Difficulties in conducting an epidemiological study for endocrine disrupting chemicals

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The 8th International Symposium on Endocrine Disruption in Okinawa, December 4-6

Evidence level of epidemiologic studies

Evidence Level	Study Design	Data collection	Unit	# subjects	Period	Cost
High	**Randomized Controlled Trial**	Pro-spective	Individual	1,000-100,000	10yrs	>$10 mil
↓	**Cohort study/Nested case-control study**	Pro-spective	Individual	10,000-1,000,000	10yrs	$10 mil
	Case-control study	Retro-spective	Individual	100-1000	2-3yrs	$1 mil
	Cross-sectional study	Cross sectional	Individual	100-1000	1yr	<$0.1 m
	Ecological study	Cross sectional	Population	<100 pops	0	0
Low	**Time series**	Cross sectional	Population	One population	0	0
	Expert opinion	-	-	-	-	-

Quality of evidence depends on the *accuracy of exposure measurements*

- Questionnaire vs. Biological marker
  - Quantitative vs. qualitative
  - Category vs. Dose response
  - Questionnaire does not take into account
    - Inter-individual variation in metabolism
    - many exposure pathway
- Measurement error in exposure assessment
  - Validity of EDC in serum/adipose tissue
  - Confounded by endogenous and other exogenous estrogen exposure

Quality of evidence also depends on the *study design*

- Prospective vs. retrospective
  - Selection bias
- Interventional vs. observational
  - Confounder assessment
- Number of high quality studies
  - Consistency of the results

I would rather emphasize the *difficulties in conducting* epi studies

Summary of EDC epi studies Report from MHLW WG for health effects of EDC

- Epidemiological study Searched by PubMed
  - Disease AND human AND
  - (insecticides OR pesticides OR chlorinated hydrocarbons OR pesticides OR chlorinated hydrocarbons OR pcbs OR bisphenol OR phenol OR phthalate OR styrene OR furan OR organotin OR diethylstilbestrol OR ethinyl estradiol)
  - Until 2004.10.31
- Diseases
  - Cancer
    - Breast, endometrium, ovary, prostate, testis, thyroid
  - Other diseases
    - Thyroid, hypospadias, cryptorchidism, child development, sperm count, allergy

List of the studies conducted for diseases and EDC by study design

	Total	Cohort	Nested CaCo	Retro. CaCo	Cross sectional	Eco-logical	For Japanese
Breast	72	8	14	38	6	6	0
Endometrium	2	0	0	2	0	0	0
Ovary	8	3	0	2	0	3	0
Prostate	24	10	3	6	0	5	0
Testis	19	7	0	9	0	3	0
Thyroid	6	3	0	0	0	3	0
hypospadias	8	2	0	6	0	0	0
cryptorchidism	13	1+1	0	11	0	0	0
Child develop.	39	35	0	1	2	1	1
endometriosis	6	0	0	4	2	0	0
Thyroid function	15	2+1	0	1	10	1	2
Sperm count	30	1	1	9	18	1	1
allergy	5	3	0	1	1	0	0

Points to consider 1

- Why are there many ecological studies in cancer but not in other diseases ?
  - Monitoring system for incidence and mortality in population differs among diseases
    - Cancer: incidence from cancer registry, mortality from vital statistics
    - Other diseases: very few diseases have disease registry, vital statistics is no use for nonfatal diseases

Points to consider 2

- Why are cohort studies common ?
  - Exposure of interest is mainly DES or occupational exposure such as pesticide users
  - Retrospective definition of cohort
    - Retrospective definition of exposure, no biological measurements
    - “historical cohort” study
- Why can nested case-control study (=prospective study using stored biological specimen) be done only for cancer ?
  - Use of already existing multipurpose cohort
    - Stored sample, other exposures, and endpoint ascertainment system can be used
    - Example: Nurses’ Health Study

