Second Cancer

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DISCLOSURES

• No financial interest

From epidemiology to clinic to basic science
Definitions & Basics

- Histologically unrelated cancer
- SMN: second malignant neoplasm
- Second cancer can be genetic
- Shared carcinogens
- Random
- Transformation \textit{low grade} $\rightarrow$ \textit{high grade}
- Second cancer can be treatment related
- Combination of all of these factors
Cancer Statistics

Cancer is a frequent disease ….
Cancer Statistics

![Graph showing incidence of cancer and major cardiovascular disease by age group](source: BMJ © 2008 BMJ Publishing Group Ltd)
Second Cancers- Historic Perspective

Lung Cancer in Chronic Leukemia and Lymphoma

Herman I. Libshitz, M.D., Jesus Zornoza, M.D., and Jerry W. McLarty, Ph.D.

Review of the number of lung cancers subsequently developing in patients with chronic leukemia or lymphoma revealed a statistically significant (p < .001) increase in the incidence of lung cancer in these patients. Of 684 patients with chronic leukemia seen between 1961 and 1972 (followed through 1976), 19 developed lung cancer versus 3 expected cases. Of 2708 patients with lymphoma seen in the same period, 23 developed lung cancer versus 7 expected cases. These data indicate that lung cancer be given serious consideration when a new pulmonary lesion is noted in these patients, and biopsy may be warranted.

INDEX TERMS: Leukemia, complications and sequelae • Lung neoplasms, diagnosis • Lymphoma • (Skeletal system, leukemia or lymphoma, 400.340)

Radiology 127:297–300, May 1978
Some Cancers Are Preventable …

Annual Number of Cancer Deaths Attributable to Smoking by Sex and Site, US, 2000-2004

Second Cancers Are Not Rare

Nine SEER registries, Morton LM et al, 2014 ASCO Educational Book, 19% of all individuals with cancer have a history of cancer
Overview of this Presentation ....

• A) Second cancers as part of inherited cancer syndromes
• B) Second cancers (SMNs) in Hodgkin’s lymphoma, head & neck cancer, and 3 other malignancies
• C) SMNs after allogeneic stem cell transplantation
• D) Prognosis of SMNs
• E) Outlook on basic research, t-AML
• F) Recommendations
Inherited Cancer and Cancer Predisposition Syndromes, a few examples…

- Li-Fraumeni
- Fanconi anemia (inherited aplastic anemia, risk of leukemia and solid tumors, especially HNSCCs)
- Inherited Breast and Ovarian Cancer
- Retinoblastoma (mutation of Rb gene, inherited form: increased incidence of osteosarcoma)
- Multiple Endocrine Neoplasia
- Von-Hippel-Lindau Disease (inherited, autosomal dominant syndrome, RCC + various other tumors, e.g. neuroendocrine tumors of pancreas)
Example for Inherited Cancer: Li-Fraumeni Syndrome

- Autosomal dominant, described 1969
- Rare, 450 families described
- Development of soft tissue and bone sarcomas, premenopausal breast cancer, glioblastoma, leukemia, adrenocortical carcinoma …
- Life-time risk of cancer 75% in men, 100% in women
- 50- 77% of patients with LFS have identifiable mutations in TP53 tumor suppressor gene, 7-10 % new mutations
- In p53-mutation negative families, CHEK2 mutations were found
- TP53 transcription factor, accumulates in response to DNA damage or other cellular stress
- Abnormal TP53 -> production of aberrant proteins -> cell cycle continues
Case report (Leukemia 2006; 20: 734): 53 y.o. female, history of breast cancer, 3 soft tissue sarcomas, anal carcinoma, now AML, son had died at age 12 from AML, same mutation in exon 8, codon 290

Pathomechanism: LFS-associated p53 mutants exert transdominant loss of function on wild-type protein
Cases of Li-Fraumeni Σ occur in all ethnicities, but some presentations are atypical …
B1) SMN in Hodgkin’s Lymphoma

• “Price of Success” (Boice 1993)
• First described in 60s, significant problem for survivors
• It was estimated that 10 or 15 years after successful treatment for HL, the risk of dying from other causes is > dying from relapse of HL

