Laurence Beels – Gent – November 16th 2019

Biomarker investigation of diagnostic x-ray exposure

Let's image wisely and gently!

1

Biomarker investigation of low-dose x-ray exposure

- Based on research of Ghent University
  - PhD thesis Laurence Beels – 2011
  - PhD thesis Charlot Vandevoorde – 2015

2

Low-dose cancer risks?

- Introduction
  - Use of x-rays in medical diagnostics
  - Risk from exposure to x-rays
  - DNA damage

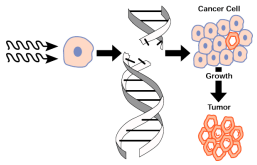


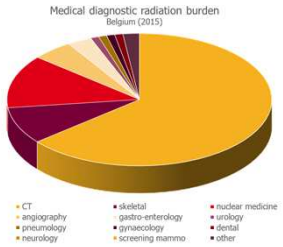
Figure 1. Development of cancer from mutation produced by ionizing radiation.

https://serc.carleton.edu

3

Use of x-rays in medical diagnostics

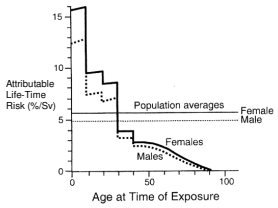
- Use of IR in medical diagnostics increases
  - Belgium – 2015: ~15 million examinations
    - 3% nuclear medicine
    - 14% CT
    - 1% screening mammo
    - 1% angiography
    - 81% RX
- Can low-dose x-rays induce cancer?



4

Risk from exposure to IR

- Current risk estimates derived from epidemiological studies
  - LSS cohort of Japanese atomic bomb survivors
  - Accidents such as Chernobyl
  - Populations that have been exposed from fallout of nuclear weapon testing
  - Medically exposed populations (high doses)
- Average for population of all ages: 5%/Sv
- Common basis for radiological protection standards
  - Age dependence
  - Gender dependence

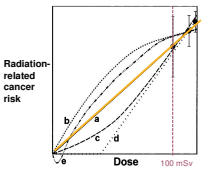


Hall et al. Pred Rad. 2002.

5

Risk from exposure to low-dose IR

- Linear-no-threshold hypothesis
  - Linear extrapolation from high dose risks
    - Epidemiological studies
    - 100 mSv – 2,5 Sv

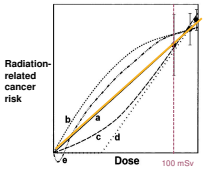


Brenner et al. Proc Natl Acad Sci USA. 2003.

6

Risk from exposure to low-dose IR

- Linear-no-threshold hypothesis
  - Linear extrapolation from high dose risks
    - Epidemiological studies
    - 100 mSv – 2,5 Sv
- Might result in under- or overestimation of radiation-related cancer risk
  - Non-targeted observations or threshold
  - Need to evaluate the risk from low-dose IR exposure
- Evaluation of low-dose risks
  - Epidemiological studies are statistically underpowered
  - Biomarker approach
  - Detection of DNA damage induced by IR in cells



Brenner et al. Proc Natl Acad Sci USA. 2003.

7

Detection of x-ray effects at DNA level

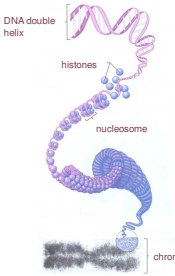
- Cytokinesis-block MN assay
  - Frequently used method to measure chromosomal damage
  - MN are result of un- or misrepaired DNA DSB's
  - Not sensitive enough for very low doses of IR
  - Starting material can be a blood sample
- γ-H2AX assay
  - Used to detect DNA DSB damage and repair
  - Sensitive enough to detect IR doses as low as 1 mGy
  - Relatively fast assay
  - Starting material can be a blood sample

https://teachnuclear.ca

8

H2AX is a histone protein

- Involved in the compaction of DNA into chromosomes

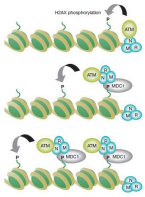


Marieb et al. Human anatomy. 2005.

9

H2AX is a histone protein

- Involved in the compaction of DNA into chromosomes
- Is phosphorylated following DSB induction
  - Different H2AX histones are phosphorylated per DSB → γ-H2AX
  - 1 γ-H2AX focus = 1 DNA DSB
- Is dephosphorylated following DSB repair

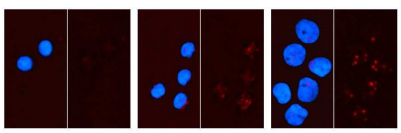


West et al. EMBO Rep. 2006.

