CANCER RISK IN PATIENTS WITH MYOTONIC DYSTROPHY:
BENCH-TO-BEDSIDE

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Outline

- Definitions
- How we got involved
- Literature review
- First analytic investigation
- Current knowledge
- Knowledge gaps
- Clinical Implications
What is a Tumor?

- **What is a tumor?**
  - Abnormal overgrowth of cells: increase in size, number, and atypical appearance
  - **Benign:** no invasion into nearby normal tissues; no spread to other body parts; not life-threatening
  - Malignant/Cancer: can come back after removal; invades surrounding tissues, or spread to other organs; cells very abnormal in appearance; potentially life-threatening

- **What does “risk” mean?**
  - Probability that an event (like “cancer”) will occur
  - **Relative:** Null, elevated, decreased - when compared with another group, e.g., 5 times more common than….
  - **Absolute:** likelihood of developing the event (“cancer”) over a specified time period in a defined population, e.g., 5 cases per 1,000 per year
Cancer in DM: Alert Clinical Observation

IGF-1: TO USE OR NOT TO USE – That was the question…..
# Tumors in Myotonic Dystrophy: Case Reports

## Malignant

<table>
<thead>
<tr>
<th>Type</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Malignant Thymoma</td>
<td>3</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>1</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal cancer</td>
<td>1</td>
</tr>
<tr>
<td>Laryngeal + Renal cell</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1</td>
</tr>
</tbody>
</table>

## Benign

<table>
<thead>
<tr>
<th>Type</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilomatrixoma</td>
<td>35</td>
</tr>
<tr>
<td>Parotid gland adenoma</td>
<td>6</td>
</tr>
<tr>
<td>Thymoma</td>
<td>5</td>
</tr>
<tr>
<td>Parathyroid adenoma</td>
<td>5</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>2</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Problems with Case Reports

- Population from which reports are drawn is unknown. **NO DENOMINATORS! Cannot infer causality.**
- Criteria which determine whether a given case will be reported are undefined.
  - The rarer the event, the more likely it is to be reported
  - If the same event has been previously reported, it is more likely to be reported again
  - If institution has a special interest, the diseases it prefers are more likely to be seen in association with other diseases
- Can get clues: **Pilomatrixoma** is SO rare, and the case reports so numerous, an association might well be real
- For valid answers, you need a **quantitative** study, formal
First Systematic Evaluation of Cancer Risk in Patients with Myotonic Dystrophy

**Discovery Set**

Swedish Hospital Discharge Registry (1987-2004)

N=669

**Validation Set**

Danish Patient Registry (1977-2008)

N=989

Follow-up *started* at first DM discharge diagnosis
Cancer Relative Risk in Myotonic Dystrophy: (N=1,658)

- Compared with expected general population cancer rates in individuals of similar age and sex, DM patients were more likely to develop cancers in the:
  - Uterus/Endometrium
  - Ovary
  - Brain
  - Colon
  - Eye
  - Thyroid
  - Pancreas

S Gadalla et al., JAMA 2011; 306:2480-2486
Frequency of Tumors in Patients with DM

N=678

Benign Tumors

- Yes: 18.6%
- No: 78.9%
- I don't know: 2.5%

Malignant Tumors (Cancer)

- Yes: 90.7%
- No: 8.8%
- I don't know: 0.5%
## Tumor Frequency: Published Literature

### Survey Studies

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>DM type</th>
<th>Benign</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Registry</td>
<td>950</td>
<td>DM1</td>
<td>781</td>
<td>10%</td>
</tr>
<tr>
<td>Rome, Italy</td>
<td>255</td>
<td>DM1</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>UK DM Registry</td>
<td>220</td>
<td>DM1</td>
<td>214</td>
<td>12%</td>
</tr>
</tbody>
</table>

Information obtained from questionnaires in which patients were asked: “In your lifetime, have you ever had...?”