Difficulties in conducting cohort study in Japan

An example from JPHC Study

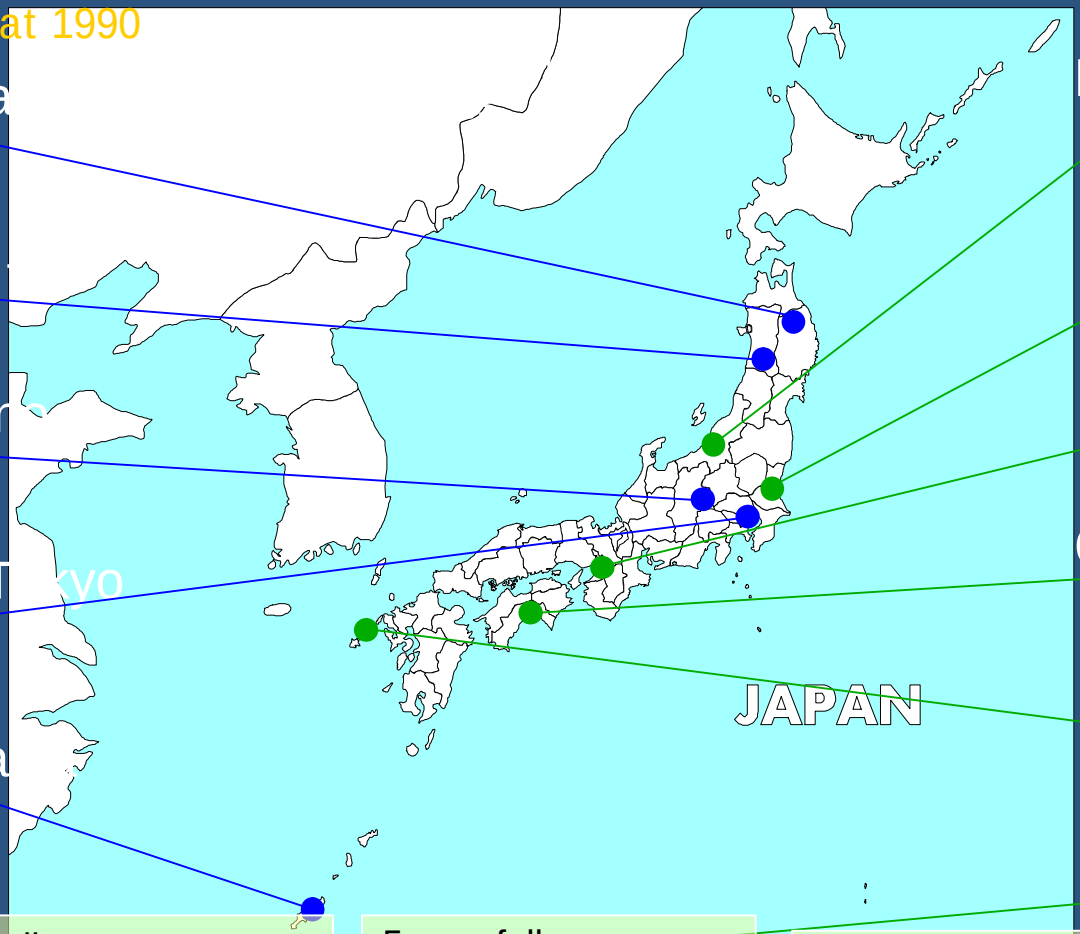
Map of JPHC Study area

Cohort I
All the residents with age 50-69 at 1990

- Ninohe, Iwa (12,291)
- Yokote, Aki (15,782)
- Saku, Nagan (12,219)
- Katsushika, T kyo (7,097)
- Chubu, Okina (14,206)

Cohort II
All the residents with Age 40-69 at 993

- Kashiwazaki, Niigata (3,571)
- Mito, Ibaraki (21,467)
- Suita, Osaka (16,437)
- Chuo-higashi, Kochi (8,606)
- Kamigoto, Nagasaki (14,624)
- Miyako, Okinawa (14,109)



Baseline survey
・questionnaire
・blood, health check-up

5 year follow-up survey
・questionnaire
・blood, health check-up

10 year follow-up survey
・questionnaire

* Public Health Center, Prefecture (# of subjects)

Cohort I: 1990 — 1995 — 2000

Cohort II: 1993 — 1998 — 2003

Self-administered questionnaire - JPHC Study, baseline survey -

- 14 pages color-printed questionnaire
  (Partly modified for Cohort II)
  - ➢Past medical/Family history
  - ➢Smoking and drinking
  - ➢Physical activity
  - ➢Stress and social support
  - ➢Residential / Occupational history
  - ➢Chemical and other environmental exposure
  - ➢Personality
  - ➢Reproductive history
  - ➢Diet
    - ➢44 or 46 food item FFQ
    - ➢4 or 5 frequency categories
    - ➢Some with portion size
- ➢Validation study was done for ~500 subjects

Cohort I (FFQ 44 items)

Cohort II (FFQ 46 items)

Collection of blood samples - JPHC Study, baseline survey -

- 10 ml peripheral blood in heparinized tube
- centrifuged within 12 hours
- 3 tubes (1 ml) for plasma
- 1 tube (1 ml) for buffy layer
- stored at -80 ℃

