THE 2ND DECADE

MYOTONIC DYSTROPHY FOUNDATION

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MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

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

NIH NATIONAL CANCER INSTITUTE

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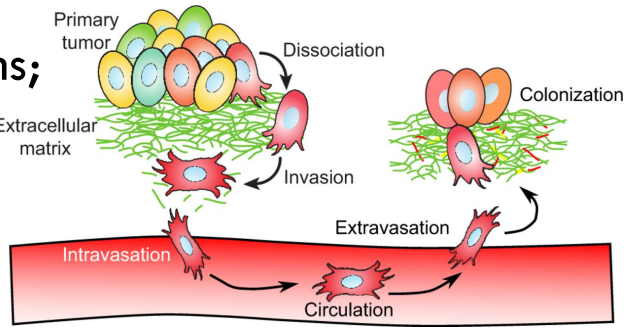
Outline

- 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-threating
  - 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

Type	Reports
Basal cell carcinoma	**5**
Thyroid carcinoma	**4**
Malignant Thymoma	**3**
Gastric cancer	**2**
Testicular cancer	**1**
Ovarian cancer	**1**
Intestinal cancer	**1**
Laryngeal + Renal cell	**1**
Lymphoma	**1**
Leukemia	**1**

Benign

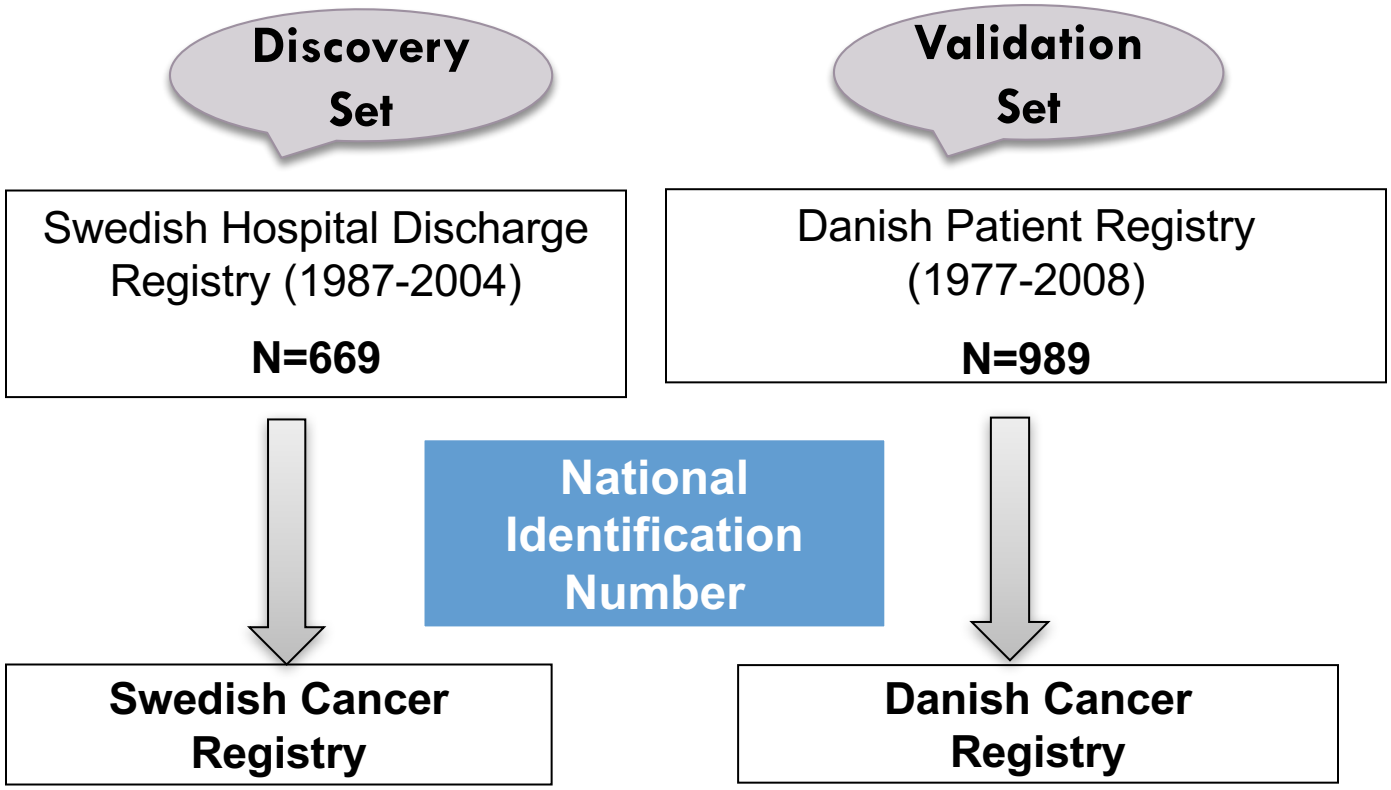
Type	Reports
Pilomatrixoma	**35**
Parotid gland adenoma	6
Thymoma	5
Parathyroid adenoma	5
Pituitary adenoma	2
Insulinoma	1
Thyroid adenoma	1