### Medical Record Studies

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>DM type</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden*</td>
<td>669</td>
<td>Unknown</td>
<td>6%</td>
</tr>
<tr>
<td>Denmark*</td>
<td>989</td>
<td>Unknown</td>
<td>6%</td>
</tr>
<tr>
<td>Basque, Spain**</td>
<td>424</td>
<td>DM1</td>
<td>14%</td>
</tr>
<tr>
<td>UK CPRD*</td>
<td>938</td>
<td>DM1</td>
<td>6%</td>
</tr>
</tbody>
</table>

*After DM diagnosis; ** Patient lifetime

Das, et al., *J Neurol* 2012; 259:2161-2166
Alsaggaf, et al., *Muscle Nerve* 2017
## Cancer Risk in Myotonic Dystrophy: Characteristics of Published Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Number of DM</th>
<th>Age at DM/Start of Follow-Up (Yrs)</th>
<th>Age at Cancer Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadalla, et al., (2011)</td>
<td>Sweden, Denmark</td>
<td>1,658</td>
<td>46 (Sweden) 38 (Denmark)</td>
<td>57</td>
</tr>
<tr>
<td>Cancer Site of Origin</td>
<td>Gadalla et al., 2011 (1658)</td>
<td>Win et al., 2012 (N=307)</td>
<td>Mohamed et al., 2013 (N=109)</td>
<td>Abbott et al., 2016 (281)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------</td>
<td>-------------------------</td>
<td>-------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Endometrium</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thyroid</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ovary</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Colon</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Testicular</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eye</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

**Strength of Association (Standard Incidence Ratio/Relative Risk)**

**++:** Statistically significant excess risk;  
**+:** Risk ≥ 2 but not statistically significant;  
**-:** No excess cancer risk
Organs with Excess Risk of Cancer: Results from Meta-analysis

Emparanza et al., IDMC-11, Unpublished
Cancer Frequency by Age at DM1 Diagnosis

- **Congenital/Childhood** (n=132): first DM1 recorded age 0-10 years
- **Classic** (n=504): diagnosed age 11-40 years
- **Late-Onset** (n=302): diagnosed after age 40 years

Alsaggaf et al, IDMC-11; unpublished
Cancer Risk: Classic versus Late-onset DM1

Classic DM1

- Overall
- Thyroid
- Melanoma
- Colorectum
- Endometrial
- Breast

Late-Onset DM1

- Overall
- Colorectum
- Esophagus
- Lung

Alsaggaf et al, IDMC-11; unpublished
Approximately 1 in 10 patients with DM will develop cancer by age 60

Cancer Absolute Risk in DM1 Relatives

Best et al., IDMC-11; Unpublished

Risk By Age 60 years

<table>
<thead>
<tr>
<th></th>
<th>DM1-Affected</th>
<th>DM1-Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Siblings</td>
<td>10%</td>
<td>29%</td>
</tr>
</tbody>
</table>
What do we Know about Cancer Risk in DM2?

- Less likely to develop cancers than DM1
- Cancer profile may be different

<table>
<thead>
<tr>
<th></th>
<th>DM1 (N=79)</th>
<th>DM2 (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Skin (All types)</td>
<td>32 (40.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>5 (6.3)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Breast</td>
<td>7 (8.9)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Cervix</td>
<td>5 (6.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Colon</td>
<td>5 (6.3)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Parotid</td>
<td>4 (5.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>3 (3.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kidney</td>
<td>3 (3.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ovaries</td>
<td>2 (2.5)</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

Das et al., *J Neurol*, 2012

**Cancer: 3rd Leading Cause of Death in DM**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>232 (55%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>95 (23%)</td>
</tr>
<tr>
<td>Malignancy*</td>
<td>42 (10%)</td>
</tr>
</tbody>
</table>

*Malignancy* includes Ovary (n=8), brain (n=7), and lung (6)

Even though the risk of cancer is significantly elevated in DM1 patients when compared with the general population, the actual number of cancer-related deaths is small, compared with the well-known complications of DM.

Gadalla et al., PLoS One 2013
Brain Cancer Survival in DM Patients

Survival in High Grade Glioma

Gadalla et al., *Eur J Neurol* 2016; 23(3):542-547
Skin cancer in DM1: UK Primary Care Physician Database (N=1,061)

- No skin cancer: 97%
- Skin cancer: 3%

Wang et al., Int J Cancer 2017; In-Press
Skin cancer in DM1: UK Primary Care Physician Database

- No skin cancer: 97%
- Skin cancer: 3%
- Basal cell carcinoma: 86%
- Melanoma: 9%
- Other skin cancer, NOS\(^1\): 6%

\(^1\) NOS: Not otherwise specified

Wang et al., Int J Cancer 2017; In-Press
UK DM1 Risk of Skin Cancers: Overall and by Histological Subtype

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer (All types)</td>
<td>5.44 (3.33-8.89)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Melanoma Skin</td>
<td>2.40 (0.56-10.31)</td>
<td>0.24</td>
</tr>
<tr>
<td>Basal Cell Carcinoma</td>
<td>5.78 (3.36-9.92)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Wang et al., Int J Cancer 2017; In-Press
DM1 and Cancer: Why?

