Non-Malignant Thyroid Diseases Following a Wide Range of Radiation Exposures

Elaine Ron
Alina Brenner

Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiologic Divide
May 4-6, 2009
Outline

• A little thyroid gland biology

• Radiation effects
  – Nodules
  – Hyperthyroidism
  – Hypothyroidism
  – Autoimmune thyroiditis or elevated levels of antibodies

• Conclusions
Thyroid Gland

- Makes and stores thyroid hormones
- Thyroid hormones instrumental in regulating growth, metabolism, reproduction, tissue function
Thyroid Gland

- Radiation effects first reported in 1920s
- 1950s clinical observations of association between external radiation and thyroid cancer
- One of the most radiosensitive organs
- Strong linear radiation dose response for cancer especially after childhood exposure
- Limited information on radiation and other thyroid diseases
Thyroid Diseases

**Structural**
- Tumors
  - Malignant
  - Benign
- Nodules
  - Hyperplastic*
  - Cyst
- Thyroid enlargement

**Functional**
- Hyperthyroidism
- Hypothyroidism
- Autoimmune thyroiditis
- Elevated levels of antibodies

*Includes nodular goiter
Thyroid Nodule Diagnosis in Transition

- Cancer is a very small proportion of nodules.
- In past, follicular adenomas defined as benign tumors and most other nodules not considered neoplastic.
- Recently, definition of benign nodules reconsidered based on clonal origin.
- Difficult to make differential diagnosis, so many studies combine all benign nodules.

*Eszlinger et al. JCEM, 2008*
Data Sources

• **Medical**
  – Children treated with radiation for benign diseases
  – Children and adults treated with radiation for cancer

• **Environmental**
  – Chernobyl
  – Nevada and Kazakhstan test sites
  – Hanford and Mayak nuclear weapons facilities
  – Marshall Islanders

• **Atomic bomb survivors (AHS)**
Thyroid Nodules
# Lower Risks for Follicular Adenoma Versus Thyroid Cancer

## Tinea Capitis Patients

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cases</th>
<th>$\text{ERR}_{\text{Gy}}$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>159</td>
<td>20 (12, 32)</td>
</tr>
<tr>
<td>Follicular adenoma*</td>
<td>42</td>
<td>8 (7, 10)</td>
</tr>
</tbody>
</table>

**Ratio:** malignant/benign = 2.5

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## Ukraine-NCI Chernobyl Screening Study

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cases</th>
<th>$\text{ERR}_{\text{Gy}}$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>45</td>
<td>5.25 (1.7, 27)</td>
</tr>
<tr>
<td>Follicular adenoma*</td>
<td>23</td>
<td>2.07 (0.3, 10)</td>
</tr>
</tbody>
</table>

**Ratio:** malignant/benign = 2.5

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*Based on pathology review of tumor tissue*

- Sadetzki et al. JECD, 2006
- Ron et al. Rad Res, 1989
- Tronko et al. JNCI, 2006
- Zablotska et al. AJE, 2008
But, for total nodules less clear

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Cases</th>
<th>$EOR_{Sv}$ (95% CI)</th>
<th>$ERR_{Gy}$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>70</td>
<td>1.95 (0.67, 4.9)</td>
<td>3.0 (0.1, 4.0)</td>
</tr>
<tr>
<td>Benign nodules*</td>
<td>156</td>
<td>1.53 (0.76, 2.7)</td>
<td>8.0 (0.3, 3.7)</td>
</tr>
</tbody>
</table>

Ratio: malignant/benign = 1.28

Ratio: malignant/benign = 0.38

*includes follicular adenoma and other nodules

Imaizumi et al. JAMA, 2006

Schneider et al. JECM, 1993
Nodules Associated with High-Dose Radiotherapy for Childhood Hodgkin Disease

- Thyroid doses ten’s of Gy (Mantle field)
- 20-40% risk of developing thyroid nodules
- Based on small numbers
  - Risk of radiation-related benign nodule slightly lower than for malignant
  - Age, gender and follow-up patterns similar to cancer patterns

Von der Weid. Support Care Cancer, 2008
Nodules Associated with High-Dose Radiotherapy for Childhood Hodgkin Disease

• Study population
  – 146 patients who developed nodules among 1,791 members of CCSS
  – 79% had radiotherapy
  – median thyroid dose, 35 Gy; maximum 55 Gy