C Mueller, *et al.*, Cancer Causes Control 2009; 20:2009-20

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

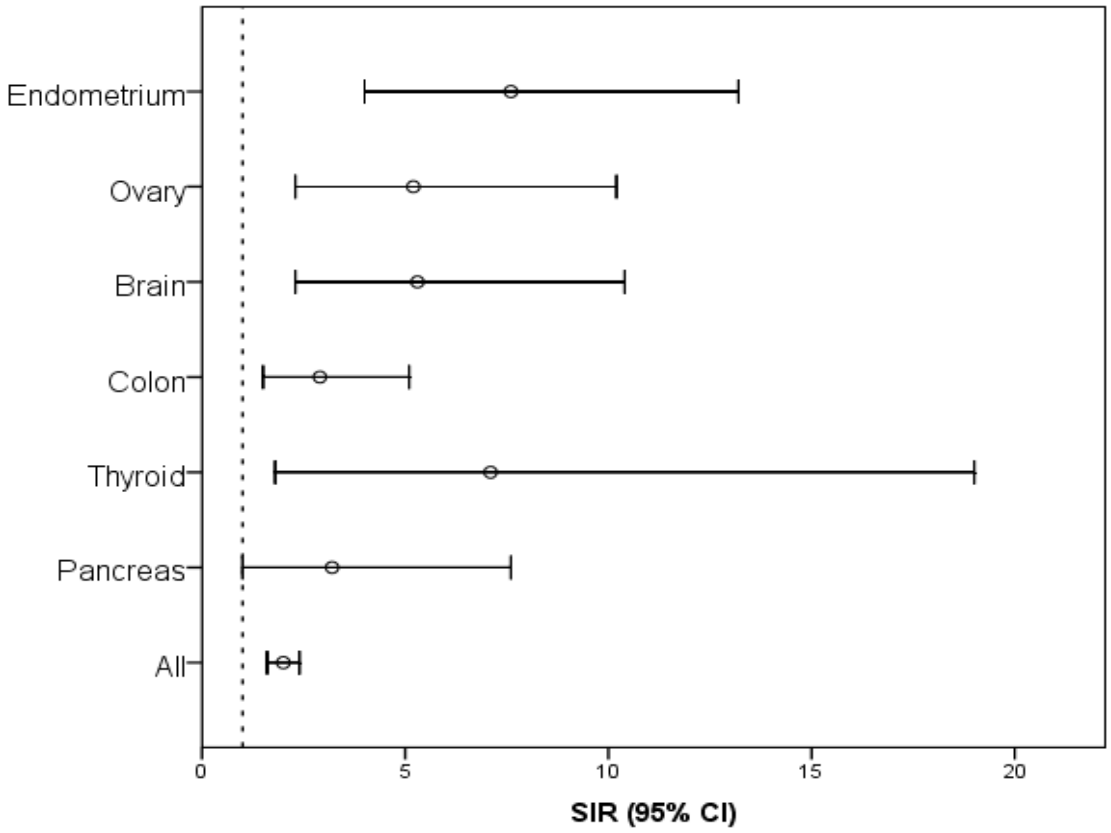
First Systematic Evaluation of Cancer Risk in Patients with Myotonic Dystrophy



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

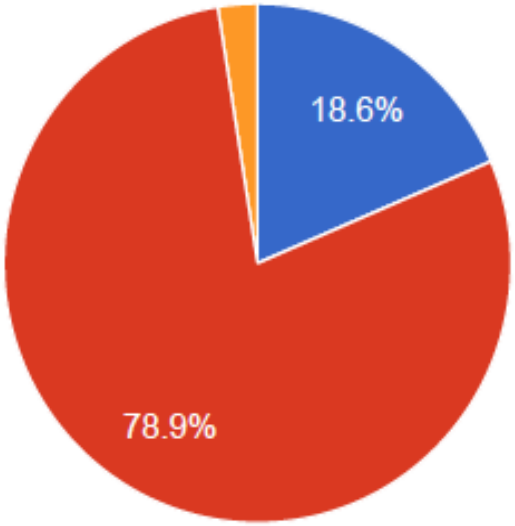


S Gadalla et al., JAMA 2011; 306:2480-2486

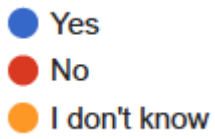
Frequency of Tumors in Patients with DM

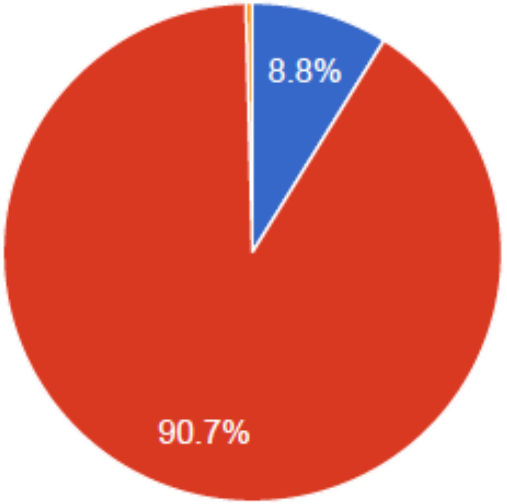
The Myotonic Dystrophy Family Registry

N=678



Benign Tumors





Malignant Tumors (Cancer)

Tumor Frequency: Published Literature

Survey Studies

	Number of patients	DM type	Benign	Cancer
US Registry	950	781 DM1	10%	
Rome, Italy	255	DM1	21%	7%
UK DM Registry	220	214 DM1	12%	6%

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

Medical Record Studies

	Number of patients	DM type	Cancer
Sweden*	669	Unknown	6%
Denmark*	989	Unknown	6%
Basque, Spain**	424	DM1	14%
UK CPRD*	938	DM1	6%

*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

Author	Country	Number of DM	Age at DM/ Start of Follow-Up (Yrs)	Age at Cancer Diagnosis
Gadalla, *et al.*, (2011)	Sweden, Denmark	**1,658**	**46 (Sweden) 38 (Denmark)**	**57**
Win, *et al.*, (2012)	US	**307** (63 DM2)	**40**	**55**
Mohamed, *et al.*, (2013)	France	**109** (DM1)	**44**	**NA**
Abbott, *et al.*, (2016)	US	**281**	NA	NA
Fernández-Torrón, *et al.*, (2016)	Spain	**424** (DM1)	NA	**47**

DM Cancer Phenotype: Specific Cancer Associations

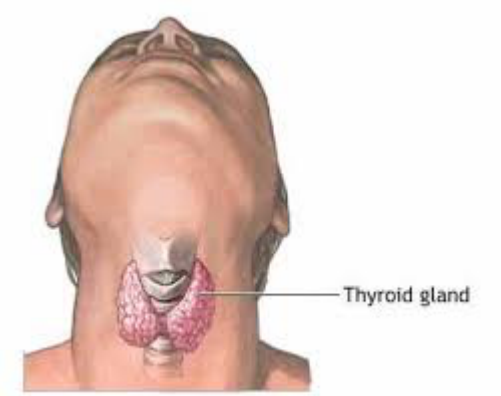
Cancer Site of Origin	Gadalla *et al.*, 2011 (1658)	Win *et al.*, 2012 (N=307)	Mohamed *et al.*, 2013 (N=109)	Abbott *et al.*, 2016 (281)	Fernandez-Torron *et al.*, 2016 (424)
	Strength of Association (Standard Incidence Ratio/Relative Risk)				
Endometrium	++	-	++	++	++
Thyroid	++	++		+	++
Ovary	++	+	+		++
Colon	++		+	+	+
Testicular	-	+		++	+
Brain	++		+		++
Cutaneous melanoma	+	+	+	-	+
Eye	++	++			

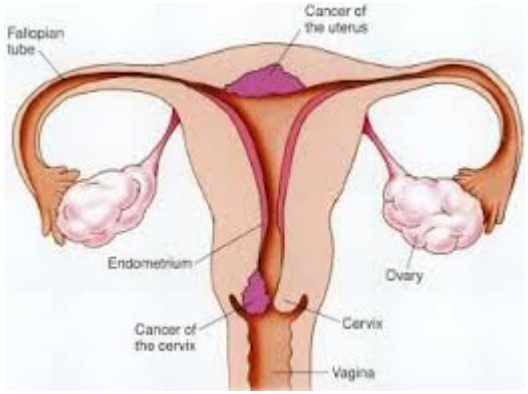
++: Statistically significant excess risk;