- Not smoking
- Not alcohol
- Not obesity

Das, et al., *J Neurol* 2012; 259:2161-2166
Bianchi et al., *J Neurol* 2016; 263(3):492-8
Alsaggaf, et al., *Muscle Nerve* 2017
**Sun Exposure & Skin Tumors in DM**

<table>
<thead>
<tr>
<th>Sunburn</th>
<th>4-fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild burn that becomes a tan</td>
<td>2-fold increase</td>
</tr>
</tbody>
</table>

Gadalla et al., *Eur J Neurol* 2017; Epub, doi:10.1111/ene.13276
Questions yet to answer?

- What is the cancer risk in DM2?
- What is the role of hormonal factors in cancers of the genital organs in DM patients?
- How does DM patients with cancer respond to therapy?
- What are the molecular factors predisposing DM patients to cancer?
- What happens at the tissue level?
Effective screening increases the chances of detecting certain cancers early, when they are most likely to be curable.

But relatively few cancers have available screening strategies that have been PROVEN to reduce the risk of dying from a particular cancer.

Routine use of unproven screening strategies can be harmful: best avoided.
Thyroid Cancer: Warning signs & Early Detection

- **Warning signs:**
  - Hoarseness, pain, difficulty swallowing
  - Lumps, swelling, asymmetry of the neck on neck examination

- **Early Detection:**
  - No *proven* screening test exists
  - Physical exam, blood tests or thyroid ultrasound may be used
  - Because of the association we have demonstrated with DM1, physicians caring for such patients should be alert to thyroid abnormalities, and not hesitate to evaluate the thyroid gland further
Skin Cancer: Prevention & Early Detection: Excessive Sunlight Exposure is the Major Risk Factor

- Seek the shade, especially from 10am to 4pm.
- Do NOT get sunburned!
- Avoid tanning and UV tanning beds.
- Wear broad-brimmed hats, long-sleeved shirts.
- Use sunscreen: SPF=30 is adequate
  - Apply generously (2 tablespoons)
  - Reapply every two hours
- Seek medical advice for suspicious lesions
- Be particularly careful if you have fair skin, blue eyes and/or red hair: more susceptible to burn
- Skin cancers can be found early, treated easily
Uterine/Endometrial Cancer

- **Warning Signs:**
  - Unusual vaginal bleeding or discharge
  - Pelvic pain
  - Unexplained weight loss

- **Risk Factors:**
  - Overweight
  - Unopposed estrogen
  - Tamoxifen

- **Screening Test:** no proven screening strategy

- **Diagnostic Tests:** Pelvic examination, ultrasound, biopsy
Ovarian Cancer

- **Warning signs:**
  - Bloating, pelvic or abdominal pain
  - Feeling full quickly
  - Increasing abdominal girth
  - Changing urinary habits (e.g., frequent urination)

- **Early detection:**
  - There is no proven screening test. (CA-125, transvaginal ultrasound are often used, but frequently yield false positive test results)
Testicular Cancer

- **Warning signs:**
  - Lump or pain in the testis
  - Accumulation of fluid in the scrotum
  - Unexplained fatigue

- **Early detection:** no screening strategy has been proven effective

- **Diagnosis:**
  - Testicular ultrasound
  - Testicular biopsy
Brain Cancer

- **Warning Signs:**
  - Severe, progressive headache
  - Unsteady gait
  - Nausea & vomiting
  - Focal neurological deficits
  - Cognitive difficulties

- **Early detection:** There is no screening strategy that has been proven to be effective for brain cancer
Colorectal Cancer

- **Warning signs:**
  - New, progressive abdominal pain
  - Progressive constipation
  - Blood in stool, black/tarry stool

- **Early detection: Proven Effective**
  - Periodic colonoscopy, interval driven by risk
  - Flexible sigmoidoscopy
  - Fecal immunohistochemical test ("FIT")
NCI Cancer in DM Research Team

NCI
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- Sania Amr
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Patients and their Families