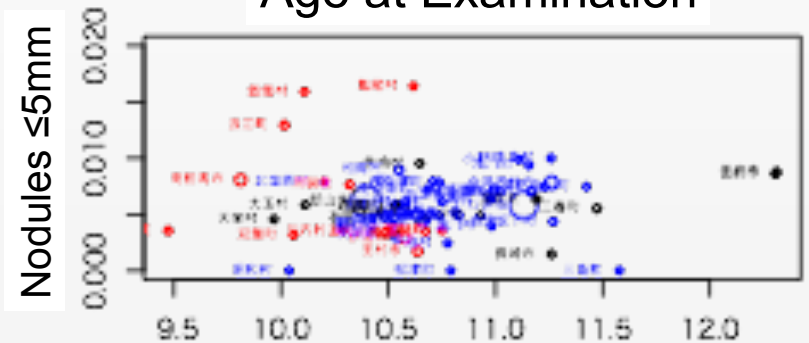


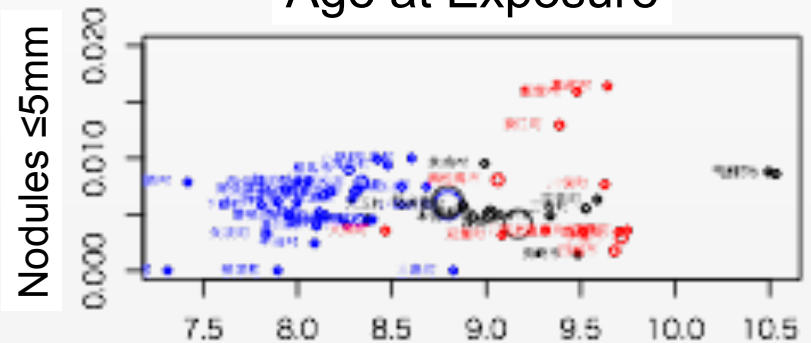
Size of circle is proportional to the number of confirmatory results.

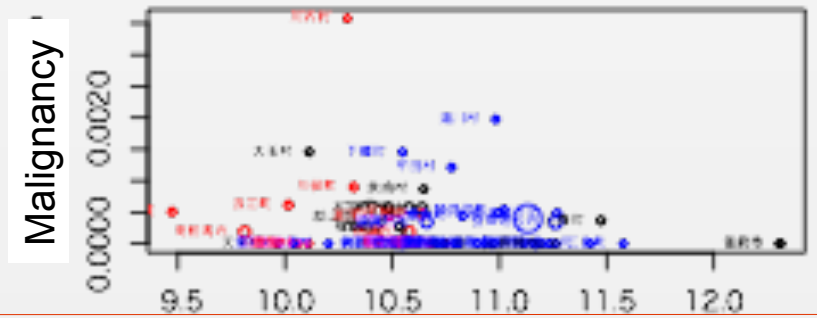
Relationships among Age at Examination, Age at Exposure &, Nodules (≤5, ≧5.1mm) and Malignancy

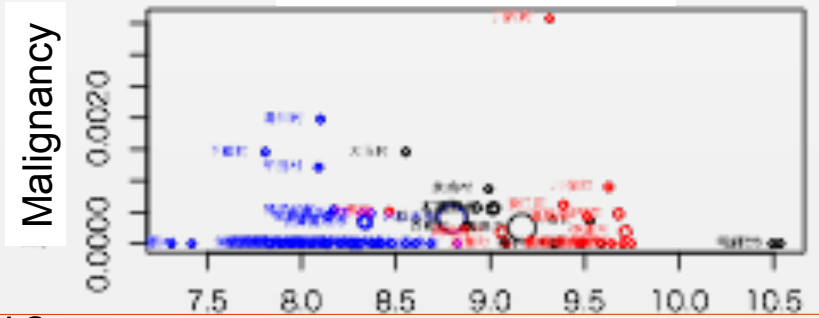












Analysis

- Samples
  - Cities and villages that completed screening between 2011 and 2013 (N=59)
- Poisson regression
  - # of confirmed test results were considered as the offset
- Dependent variables
  - # of nodules with diameter ≤5 mm, ≥5.1 mm, and thyroid cancer (including suspicious cases)
- Explanatory variables (Expected sign)
  - Thyroid Dose (+)
  - Mean age at exposure (−)
  - Mean age at screening (+)