Stanford data base
B1) SMN in Hodgkin’s Lymphoma

- MUNICH STUDY ON SMN
B1) SMN in Hodgkin’s Lymphoma

- **MUNICH STUDY ON SMN**

  ![Graph showing incidence at 15 years]

  **Incidences at 15 years:**
  - All SMN: 11.7%
  - Solid tumors: 7.7%
  - NHLs: 3.0%
  - Leukemias: 1.0%
## B1) SMN in Hodgkin’s Lymphoma

**MUNICH STUDY ON SMN**

### Table 2: Relative risk of second malignancy after Hodgkin’s disease (P-Y person-years)

<table>
<thead>
<tr>
<th>Type of second cancer</th>
<th>No. of cases observed/expected</th>
<th>Relative risk (95% C.I.)</th>
<th>Absolute risk per 10,000 P-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SMs</td>
<td>85/27.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.1 (2.6–3.7)</td>
<td>56.6</td>
</tr>
<tr>
<td>Leukemias</td>
<td>8/0.4</td>
<td>20.5 (10.3–37.4)</td>
<td>7.4</td>
</tr>
<tr>
<td>(6 AML, 2 CML)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>22/0.8</td>
<td>25.9 (17.6–37.2)</td>
<td>20.7</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>2/0.3</td>
<td>7.4 (1.3–24.1)</td>
<td>1.7</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>53/29.9</td>
<td>1.8 (1.4–2.3)</td>
<td>22.6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>9/3.8</td>
<td>2.4 (1.3–4.2)</td>
<td>5.1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4/0.2</td>
<td>20.0 (6.9–46.8)</td>
<td>3.7</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>6/3.8</td>
<td>1.6 (0.7–3.2)</td>
<td>2.2</td>
</tr>
<tr>
<td>Genitourinary c.</td>
<td>9/5.9</td>
<td>1.5 (0.8–2.6)</td>
<td>3.0</td>
</tr>
<tr>
<td>Head and neck c.</td>
<td>4/1.4</td>
<td>2.8 (1.0–6.5)</td>
<td>2.5</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>2/0.5</td>
<td>4.0 (0.7–13.1)</td>
<td>1.5</td>
</tr>
<tr>
<td>Malign. melanoma</td>
<td>2/0.8</td>
<td>2.5 (0.4–8.2)</td>
<td>1.2</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>10/3.6</td>
<td>2.8 (1.5–4.8)</td>
<td>6.3</td>
</tr>
<tr>
<td>Other cancers</td>
<td>7/N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excluding cases of HD and basal cell cancer in the reference population

26 citations
### B1) SMN in Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patients</th>
<th>Median Age at Dx</th>
<th>Country</th>
<th>Cumulative Incidence (%)</th>
<th>Time of follow-up (years)</th>
<th>Relative Risk **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Leeuwen et al</td>
<td>1994</td>
<td>1,939</td>
<td>34</td>
<td>Netherlands</td>
<td>20</td>
<td>20</td>
<td>3.5</td>
</tr>
<tr>
<td>Munker et al</td>
<td>1999</td>
<td>1,120</td>
<td>34.2</td>
<td>Germany</td>
<td>12</td>
<td>14</td>
<td>3.1</td>
</tr>
<tr>
<td>Swerdlow et al</td>
<td>2000</td>
<td>5,519</td>
<td>30</td>
<td>Great Britain</td>
<td>n.r.</td>
<td>n.r.</td>
<td>2.9</td>
</tr>
<tr>
<td>Ng et al</td>
<td>2002</td>
<td>1,319</td>
<td>25</td>
<td>USA</td>
<td>23</td>
<td>20</td>
<td>4.6</td>
</tr>
<tr>
<td>Foss Abrahamsham et al</td>
<td>2002</td>
<td>1,024</td>
<td>40</td>
<td>Norway</td>
<td>19</td>
<td>28</td>
<td>3.5</td>
</tr>
<tr>
<td>Constine et al</td>
<td>2008</td>
<td>930</td>
<td>13.6</td>
<td>USA</td>
<td>19</td>
<td>25</td>
<td>14.2</td>
</tr>
<tr>
<td>Engert et al</td>
<td>2009</td>
<td>1,196</td>
<td>32.3</td>
<td>Germany</td>
<td>7</td>
<td>10</td>
<td>n.r.</td>
</tr>
<tr>
<td>O’ Brien et al</td>
<td>2010</td>
<td>112</td>
<td>12.9</td>
<td>USA</td>
<td>17</td>
<td>20</td>
<td>22.9</td>
</tr>
<tr>
<td>Schaapveld et al</td>
<td>2015</td>
<td>3905</td>
<td>15-50</td>
<td>Netherlands</td>
<td>48</td>
<td>40</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* For cumul. incidence; ** compared with general population
Second Cancer Risk Up to 40 Years after Treatment for Hodgkin’s Lymphoma