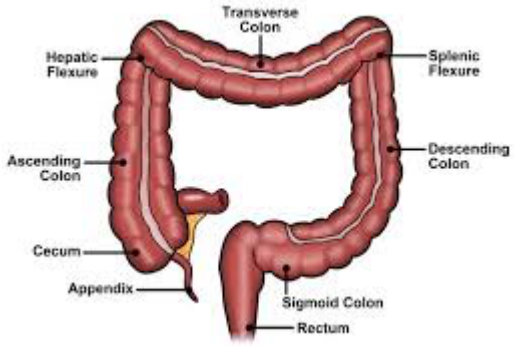
+: Risk ≥ 2 but not statistically significant;

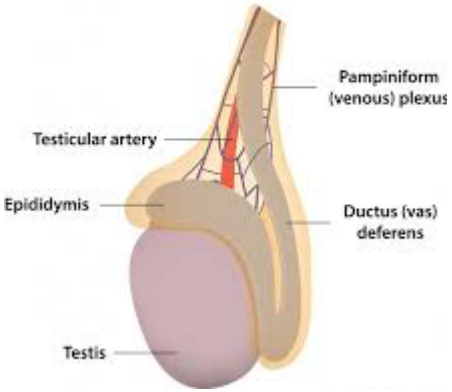
-: No excess cancer risk

Organs with Excess Risk of Cancer: Results from Meta-analysis





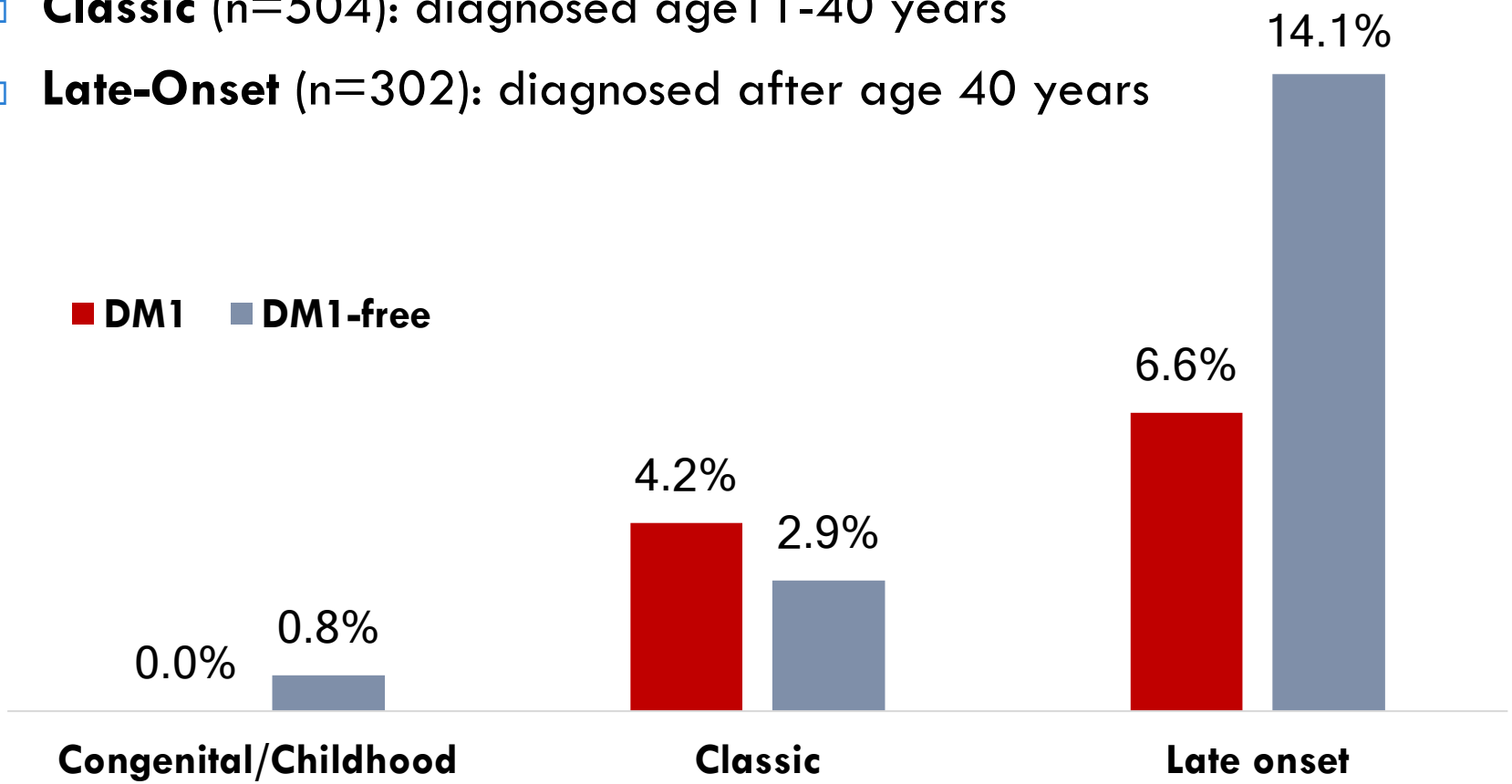




Emparanza et al., IDMC-11, Unpublished

Cancer Frequency by Age at DM1 Diagnosis

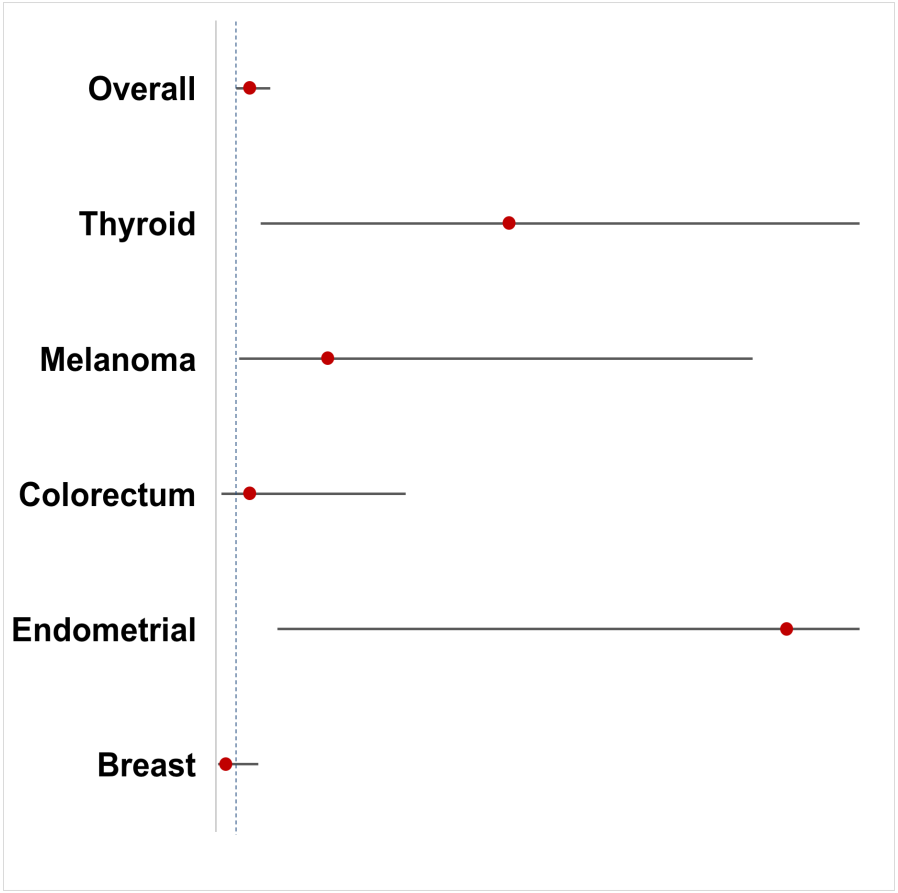
- **Congenital/Childhood** (n=132): first DM1 recorded age 0-10 years
- **Classic** (n=504): diagnosed age11-40 years
- **Late-Onset** (n=302): diagnosed after age 40 years