• Relative Risks
  – compared to siblings = 27 ($P <0.001$)
  – at $\geq 25$ Gy = 2.9 (1.4, 6.9)

Sklar et al. JECD, 2000
# Thyroid Nodules and Radioactive Iodine Exposure from Fallout

## Nevada Weapons Test Site
- 2500 study subjects
- Mean dose 120 mGy
- Benign tumors (n=15)
  \[ \text{ERR}_{Gy} \text{ not estimated, } P_{trend} \leq 0.001 \]
- Total nodules (n=54)
  \[ \text{ERR}_{Gy} = 4.65; (CI 1.1, 12.3) \]

## Semipalatinsk Weapons Test Site
- 3000 study subjects
- Mean dose: 40 mGy external; 300 mGy internal
- Total nodules (n=916) increased with dose, \( P_{trend} \leq 0.001 \)
- \( \text{EOR}_{Gy} = 0.74 \text{ (CI 0.22, 1.24)} \)

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*Lyon et al. Epidemiol, 2006*  
*Land et al. Radiat Res, 2008*
Benign Nodules and Environmental I-131

• Marshall Islands fallout
  – High doses on Rongelap, Ailinginae and Utrik
    • Clear increase of nodules
  – Low doses on other islands
    • Results inconsistent and not well quantified
    • Inverse relationship - nodules and distance from test site (Hamilton et al 1987)
    • Positive relationship - nodules and distance from test site (Takahashi et al 2001)

• Ozyorsk (Mushkacheva et al 2006)
  – Nodules (n=165); RR= 1.4 (CI 1.0, 1.9)

• Hanford Nuclear Site (Davis et al 2004)
  – Nodules (n=249); ERR_{Gy} = -0.008 (CI <-0.02, 0.04)
Functional Thyroid Diseases

• Excess or deficit of blood levels of thyroid hormones (T4, T3, TSH) alone or in combination

• Can occur in association with thyroid nodules
Hyperthyroidism Following High-Dose Radiotherapy

• Overactive thyroid
  – Thyroid produces too much thyroxine (T4)
  – Pituitary produces too little TSH

• Relatively rare

• Reported infrequently following radiotherapy for Hodgkin disease in adults, adolescents and children

• Most studies small and do not have individual doses
Hyperthyroidism

Atomic Bomb Survivors (AHS)

4091 survivors
51 cases

P = 0.10

CCSS
Probability of developing hyperthyroidism by dose

1791 survivors, 2808 siblings
82 cases; 13 control cases
RR = 8.0 (4.6, 15)

Imaizumi et al. JAMA, 2006

Sklar et al. JCEM, 2000
Hypothyroidism

• Underactive thyroid
  – Thyroid doesn't produce enough thyroxine (T4)
  – Pituitary produces too much TSH in an attempt to compensate

• Most common thyroid disease
  – Overt (low T4, normal TSH) - requires treatment
  – Subclinical (high TSH, normal T4) - sometimes treated

• A known late effect of high-dose exposure

• Effects after low or moderate doses less clear
  – Lack of individual doses
  – Study design
Hypothyroidism following High-Dose Radiotherapy in Childhood

- 1,791 members of CCSS; 2808 siblings
- 456 CCSS cases; 39 control cases
- RR = 17.1 (12, 24), p<0.0001

Sklar et al. JCEM, 2000

Probability of developing hypothyroidism by thyroid dose
Mild Hypothyroidism and I-131 Dose from Chernobyl Accident

Ukraine-NCI Thyroid Screening Study

- 11,853 people <18 yrs at accident
- Individual thyroid measurements;
  - mean thyroid dose = 0.79 Gy; range, 0-40.7
- Clinical exam including lab tests
- 719 cases with hypothyroidism
  - TSH > 4 mIU/L
- Significant relation between prevalence of hypothyroidism and $^{131}$I dose from environmental exposure

Ostroumova et al. EHP, in press

See Poster by M. Hatch
Hypothyroidism

**Definite Effect**
- Irradiated cancer patients
- I-131 treated hyperthyroid patients
- Marshall Islanders

**Possible Effect**
- Chernobyl residents
- Nevada Test Site
- Atomic bomb survivors (AHS)

**No Effect**
- Hanford
Autoimmune Thyroiditis (AIT)

- Relatively common
- Even a weak relationship with I-131 may result in significant morbidity
  - hormone replacement to treat thyroid failure or prevent cardiovascular complications
  - could increase risk of thyroid cancer
- Various clinical manifestations and degree of thyroid dysfunction
- No internationally accepted classification
  - High thyroid antibodies, ATPO $\geq 250$ U/ml
  - High thyrotropin, TSH $\geq 10.0$ mIU/L
  - Ultrasound, heterogeneous and hypoechoic
# Prevalence of AIT and I-131 Dose
## Ukraine-NCI Screening Study