Figure 2. Cumulative Incidence of Subsequent Malignant Neoplasms, According to Treatment Period, with Death as a Competing Risk. Solid lines represent the observed incidence, and dashed lines the expected incidence in the general population. The insets show the same data on enlarged y axes.
B2) SMN following Testicular Cancer

- Highly curable, 5 year survival 95%
- International Study based on 40,576 patients
- (Travis et al, J Natl Cancer Inst, 2005)
- 10 year survivors (20,984 patients)
- Statistically increased risks observed for malignant melanoma, cancers of lung \((1.5)\), thyroid, esophagus, pleura, stomach \((4.0)\), pancreas, colon, rectum, kidney, bladder, connective tissue \((4.0)\) (RR)
- Life time-risk of SMN (35 + 40 years)
- Seminomas: 36%, non-seminomas: 31%
B3) SMN following Head and Neck Cancer


Cumulative Overall Survival (OS) 38.7% at 4 years

7 patients developed SMN, cumulative risk 8.7% at 6 years, 4 lung cancers, 2 colon cancers, 1 aggressive BCC
B3) SMN following Head and Neck Cancer

- Data from Chicago, 324 patients with stage IV squamous HNC, concurrent chemoradiotherapy, treated 1989-99
- Clin Cancer Res 2004, Argiris et al.

26 patients developed SMN, lung=13, esophagus=3, head and neck=2, cumulative incidence 5%, 7%, 13% at 3, 5, 10 years
Does HPV-related cancer predispose to SMN?

At present there is no definite answer.
B4) SMN in Multiple Myeloma

- Prognosis in MM improved
- Increase in Second Cancers
- Which Second Cancers
Outcomes for patients are clearly improved
The use of novel agent for induction and melphalan and ASCT have doubled median survival for nearly all patients

ASCT = autologous stem cell transplant.
December 5, 2010: Celgene stock market price drops 8% because of SMN

Risk of Second Primary Malignancies With Lenalidomide

Update of MM-015 (MP vs MPR vs MPR + R maintenance)

- SPMs more common with versus without R therapy involving melphalan (previously reported)
- R maintenance improves PFS and OS (previously reported)
- **Conclusions:** MPR-R reduces PD/death much more significantly than it increases SPMs (Figure)

M=melphalan; OS=overall survival; P=prednisone; PD=progressive disease; PFS=progression-free survival R=lenalidomide; SPM=second primary malignancy.

Palumbo AP et al, Abstract 8007.
B4) SMNs in Multiple Myeloma

Data from Houston VA, Munker et al Clin Lymph Myeloma Leuk 2014; 14: 102

197 pts, median age 67 years, 1995-2010, 39 cancers observed in 33 pts, only 5 after MM, prognosis worse if SMN
B4) SMNs in Multiple Myeloma

- **Shreveport Myeloma Project**
- **Acta Haematologica, 2015**
- 215 patients diagnosed between 1998-2009, median age 58.7 y, last FU 2013, 16 patients already had, 10 developed SMNs
- SEER: no statistical increase
- No prognostic impact of SMN

![Graph showing risk of developing a secondary malignancy over years after diagnosis with MM.](image)

**Fig. 5.** Risk of developing a secondary malignancy: cumulative incidence of second malignancies (from time of diagnosis of MM, excluding patients with a preexisting or concomitant unrelated malignancy).
B5) Other New Drugs: Tyrosine Kinase Inhibitors ….