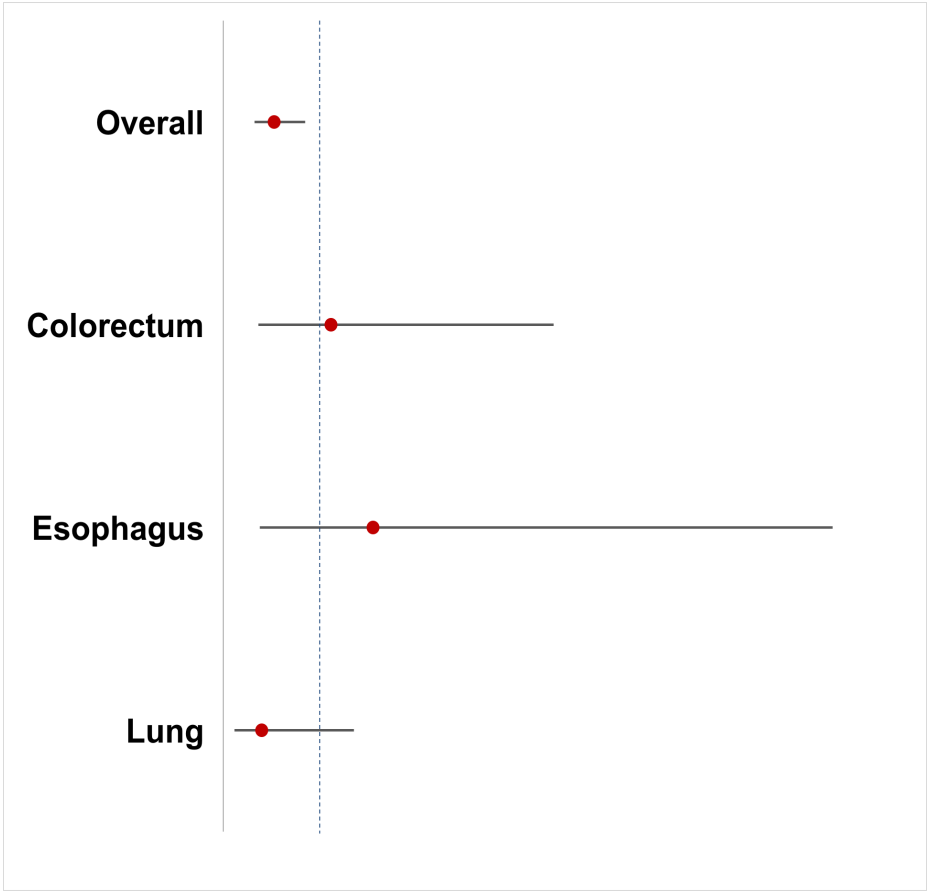
Alsaggaf et al, IDMC-11; unpublished

Cancer Risk: Classic *versus* Late-onset DM1

Classic DM1

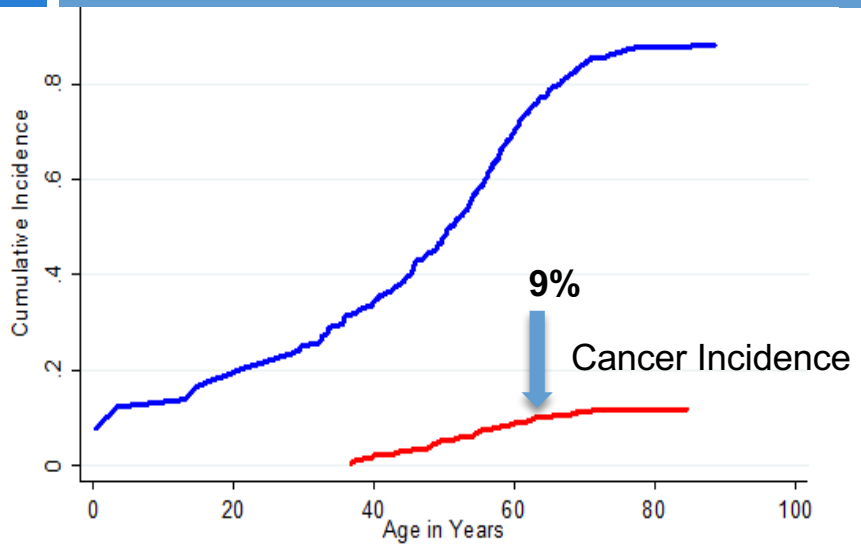


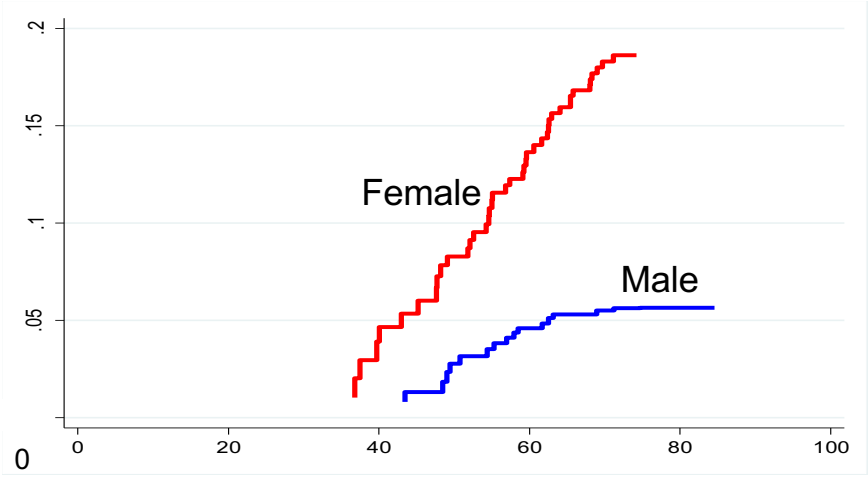
Late-Onset DM1



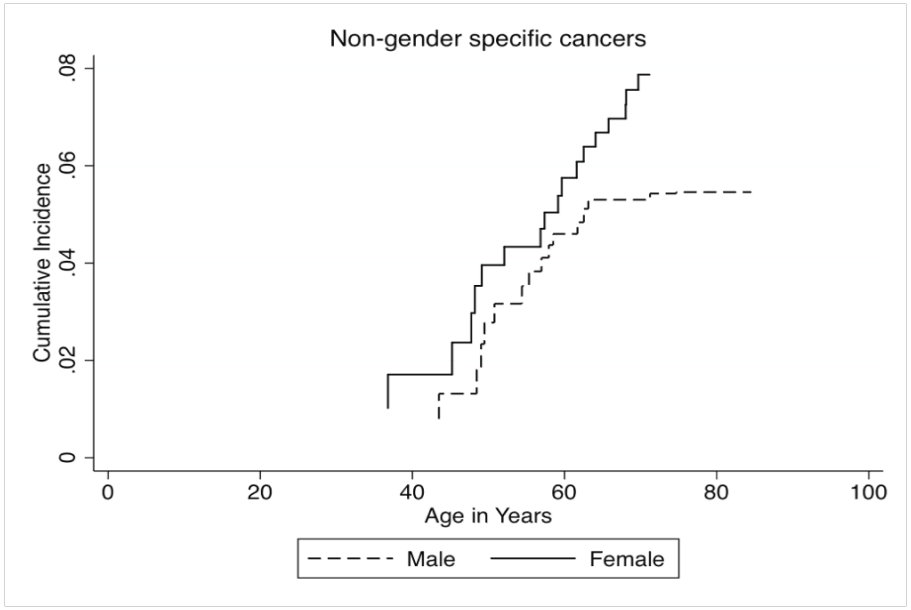
Alsaggaf et al, IDMC-11; unpublished

Absolute Risk of Cancer after DM Diagnosis