<table>
<thead>
<tr>
<th>AIT</th>
<th>Thyroid dose, Gy</th>
<th>Cases</th>
<th>Non-cases</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.14</td>
<td>65</td>
<td>3,938</td>
<td>1.0</td>
<td>0.8, 1.7</td>
</tr>
<tr>
<td></td>
<td>0.14-</td>
<td>50</td>
<td>2,776</td>
<td>1.1</td>
<td>0.8, 1.9</td>
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<tr>
<td></td>
<td>0.34-</td>
<td>41</td>
<td>1,906</td>
<td>1.3</td>
<td>0.7, 2.2</td>
</tr>
<tr>
<td></td>
<td>0.66-</td>
<td>14</td>
<td>812</td>
<td>1.2</td>
<td>0.6, 2.0</td>
</tr>
<tr>
<td></td>
<td>0.96-</td>
<td>10</td>
<td>727</td>
<td>1.1</td>
<td>0.4, 1.5</td>
</tr>
<tr>
<td></td>
<td>1.5-</td>
<td>15</td>
<td>998</td>
<td>0.7</td>
<td>0.4, 1.9</td>
</tr>
<tr>
<td></td>
<td>3+</td>
<td>9</td>
<td>530</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for family history of thyroid disease, smoking, thyroid volume, presence of nodules, serum Tg, sex and age

Tronko et al. JCEM, 2006
# Anti-Thyroid Antibodies

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Subjects</th>
<th>End points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utah, Nevada, Arizona</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kerber et al, 1993</td>
<td>2,473</td>
<td>AMA, ATG, TSH</td>
<td>Null</td>
</tr>
<tr>
<td>Lyon et al, 2005</td>
<td>2,497</td>
<td>AMA, ATG, TSH</td>
<td>Positive</td>
</tr>
<tr>
<td>A-bomb survivors (AHS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagataki et al, 1994</td>
<td>2,587</td>
<td>AMA, ATG, TSH</td>
<td>Positive</td>
</tr>
<tr>
<td>Imaizumi et al, 2006</td>
<td>4,091</td>
<td>ATPO, ATG, TSH</td>
<td>Null</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takashi et al, 1999*</td>
<td>4,766</td>
<td>AMA, ATG, TSH</td>
<td>Null</td>
</tr>
<tr>
<td>Hanford</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis et al, 2004</td>
<td>3,440</td>
<td>AMA or ATPO,</td>
<td>Null</td>
</tr>
<tr>
<td>Western Pomerania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltzke et al, 2005*</td>
<td>4,299</td>
<td>ATPO, US</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*No individual doses
Prevalence of ATPO and I-131 Dose
Ukraine-NCI Screening Study

ATPO positively related to dose

- Dose response consistent with linear-exponential or power model
- Dose response not driven solely by people with high ATPO levels
- ATPO dose response not due to other thyroid disorders

Tronko et al. JCEM, 2006
Mechanisms for Radiation-Induced Thyroid Nodules

• Thyroid cancer
  – Papillary: chromosomal rearrangements
  – Follicular: point mutations

• Benign Nodules
  – Mechanism unknown
  – Speculation: nodules often have a follicular component, so possibly point mutations involved
Mechanisms for Radiation-Induced Thyroid Dysfunction

- Direct thyroid cell injury or death
- Prevention of cell division
- Immune-mediated damage
- Inflammatory reaction
- Damage to small thyroid vessels and gland capsule
Conclusions

Significant dose-response for benign nodules

- Dose-response appears to be linear
- May be somewhat weaker than for malignant tumors
- Age and latency patterns similar
Conclusions

• Data on hyperthyroidism sparse, but suggestion of an elevated risk in a few high-dose radiotherapy studies

• Overt hypothyroidism observed after high-dose radiotherapy; dose-response relation

• Subclinical hypothyroidism, autoimmune thyroiditis and/or elevated ATPO may occur at lower doses, but
  – Results are inconsistent
  – Shape of the dose response is unclear
  – Some of the effects may be transient

• Data not sufficient to describe effect modification for any outcome