- 1445 patients treated with imatinib, dasatinib or nilotinib
- Median follow-up of 107 months …
- 66 patients developed 80 second cancers
Table 5. Comparison of the CML patients with 2nd cancers other than non-melanoma skin cancers with the SEER data. O: observed number of cases, E: expected number of cases, SIR: standardized incidence ratio, CI: confidence interval (CI).

<table>
<thead>
<tr>
<th>Variable*</th>
<th>O</th>
<th>E</th>
<th>SIR (O/E)</th>
<th>95% CI for O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44</td>
<td>73</td>
<td>0.60</td>
<td>0.44-0.81</td>
</tr>
<tr>
<td>Males</td>
<td>30</td>
<td>45</td>
<td>0.67</td>
<td>0.45-0.95</td>
</tr>
<tr>
<td>Females</td>
<td>14</td>
<td>28</td>
<td>0.50</td>
<td>0.27-0.84</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>23</td>
<td>34</td>
<td>0.68</td>
<td>0.43-1.01</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>21</td>
<td>40</td>
<td>0.63</td>
<td>0.32-0.80</td>
</tr>
<tr>
<td>2nd Cancer Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>11</td>
<td>16</td>
<td>0.69</td>
<td>0.34-1.23</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9</td>
<td>3</td>
<td>3.13</td>
<td>1.37-5.7</td>
</tr>
<tr>
<td>Digestive system</td>
<td>6</td>
<td>16</td>
<td>0.38</td>
<td>0.18-0.82</td>
</tr>
<tr>
<td>Kidney</td>
<td>3</td>
<td>2</td>
<td>1.5</td>
<td>0.31-4.38</td>
</tr>
<tr>
<td>Endocrine</td>
<td>3</td>
<td>0.1</td>
<td>30</td>
<td>6.18-87.60</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>8</td>
<td>0.24</td>
<td>0.03-0.86</td>
</tr>
</tbody>
</table>

* Analysis conducted for the first invasive 2nd cancers (2nd cancers other than non-melanoma skin cancers)
Swedish Cancer Registry, Br J Haematol 2015, 868 patients with CML diagnosed between 2002 and 2011, median FU 3.7 y

The discrepancy between these 2 studies is probably caused by incomplete data...

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (observed/expected)</th>
<th>95% CI for SIR</th>
<th>Test of difference between SIRs (P-value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>52</td>
<td>34</td>
<td>1.52</td>
<td>1.13–1.99</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
<td>20</td>
<td>1.30</td>
<td>0.85–1.91</td>
<td>0.233</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>14</td>
<td>1.87</td>
<td>1.18–2.96</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>16</td>
<td>15</td>
<td>1.14</td>
<td>0.99–1.52</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>42</td>
<td>29</td>
<td>1.45</td>
<td>1.05–1.96</td>
<td></td>
</tr>
<tr>
<td>Second cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>14</td>
<td>10</td>
<td>1.80</td>
<td>0.98–3.39</td>
<td>0.0465</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>13</td>
<td>4</td>
<td>3.02</td>
<td>1.61–5.17</td>
<td>0.009</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>4</td>
<td>1</td>
<td>3.63</td>
<td>0.98–9.30</td>
<td>0.077</td>
</tr>
<tr>
<td>Nose and throat</td>
<td>3</td>
<td>0.1</td>
<td>37.12</td>
<td>7.46–108.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>3</td>
<td>0.74</td>
<td>0.08–2.67</td>
<td>0.291</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>4</td>
<td>0.96</td>
<td>0.26–2.45</td>
<td>0.326</td>
</tr>
</tbody>
</table>

SIR, standardized incidence ratios; 95% CI, 95% confidence interval.