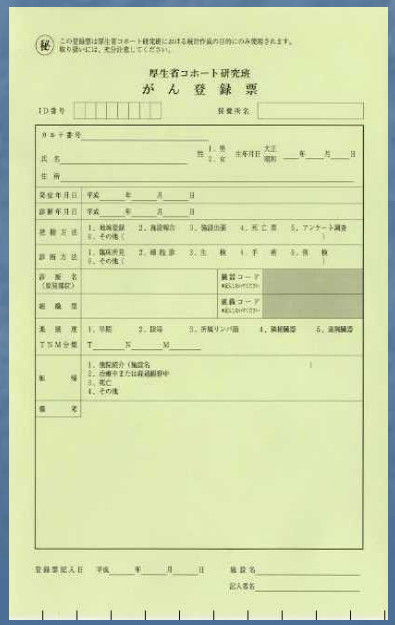
Conduct of questionnaire survey

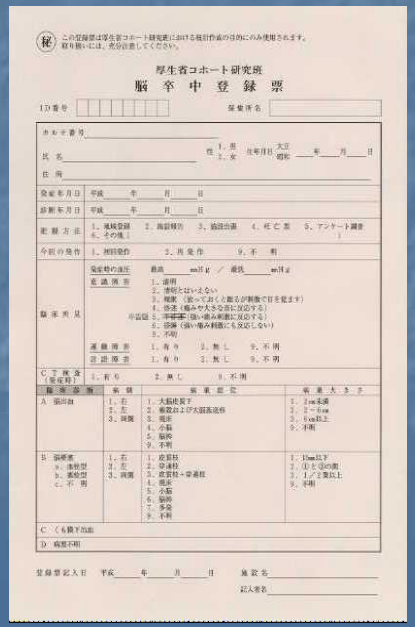
- >80% participation rate for 140,000 subjects
  - Questionnaire delivered to house and collected several days later
  - >1,000 coordinators
- ~35% Participation rate for Blood sampling
  - Collected at the health check-up examination
  - Informed consent and voluntarism in Japanese
- Costly

Events collected during the follow-up

- **Mortality:** Population registry at local municipalities
  Death certificates at public health center
- **Migration:** Population registry at local municipalities
- **Incidence** (cancer, cerebrovascular disease and ischemic heart disease):
  Medical records at local hospitals
  Population-based registry (Prefecture-wide) for cancer

Registration Form for Cancer, CVD, IHD


厚生省コホート研究班
がん登録票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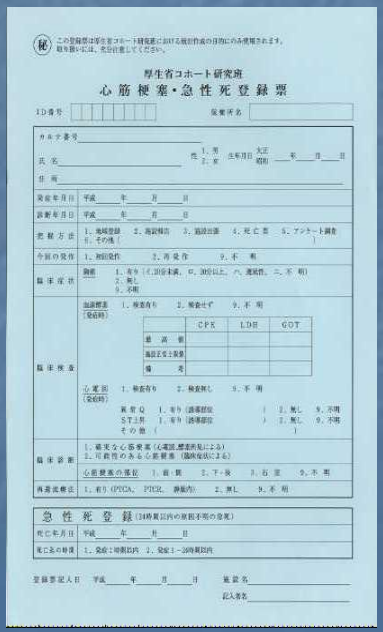
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Difficulties in follow-up ascertainment of diseases

- No good existing source of monitoring diseases
  - Only cancer registry but quality is not so good
- Voluntary report from hospitals
  - No incentives of hospital doctors
- Active collection by hospital visit
  - Many hospitals should be covered in study areas (esp. if Tokyo, Osaka, etc.)
- Self-report is not reliable
  - Poor: cancer, cardiovascular diseases
  - Moderate: Diabetes Mellitus
    - Health check-up exam
  - Good: Cataract

Difficulties in follow-up

- Many resources are needed
  - money, organization, people
- Poor Social understanding for research
  - Privacy protection regulations and informed consent
  - No unique ID such as social security number

Required events and sample size for 10 year follow-up in crude analysis

Rate in the 1st exposure quintile (1/100,000)		Relative Riks in the 5th quintile 1.5	2.0	3.0
1	n	3,979,000	1,225,000	434,000
	# of death	497	184	87
5	n	796,000	245,000	87,000
	# of death	497	184	87
10	n	398,000	123,000	43,000
	# of death	497	184	87
20	n	199,000	61,000	22,000
	# of death	497	184	87
30	n	133,000	41,000	14,000
	# of death	497	184	87
100	n	40,000	12,000	4,000
	# of death	497	184	87

2 sided alpha=0.05 and power=80%

Why few studies conducted in Japan?

- Poor availability of disease monitoring system
- Costly
- Few existing cohort with sufficient cases and biological specimen

Other available designs ?

