Late Cancer-Related Health Effects in the General Population

Thyroid Cancer

Dr Ausrele Kesminiene
Environment and Radiation Section

International Agency for Research on Cancer
Lyon, France
outline

• thyroid disease studies for the general population:
  ❖ exposure in childhood and adolescence, including effect modification
  ❖ exposure in adulthood

• summary of findings
• open questions and…
• future plans
introduction

• first reports on thyroid cancer increase after Chernobyl were met with scepticism because:
  - susceptibility of thyroid gland to internal exposure from radioactive iodine was less established, compared to external radiation exposure
  - main evidence came from studies of medically exposed populations with underlying thyroid conditions and limited data on childhood exposure
introduction (2)

• 2008 UNSCEAR reported 6,848 cases of thyroid cancer diagnosed amongst those under 18 y in 1986 between 1991 and 2005 in the whole of Belarus and Ukraine and in the 4 most affected regions of the Russian Federation

• by 2016, more than 11,000 thyroid cancer cases had been diagnosed in this group

http://www.who.int/ionizing_radiation/chernobyl/Chernobyl-update.pdf?ua=1

• It is most likely that a fraction of these is attributable to radiiodine intake in 1986
thyroid doses in children

• average country-specific thyroid doses from Chernobyl in Europe to children aged 1 y at the time of the accident

Drozdovitch et al, 2006
**TC: exposure early in life**

- study jointly led by the US NCI, Institute of Endocrinology and Metabolism (IEM), Ukraine & Republican Research Centre for Radiation Medicine and Human Ecology (RRCRM&HE), Belarus

- recent reports from Belarus:

- recent reports from Ukraine:
  - Brenner et al, EnvHP, 2011
  - Tronko et al, J Radiol Prot 2012

- individuals ≤18y.o. with thyroid radioactivity measured in April-June 1986
  - 38,543 in Belarus
  - subsample of 32,385 in Ukraine
screened cohort study: BelAm & UkrAm

• 4 biennial screening cycles in Ukraine*:
  ❖ 13,243 subjects screened in 1st cycle
  ❖ from 93.8% to 76.9% in the next 3 cycles (between 2001 and 2007)

• 3 screening cycles in 1997-2008 in Belarus*:
  ❖ 11,644 individuals were screened 1st time during 1997-2000
  ❖ two more cycles during 2002-04 and 2004-06 (ext up to 2008)

* 5th cycle completed recently
**by Belarussian decree persons under 18y are recalled annually
screened cohort study: BelAm & UkrAm (2)

- individual doses (and uncertainties) estimated based on:
  - thyroid activity measurement
  - individual data on dietary, lifestyle habits and residential history
  - environmental transfer models

Zablotska et al, 2011

Belarus

Mean dose = 0.56 Gy (s.d. = 1.18)
Min = 0.0005 Gy, Max = 32.80 Gy
Median dose = 0.23 Gy
Nsubjects = 11,611

Ukraine

Mean dose = 0.78 Gy (s.d. = 1.85)
Min = 0 Gy, Max = 47.63 Gy
Median dose = 0.26 Gy
Nsubjects = 13,127

Tronko et al, 2006
TC: dose-response with I-131

Ukraine (Brenner et al, 2011)

ERR/Gy 1.91 (95% CI: 0.43-6.34)

Belarus (Zablotska et al, 2010)

<5Gy: EOR/Gy 2.15 (95% CI: 0.81-5.47)
**TC: latency**

- very early onset (first cases appeared only 3 to 4 years after the accident) was unexpected based on existing knowledge from externally exposed populations*

* Ron et al, 1995; Veiga et al, 2016

**Caution:** the first cases demonstrated very clear clinical symptoms, they were not detected by screening

Photo: http://renaissanceresearch.blogspot.fr/2006_04_01_archive.html
TC: effect modifiers