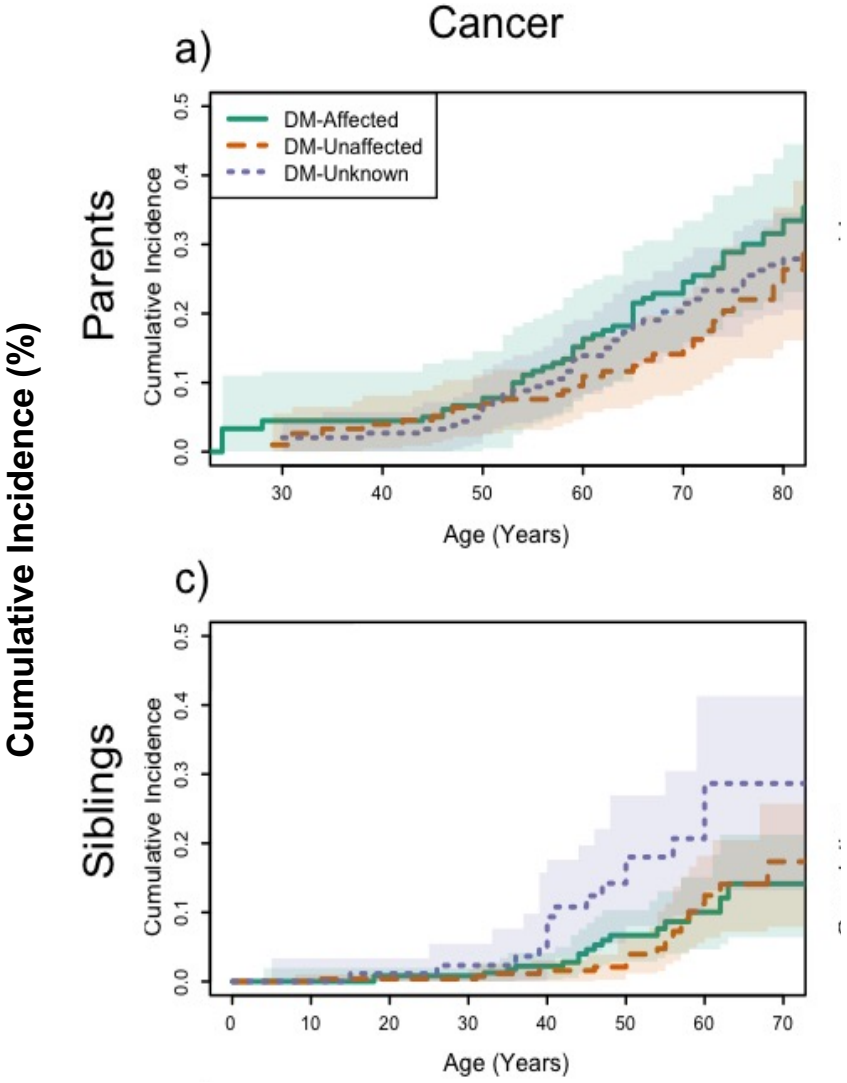


Approximately 1 in 10 patients with DM will develop cancer by age 60



Gadalla *et al.*, PLoS One *2013; 8(11):e79851*

Cancer Absolute Risk in DM1 Relatives



Risk By Age 60 years

	DM1-Affected	DM1-Unknown
Parents	16%	14%
Siblings	10%	29%

Best *et al.*, IDMC-11; Unpublished

What do we Know about Cancer Risk in DM2?