*P-value for the hypothesis of no difference in SIR between the sexes, between the two age groups, or between the cancer subgroup of interest compared with all other cancers.
C) SMN following Allogeneic Stem Cell Transplantation

- Majority younger patients
- Graft versus host disease

Deeg et al, Blood 1998
C) SMN following Allogeneic Stem Cell Transplantation

- PTLD (Post-Transplant Lymphoproliferative Disorder)
- Related to EBV and severe immunosuppression (HLA disparity, T cell depletion, use of ATG …)
- WHO classification: ● early lesions (polyclonal), ● polymorphic PTLD (mostly polyclonal), ● monomorphenic PTLD (monoclonal)
- Incidence after allogeneic transplant 0.5- 1.8%, majority within 1st year
- Treatment: reduction in immunosuppression, rituximab, cytotoxic T cells, chemotherapy
C) SMN following Allogeneic Stem Cell Transplantation

- Secondary leukemias and myelodysplastic syndromes
- “extremely rare”
- After autologous transplant, alkylating agents and TBI are recognized as risk factors
- Problem of leukemia in donor cells, “extremely rare”, … “up to 5%”

Child with SAA, developed leukemia after allogeneic transplant …
C) SMN following Allogeneic Stem Cell Transplantation

- Secondary solid tumors
- Much later
- Risk factors irradiation, use of ATG for immunosuppression
- Curtis et al analyzed 19,229 patients (97% allogeneic, 3% syngeneic) transplanted between 1964 and 1992 at 235 centers, NEJM 1997, IBMTR + Seattle
- 80 solid tumors, RR 2.7, patients surviving at least 10 years risk increased 8 fold
- Chronic GVHD strongly associated with squamous cell carcinoma, male sex
- Allogeneic transplant for Fanconi anemia: 40% risk of solid tumors at 15 years
C) SMN following Allogeneic Stem Cell Transplantation

- Secondary solid tumors

Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning

Navneet S. Majhail,1 Ruta Brazauskas,2 J. Douglas Rizzo,2 Ronald M. Sobecks,3 Zhiwei Wang,2 Mary M. Horowitz,2 Brian Bolwell,4 John R. Wingard,4 and Gerard Socie5

1Center for International Blood and Marrow Transplant Research, Minneapolis, MN; 2Center for International Blood and Marrow Transplant Research, Milwaukee, WI; 3Cleveland Clinic Foundation, Cleveland, OH; 4Shands Hospital at the University of Florida, Gainesville, FL; and 5Hospital St Louis, Pans, France

- CIBMTR data: Blood 2011; 117: 316-22
- 1742 pts with AML * in CR1, 2576 patients with CML * in CP
- Cumulative incidence of SST at 5 and 10 years 0.6/1.2 % and 0.9/2.4 %
- RR 1.4 fold (O/E)
- * Median age 29 / 36
D) Prognosis of SMN

- **Testicular cancer**: “not different from other cancers”
- **Breast cancer** JCO, 2010: Long-term survival among patients with Hodgkin’s lymphoma who developed breast cancer (BC): a population-based study (SEER9)
- 289 HL survivors with BC compared with 405,223 women who developed only BC
- 15 y OS 48 vs 69% for localized BC and 33 vs 43% for distant/regional BC
- Surprising finding: difference not due to cause-specific survival
- Patients with HL-BC had 7 fold increased risk of dying from other cancers
- Mortality from heart disease increased 2.2 fold and 4.3 fold (in localized or distant/regional disease)
Prognosis of SMN after Hodgkin Lymphoma (Munich Data)

Munker et al, 1999
Outlook on Basic Research
What Causes Second Cancer?

- Genes $\leftrightarrow$ Environment
- Genome Wide Association Studies
- Telomerase
- Clonality of Secondary Acute Myelogenous Leukemias (mechanism of transformation?)
A GWAS was performed in 100 cases of SMN after pediatric HL and 89 controls.
All treated with 25-44 Gy Rx ± chemotherapy.
3 SNPs reached genome-wide significance:
[rs4946728, rs1040411, rs8083533]
Independent verification confirmed, none in adults.
RR of heterozygous risk allele (compared to homozgous protective allele): 3.2.
Variants comprise a risk locus associated with decreased basal expression of PRMD1 and impaired induction of PRDM1 protein after radiation exposure.

Suggests PRDM1 as a radiation responsive tumor suppressor.