- age at exposure and gender

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ratio ERR/Gy girls/boys</th>
<th>Age at exposure effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardis et al, 2005</td>
<td>0.9</td>
<td>NA</td>
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<tr>
<td></td>
<td>(p=0.9)</td>
<td></td>
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<tr>
<td>Kopecky et al, 2006</td>
<td>NA</td>
<td>No monotone trend with increasing age; (p=0.7)</td>
</tr>
<tr>
<td>Tronko et al, 2006</td>
<td>7.5</td>
<td>ERR decreased with increasing age at exposure; (p=0.6)</td>
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<td></td>
<td>(p=0.14)</td>
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</tr>
<tr>
<td>Brenner et al, 2011</td>
<td>2.2</td>
<td>ERR decreased with increasing age at exposure; (p=0.4)</td>
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<tr>
<td></td>
<td>(p=0.9)</td>
<td></td>
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<tr>
<td>Zablotska et al, 2010</td>
<td>3.0</td>
<td>No significant effect of age at exposure; (p=0.9)</td>
</tr>
<tr>
<td></td>
<td>(p=0.13)</td>
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<tr>
<td>Ron et al, 1995</td>
<td>2</td>
<td>ERR decreased with increasing age at exposure; (p=0.004)</td>
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<tr>
<td></td>
<td>(p=0.07)</td>
<td></td>
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<tr>
<td>Veiga et al, 2016</td>
<td>0.8</td>
<td>ERR varied significantly with age at exposure; (p=0.001)</td>
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<tr>
<td></td>
<td>(p=0.37)</td>
<td></td>
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</tbody>
</table>

- effect of gender not clear because most of TC diagnosed at very young age (mean age ATD-11.7) (Demidchik et al 2006)

Overall, risk decreases with increasing age at exposure although trends are not always significant or monotonous.
TC: effect modifiers (2)

- risk pattern over time

- I-131-related risk persisted more than 20 y after exposure, with no evidence of decrease

Demidchik, Saenko and Yamashita, 2007
Brenner et al, 2011
TC: effect modifiers (3)

- iodine deficiency and iodine supplementation

<table>
<thead>
<tr>
<th>Consumption of potassium iodide</th>
<th>OR at 1 Gy (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Highest two tertiles of soil iodine</td>
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<tr>
<td>No</td>
<td>3.5 (1.8 to 7.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.1 (0.3 to 3.6)</td>
</tr>
</tbody>
</table>

Cardis et al, 2005

- in Belarus, diffuse goitre and thyroid enlargement were modifiers of TC risk (Zablotska et al, 2010)
- in Ukraine, data not strong enough to support a modifying effect of iodine deficiency (Brenner et al, 2011)
- indicators of past stable iodine intake are difficult to reconstruct
TC: role of uncertainties in dose estimates on risk

• relatively small contribution of unshared classical dose error

• effects of adjusting for dose error were minimal, resulting in changes to risk estimates:
  ❖ in Ukraine between -11% and +7% (Little et al., 2014)
  ❖ In Belarus between -23% and -2% (depending on the method) (Little et al., 2015)

• new effort to characterise uncertainties in doses and their role on risk estimate in the IARC c-c study
non-malignant thyroid diseases
BelAm and UkrAm studies

• follicular adenoma:
  ❖ in Ukraine (Zablotska et al, 2008) n=23:
    ✓ ERR/Gy 2.07 (95%CI: 0.28, 10.31)
    ✓ risk higher in women
  ❖ in Belarus (Zablotska et al, 2015) n=38:
    ✓ ERR/Gy 2.22 (95% CI: 0.41, 13.1)
    ✓ similar in males and females

• hyperthyroidism (Hatch et al, 2010):
  ❖ In Ukraine: n=76; no dose-response relationship

• autoimmune thyroiditis (AIT) (Tronko et al, 2008):
  ❖ in Ukraine: no dose-response relationship for AIT;
significant association between elevated ATPO levels and $^{131}$I
TC: exposure in adulthood

• recent studies of residents of contaminated territories >18 y at the time of accident:
  ❖ ecological study in Ukraine compared TC incidence rates – between high and low exposure regions in 1989-2007 (Fuzik et al, 2011)
  ❖ incidence rate ratios in females was significantly higher in high exposure regions in those exposed at ages of 20–49 years, in males, this tendency was less clear

(Fuzik et al, 2011)
TC: exposure in adulthood (2)

• in Russia (Ivanov et al, 2012):
  - TC incidence in the contaminated territories of Bryansk, Kaluga, Oryol and Tula evaluated in 1991-2008
  - no dose-response relationship found in exposed adults based on average residential doses

• caution:
  - possible surveillance bias
  - no individual dosimetry, doses intend to be low

• In Finland (Auvinen et al, 2013):
  - cancer incidence data obtained for 1988-2007 for the cohort divided into 4 exposure categories (the lowest <0.1 mSv and the highest 0.5 mSv)
  - weak, non-significant positive relation was observed in females

• No convincing evidence of effect of exposure as an adult
**TC: risks after exposure in childhood and adolescence**