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

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

Das *et al.*, J Neurol, 2012

	Type 1				Type 2			
Cancer	O	E	SIR (95% CI)	*P* value	O	E	SIR (95% CI)	*P* value
Thyroid	2	0.27	7.40 (0.90-26.71)	.02	2	0.35	5.70 (0.69-20.59)	.05
Choroidal melanoma	2	0.02	92.94 (11.26-335.72)	<.001	0			
Testis	1	0.12	8.27 (0.21-46.08)	.12	0			
Prostate	1	0.87	1.15 (0.03-6.43)	.37	6	1.79	3.36 (1.23-7.32)	.008

Win *et al.*, Mayo Clin Proc, 2012

Cancer: 3rd Leading Cause of Death in DM

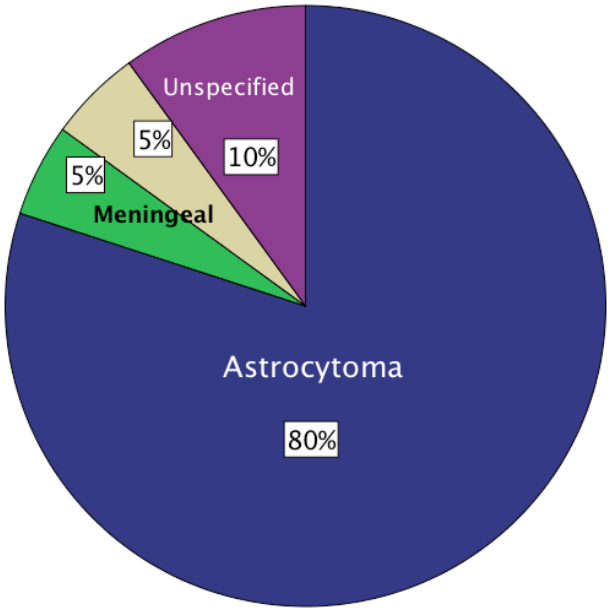
Cause of Death	N (%)
DM	232 (55%)
Cardiovascular disease	95 (23%)
Malignancy*	42 (10%)

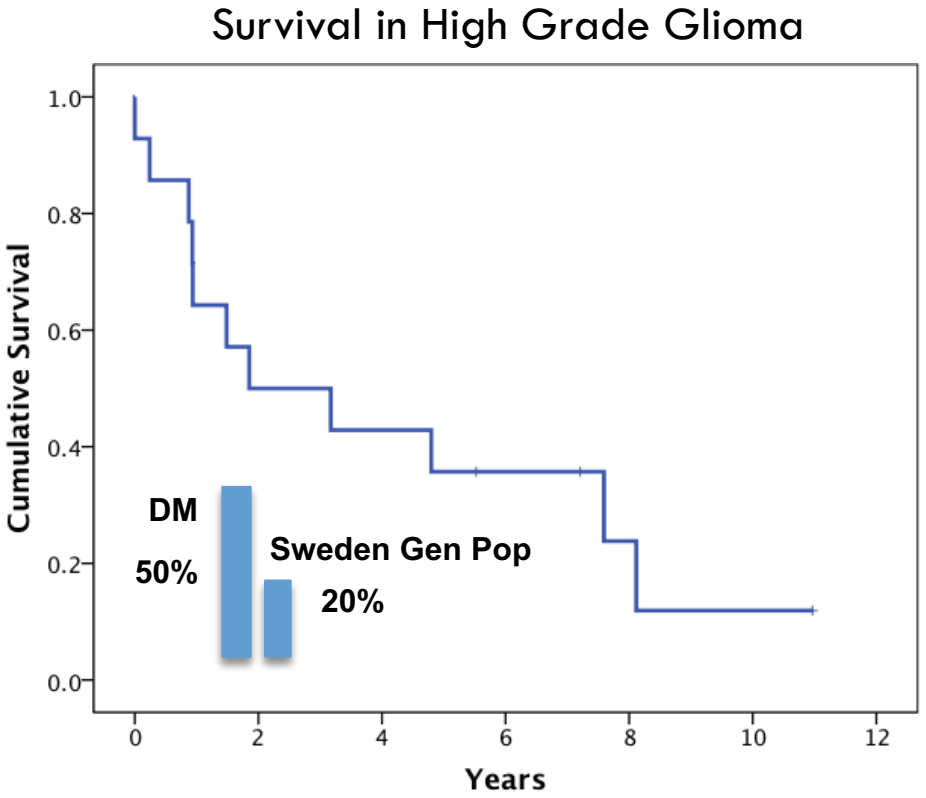
* Ovary (n=8), brain (n=7), and lung (6)