Previously identified (BLIMP1) as tumor suppressor in activated B-cell like DLBCL, lost in many cancer types.
Genome-wide association studies

Unbiased screen for genetic loci potentially associated with phenotypes of clinical interest

DNA, genotyping arrays, 500 K or 1 M SNPs

Several gigabytes of data

108 genes associated with schizophrenia
A GWAS was performed in 100 cases of SMN after pediatric HL and 89 controls

All treated with 25-44 Gy Rx ± chemotherapy

3 SNPs reached genome-wide significance

[rs4946728, rs1040411, rs8083533]

Independent verification confirmed, none in adults

RR of heterozygous risk allele (compared to homozgous protective allele): 3.2

Variants comprise a risk locus associated with decreased basal expression of PRMD1 and impaired induction of PRDM1 protein after radiation exposure

Suggests PRDM1 as a radiation responsive tumor suppressor

Previously identified (BLIMP1) as tumor suppressor in activated B-cell like DLBCL, lost in many cancer types
GWAS and Second Cancer

• Regional association blot of 6q21 locus. The p value of SNPs is shown with respect to genomic disposition, line denotes threshold for genome-wide significance
Can the length of telomeres predict SMN?

What We Lose With Age

Chromosome

Telomeres end caps that protect the chromosome

As cells divide over time...

telomeres shorten, and eventually cell division stops
Can the length of telomeres predict SMN?

147 cancer survivors with breast cancer, thyroid cancer or sarcoma were matched with 147 cancer survivors without SMN. DNA was extracted from blood, buccal samples, or fibroblasts, PCR was performed, Gramatges MM et al, Clin Cancer Res 2014; 20: 904.

Table 3. Association between telomere content and SMN, cases versus controls

<table>
<thead>
<tr>
<th>SMN</th>
<th>Number of case–control pairs</th>
<th>Mean telomere content ± SD</th>
<th>Unadjusted OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>All SMN</td>
<td>147</td>
<td>0.56 ± 0.21</td>
<td>0.58 ± 0.26</td>
<td>0.64</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>68</td>
<td>0.55 ± 0.18</td>
<td>0.55 ± 0.25</td>
<td>0.87</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>48</td>
<td>0.54 ± 0.21</td>
<td>0.63 ± 0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>31</td>
<td>0.63 ± 0.27</td>
<td>0.54 ± 0.23</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Adjusted for sex, race, family history, smoking status, and age at diagnosis of the primary disease.
What is the relationship of CHIP with treatment-related Acute Myelogenous Leukemia?

CHIP = Clonal Hematopoiesis of Indeterminate Potential

Link et al. 2016 Leukemia 30: 1633
How frequent is CHIP?
St. Louis 5-6% > 70 years
Sweden 10% > 65 years
What is the relationship of CHIP with treatment-related Acute Myelogenous Leukemia? CHIP = Clonal Hematopoiesis of Indeterminate Potential

Link et al. 2016 Leukemia 30: 1633
The progression from CHIP to a myeloid malignancy or aplastic anemia likely depends on the type of CHIP associated gene mutation(s) and on the presence of specific environmental stressors...
LETTER TO THE EDITOR
Donor cell leukemia arising from clonal hematopoiesis after bone marrow transplantation

Gondek et al Leukemia, 2016

Targeted sequencing

STRs
Recommendations, Outcome

- Always take a thorough family history
- Think about SMN
- Report SMN to cancer registries
- Screening in high risk situations:
  - **BREAST CANCER:** women who had thoracic or axillary radiation, begin 8 or 10 years after trt or at age 40 (25), ± ultrasound ± MRT (if radiation 20 Gy or higher)
  - **LUNG CANCER:** if increased risk (smokers, mantle field)
  - **COLON CANCER:** (no consensus) begin 5 or 10 years earlier
- Prophylaxis ?
- “Eat right” COG 2008
- Develop genomic tests to find out highest risk for SMN, study mechanisms of oncogenesis
Conclusions

• Important, interesting and increasing problem
• What can we do to keep the price of success as low as possible?
• Research: what causes cancer?
  – Can we predict who develops second cancer?
  – Is there a signature of second cancer caused by radiation, alkylators, anti-angiogenic agents?
References


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