**Summary of most informative analytical studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ascertainment period</th>
<th>Number of cases</th>
<th>Number of controls/size of study population/PY</th>
<th>ERR* at 1 Gy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chernobyl studies</strong></td>
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<td><em>Case-control studies</em></td>
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<tr>
<td>Astakhova <em>et al</em>, 1998</td>
<td>1988-1992</td>
<td>107</td>
<td>214</td>
<td>OR &gt;=1 Gy vs. &lt;0.3Gy:</td>
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<td></td>
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<td></td>
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<td>5.0 (1.5-16.7) to</td>
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<td></td>
<td></td>
<td></td>
<td>5.8 (2.0-17.3)</td>
</tr>
<tr>
<td>Cardis <em>et al</em>, 2005</td>
<td>1992-1998</td>
<td>276</td>
<td>1,300</td>
<td>4.5 (2.1-8.5) to</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>7.4 (3.1-16.3)</td>
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<tr>
<td><strong>Screened cohort study</strong></td>
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<td></td>
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<tr>
<td>Tronko <em>et al</em>, 2006</td>
<td>1998-2000</td>
<td>45</td>
<td>13,127</td>
<td>5.25 (1.7-25.5)</td>
</tr>
<tr>
<td>Brenner <em>et al</em>, 2011</td>
<td>2001-2007</td>
<td>65</td>
<td>12,514</td>
<td>1.91 (0.43–6.34)</td>
</tr>
<tr>
<td>Zablotska <em>et al</em>, 2010</td>
<td>1996-2004</td>
<td>133</td>
<td>11,611</td>
<td>3.16 (1.49 – 6.95)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.15 (0.81 - 5.47)</td>
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<td><strong>Exposure in utero</strong></td>
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<tr>
<td>Hatch <em>et al</em>, 2009</td>
<td>2003-2006</td>
<td>7</td>
<td>2,582</td>
<td>11.7 (NE – 1,982)</td>
</tr>
<tr>
<td><strong>External exposures - Pooled analyses</strong></td>
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<tr>
<td>Ron <em>et al</em>, 1995</td>
<td>458</td>
<td></td>
<td>1,400,000 PY</td>
<td>7.7 (2.1-28.7)</td>
</tr>
<tr>
<td>Veiga <em>et al</em>, 2016</td>
<td>927</td>
<td></td>
<td>3,400,000 PY</td>
<td>5.5 (4.1–7.5)</td>
</tr>
</tbody>
</table>

*ERR=excess relative risk*
TC and screening

• effect of large scale screening efforts in contaminated areas:
  ❖ *absolute rate of thyroid cancer increases in a screened population*
  ❖ *ERR estimate can be biased upward, if there is a correlation between thyroid dose and frequency of screening*
  ❖ BelAm and UkrAm cohort studies provided an estimate of the risk where confounding effect of screening is unlikely (all subjects were screened, regardless of dose)

• however:
  ❖ whether the detection of additional small thyroid cancers affects the excess radiation risks
  ❖ whether these small tumours are induced by radiation to the same extent as large tumours
**worldwide: rise in thyroid cancer incidence**

- estimated number of cases attributable to increased thyroid-gland surveillance:
  - in women:
    - 90% in South Korea;
    - 50% in Japan
  - in men:
    - 70% in South Korea;
    - less than 25% in Japan

"careful data interpretation needed in the context of screening after radiation exposure"

Vaccarella *et al*, 2016
from Chernobyl to Fukushima

• subtask 1.2: Critical review of long-term medical surveillance programmes

  to provide a set of lessons learned from medical surveillance on physical and mental health of populations exposed to fallout from the Chernobyl and Fukushima accidents

  recommendations for setting up criteria to:
  – justify long-term medical surveillance programmes of affected populations
  – evaluate their effectiveness
summary

• risks following exposure to I-131 are somewhat smaller, but compatible with estimates from external irradiation

• latency period less than 5 years

• sensitivity to I-131 in children is much greater compared to adults

• I-131-related risk persists nearly 3 decades after Chernobyl accident

• most of observed thyroid malignancies are papillary carcinomas
there is more to be learned…

• about the impact of:
  ❖ gender,
  ❖ age at exposure, including in adulthood,
  ❖ stable iodine intake
  ❖ increased surveillance
  ❖ uncertainties in doses on risk estimates…

• there is a need for studies to better understand natural history of thyroid cancer (progression and regression of thyroid tumours over life span)

• importance of international cooperation in science is explicitly recognised and has been proven after Chernobyl
CO-CHER: setting the scene for future research on Chernobyl

- development of a long-term research programme with agreed research priorities
- Chernobyl Research Programme highlights:
  - establishment of Chernobyl Life Span cohort
  - convening a multinational body - International Chernobyl Research Committee
  - conducting prioritized multidisciplinary studies
  - more info: http://co-cher.iarc.fr/
Thank you!