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

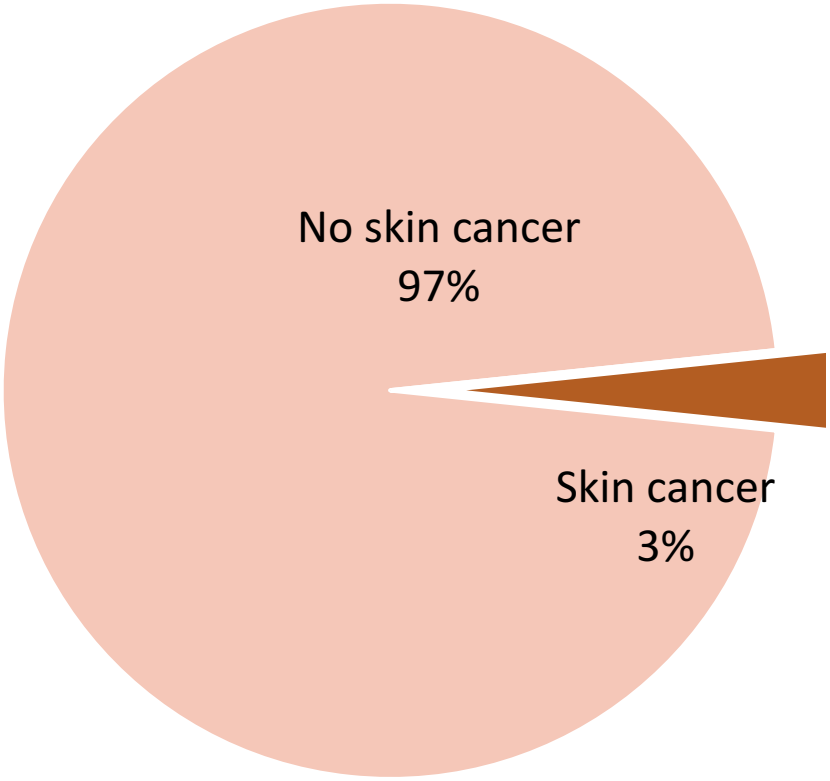
Brain Cancer Survival in DM Patients





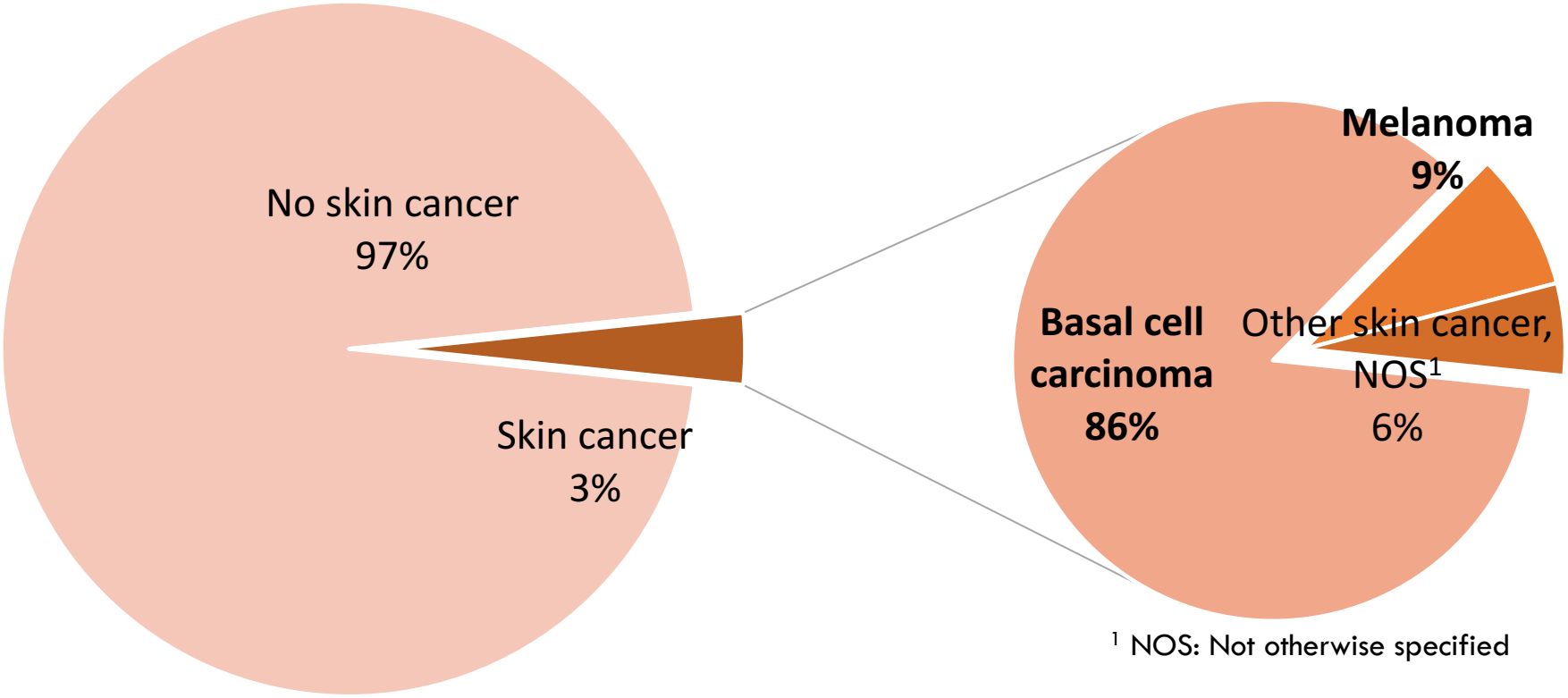
Gadalla *et al.*, Eur J Neurol 2016; 23(3):542-547

Skin cancer in DM1:
UK Primary Care Physician Database (N=1,061)



Wang *et al.*, Int J Cancer 2017; In-Press

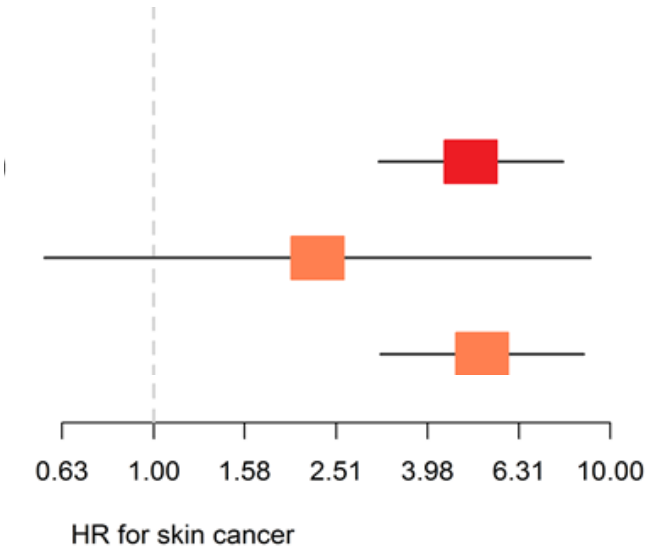
Skin cancer in DM1: UK Primary Care Physician Database



[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

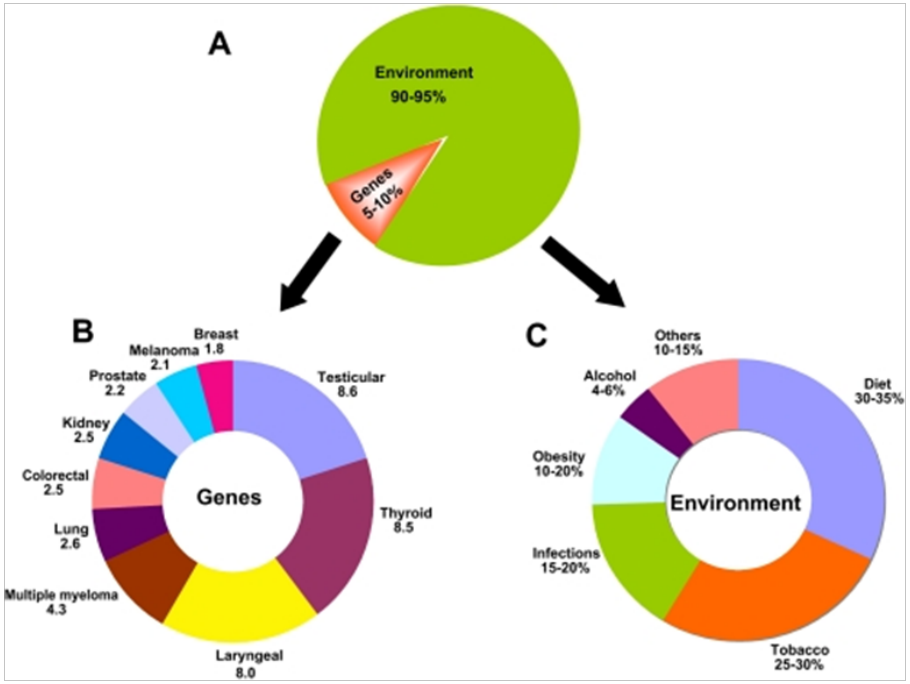


	HR (95% CI)	p
Skin cancer (All types)	*5.44 (3.33-8.89)*	*<.0001*
Melanoma Skin	2.40 (0.56-10.31)	0.24
Basal Cell Carcinoma	*5.78 (3.36-9.92)*	*<.0001*

Wang *et al.*, Int J Cancer 2017; In-Press

DM1 and Cancer: Why?