Table 4. Results of Poisson Regression

(a) Nodule ≤5 mm						
	Coeff.	s.e.	t-value	p-value	95% CI	
Intercept	-1.55	0.83	-1.88	0.06*	(-3.17,	0.07)
Age at screening	0.04	0.05	0.74	0.46	(-0.06,	0.13)
Age at exposure	-0.47	0.07	-7.13	0.00***	(-0.60,	-0.34)
Thyroid dose (Sv)	18.76	3.79	4.95	0.00***	(11.33,	26.18)
(2) Nodule ≥5.1 mm						
	Coeff.	s.e.	t-value	p-value	95% CI	
Intercept	-5.44	1.12	-4.85	0.00***	(-7.64,	-3.24)
Age at screening	0.23	0.07	3.36	0.00***	(0.09,	0.36)
Age at exposure	-0.31	0.09	-3.53	0.00***	(-0.48,	-0.14)
Thyroid dose (Sv)	11.45	5.3	2.16	0.03**	(1.06,	21.85)
(c) Nodule (Total)						
	Coeff.	s.e.	t-value	p-value	95% CI	
Intercept	-2.27	0.67	-3.41	0.00***	(-3.57,	-0.96)
Age at screening	0.1	0.04	2.59	0.01***	(0.03,	0.18)
Age at exposure	-0.41	0.05	-7.84	0.00***	(-0.52,	-0.31)
Thyroid dose (Sv)	16.26	3.09	5.27	0.00***	(10.21,	22.31)
(d) Malignancy (including suspicious)						
	Coeff.	s.e.	t-value	p-value	95% CI	
Intercept	-8.03	3.67	-2.19	0.03**	(-15.23,	-0.84)
Age at screening	0	0.22	-0.02	0.99	(-0.44,	0.43)
Age at exposure	-0.03	0.29	-0.09	0.93	(-0.58,	0.53)
Thyroid dose (Sv)	15.9	15.78	1.01	0.31	(-15.03,	46.83)

Significance levels: ***1%, **5%, and *10%

Summary and Discussion (1/2)

- The UNSCEAR thyroid dose had positive and significant coefficients for both smaller and larger nodules.
- Age at screening was positive, and age at exposure was negative, as we expected.
  - For the thyroid dose estimate by WHO (2013) and National Institute of Radiation Science (2012), similar results were obtained. However, for the external dose estimates by Fukushima Basic Survey, the coefficient was insignificant.
  - Reconstruction of dose is necessary.
- They were insignificant for malignancy, due to lack of statistical power to detect differences at prevalence of malignancy of 0.03% with sample size of 59 municipalities.
  - Individual level analysis should be conducted. Case-control study would be efficient.

Summary and Discussion (2/2)

- Although this was an ecological study at the municipality level, our results are consistent with previous studies.
- According to follow up studies of a-bomb (Imaizumi et al 2005) and Chernobyl (Hayashida et al. 2012), nodule group has larger risk of thyroid cancer. Our results might indicate an early warning for future incidence of thyroid cancer.
  - An immediate measure is urgently needed.
- Additionally, insufficient information disclosure caused distrust of the Japanese central and local governments. Proper measurement, timely provision of information, and information disclosure are necessary.

Concluding Remarks

- For Experts
  - Radiation epidemiologists, doctors, and other “experts” seems to lack in knowledge on statistics. As experts, they should learn statistics.
- Data analysis
  - Standard analysis procedure that tabulates individual level data has serious limitations. Re-analysis with individual level data and modeling is necessary to detect lower dose effect.
  - Opening anonymized individual data will be effective to promote research in the field.
- Policy making
  - Policy making on radiation protection needs long time: UNSCEAR reviews and publishes reports every some ten years, ICRP publishes recommendations based on the UNSCEAR reports, and each country government makes policy based on their recommendations (Crick 2011). The base of present recommendation and policy is the UNSCEAR 2006 report that stands on findings of LSS13 (Preston et al.). Reformation of decision making system that can update policy promptly is necessary.
  - Experts and policy makers should understand that UNSCEAR reports, ICRP recommendations, and government policies stand on “old” knowledge. They should review the latest findings and respond promptly with “precautionary principle.”

Acknowledgement

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- Access to nuclear worker data was granted by the US DOE CEDR project. The protocol and results of this study were not reviewed by the DOE. The results and conclusions do not necessarily reflect those of the US Government or DOE.

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