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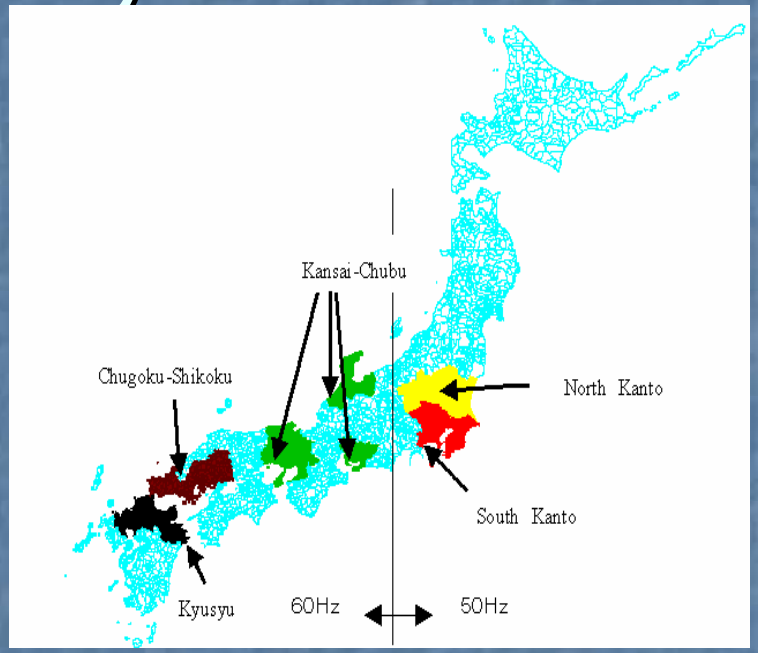
allergy	5	3	0	1	1	0	0

Points to consider 3

- New study is necessary
  - To obtain sufficient biological materials
  - Prospective study takes cost and time
  - evidence level should be as high as possible
- Available design is retrospective case-control study

An example from Childhood leukemia Study

- Objective
  - To investigate the factors related to the incidence of childhood *LK*
- Study design
  - Population-based
  - retrospective case-control study
- Factors of interest
  - Life-style factors and family history
  - Electric Magnetic Field exposure
  - Chemical and other environmental exposure



Kabuto et al. Int J Cancer *(in press)*

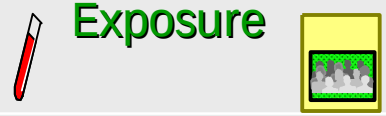
Biggest difficulty: Low participation rate

- 312 cases and 603 controls from all over Japan
  - Originally 500 cases and 3 matched controls were planned
- Case participation rate: 50%
  - Case referrals from childhood leukemia group
  - Accessibility to cases was difficult
  - ~80% participation once referred
- Control participation rate: 30%
  - 10 Control candidates were selected from the resident registration system
    - Handwriting from the list
  - Participation request by Mail
    - ~30% is typical for mail survey
    - 30% cannot rule out selection bias
    - Validation study to prove no selection bias

Retrospective Case-Control study

- Population-based
  - Better but difficult to sample control randomly from the population which case arises
    - Difficulty in identifying source population for cases
    - Difficulty in random sampling
      - List making, rejection to participate in the study
  - Costly to obtain measurements at home
  - Not feasible in Japan
- Hospital-based
  - More feasible but not a random sample from the population which case arises
    - No assurance of randomness
    - Risk of exposure is underestimated if disease of control subjects is associated with the exposure
  - *Feasible in Japan*

Feasible design for new EDC epi study

Historical cohort study		Retrospective case-control study
Drug use/occupational exposure in category	Exposure 	Biological measurements but after diagnosis
Few information	Confounder	Questionnaire but after diagnosis
Same	Population which cases and controls occur	No assurance
Multiple if registry or data is available	Target Diseases	One
~1 year	Research Period	Several years
Several hundreds	# of cases needed	Several hundreds
>\# cases x 100	Number of subjects	# cases x 2-6
<$ million	Cost	$ several million
accuracy of exposure & confounder information	Quality depends on:	selection bias & confounder information

Summary of difficulty and proposal for conducting Prospective study

- Historical cohort study
  - Difficulty depends on collection of incidence data
  - Exposure information may be obtained if past exposure is identified retrospectively such as DES use or occupational exposure
- Nested case-control studies (w/biological specimen)
  - New study is very costly
  - Use of existing cohort studies is practical if it exists
- Collaboration with other epidemiologists is critical

Summary of difficulty and proposal for conducting retrospective study

- Case-control study
  - Population-based case-control studies
    - Impossible if the list of population is not available
    - Low participation rates does not assure no selection bias
  - Hospital-based case-control studies
    - *Most feasible design* but no assurance of no selection bias, i.e. comparability of cases and control
- Collaboration with clinicians is critical

Thank you for your attention!