In the Population



In DM

- 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

Sunburn	4-fold increase
Mild burn that becomes a tan	2-fold increase

Gadalla *et al.*, Eur J Neurol *2017; Epub, doi:10.1111/ene.13276*

Questions yet to answer?

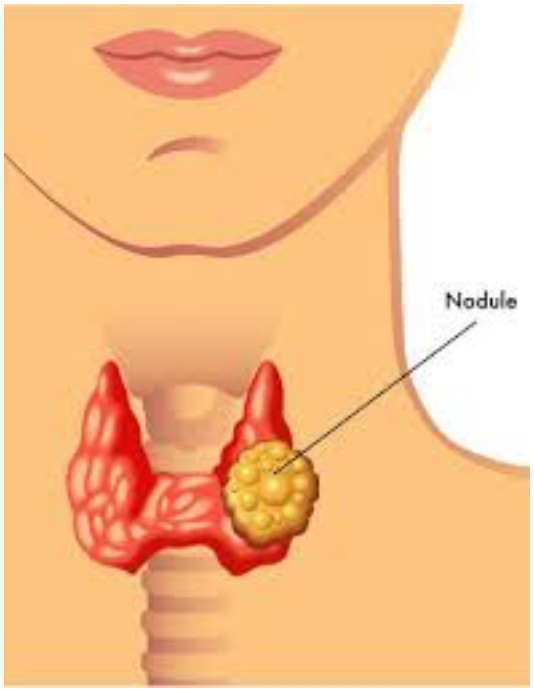
- What is the cancer risk in DM2?
- What is the role of hormonal factors in cancers of the genital organs in DM patients?
- How does DM patients with cancer respond to therapy?
- What are the molecular factors predisposing DM patients to cancer?
- What happens at the tissue level?

Population Cancer Screening: Why?

- 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

Basal Cell Carcinoma

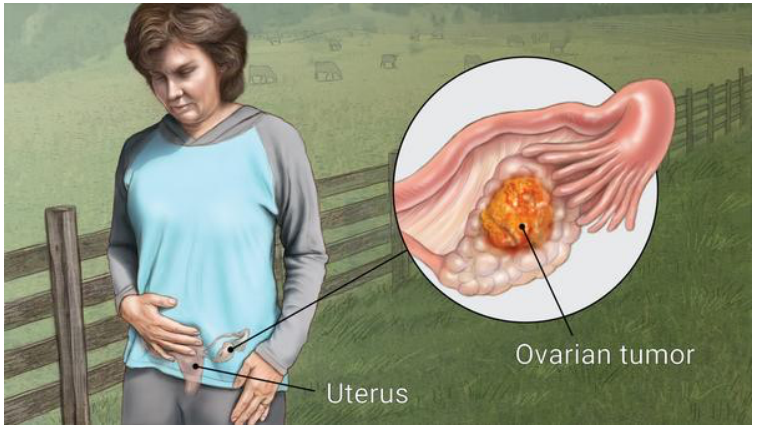
Melanoma

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

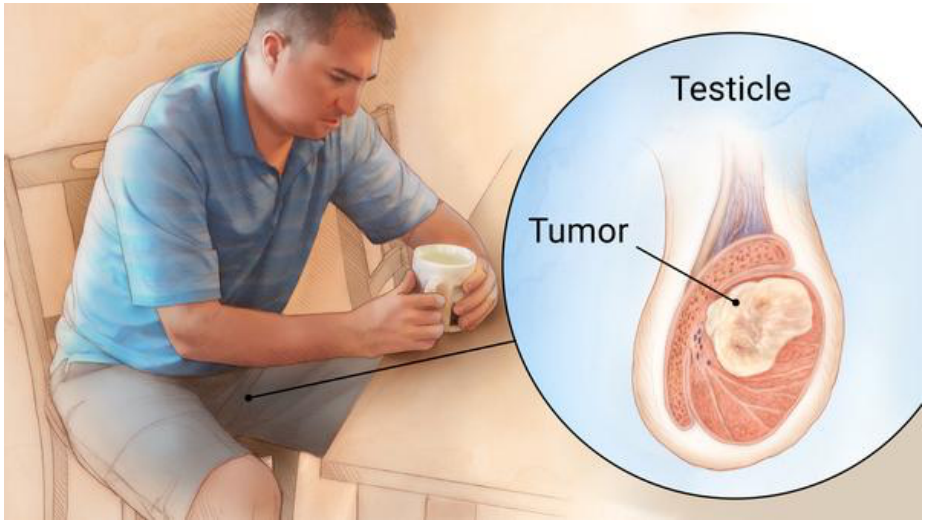
- **Warning signs:**
  - Bloating, pelvic or abdominal pain
  - Feeling full quickly
  - Increasing abdominal girth
  - Changing urinary habits (e.g., frequent urination)



- **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

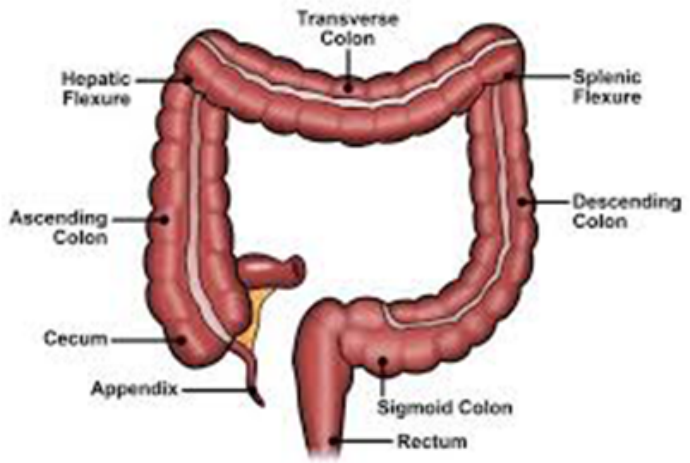
Brain Cancer

- **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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- Youjin Wang
- Rotana Alsagaff
- Ana Best
- Renée Bremer
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Patients and their Families

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