10

Microscopic scoring of γ-H2AX foci

- Double immunostaining
  - First antibody binds to γ-H2AX
  - Second antibody (with immunofluorescence signal) binds to first antibody
- Manual counting of foci spots



0 mGy 10 mGy 200 mGy

11

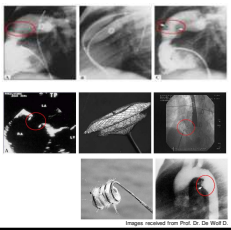
Low-dose cancer risks?

- Results
  - Paediatric patients undergoing a cardiac catheterization
  - Adult patients undergoing a contrast CT examination
  - Paediatric patients undergoing a contrast CT examination (multi-center study)

12

Paediatric patients – cardiac catheterization

- Concern about radiation dose
  - (very) young patients
    - Children are 3 times more radiosensitive for cancer compared to adults
  - Relatively high doses of ionizing radiation
    - High complexity of the catheterization procedure
    - Often need to repeat the examination
- Examples of cardiac catheterization
  - Balloon dilatation
    - Enlarge stenosis of pulmonary or aortic vessels or valve
  - Closure using umbrella
    - Atrial septal defect (foramen ovale)
  - Closure using coil
    - Patent ductus arteriosus



Images received from Prof. Dr. De Wolf D.

13

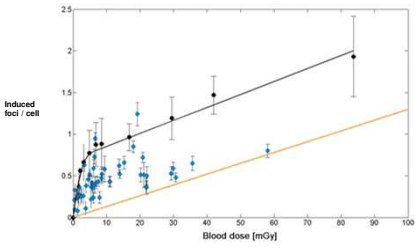
Paediatric patients – cardiac catheterization

- Study population
  - 49 children
  - Mean age = 2,4 y (26 children < 1 year)
- X-ray system
  - Integris BH5000 biplane system
- Collection of blood sample (+/- 2 ml)
  - 1 sample before the use of x-rays
  - 1 sample after the x-ray procedure
  - → calculation of 'induced' number of γ-H2AX foci
- Preparation of the microcope slides
  - T-lymphocyte isolation
  - Double immunostaining
  - Manual scoring of γ-H2AX foci
- Calculation of patient-specific blood dose
  - Monte Carlo simulation

https://www.philips.be/healthcare

14

Paediatric patients – cardiac catheterization



Beels et al. Circ. 2009.

15

Paediatric patients – cardiac catheterization

- Lifetime attributable risk for cancer mortality
  - Monte Carlo organ doses
  - Age dependance
  - LNT hypothesis
- LAR for the study population = 0,134% (~1/1000)

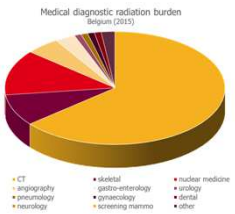
→ might be underestimated!!

https://riskmanagement365.wordpress.com

16

Adult patients – contrast CT

- Concern about radiation dose
  - Increasing number of examinations
    - Belgium: yearly 200 examinations per 1000 Belgians
  - Higher radiation doses compared to conventional RX



17

Adult patients – contrast CT

- Concern about radiation dose
  - Increasing number of examinations
    - Belgium: yearly 200 examinations per 1000 Belgians
  - Higher radiation doses compared to conventional RX

	X-ray (mSv)	CT (mSv)
Chest	0,1	7
Abdomen	0,5	10
Spine	1,5	6
Ankle / foot	0,0007	0,07
Elbow	0,0007	0,14
Wrist / hand	0,0001	0,0003
Knee	0,001	0,16

https://research.lu.edu

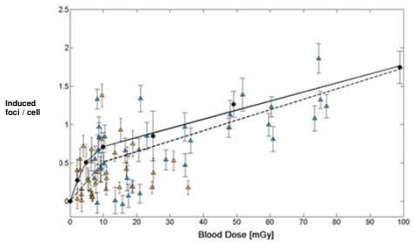
18

Adult patients – contrast CT

- Study population
  - 69 adults
  - Mean age = 57,8 y (mean BMI = 24,5)
- CT systems
  - Toshiba Aquilion 32
  - Siemens Somatom Definition Flash
- Collection of blood sample (+/- 2 ml)
  - 1 sample before the use of CT x-rays
  - 1 sample after the CT x-ray procedure
  - → calculation of 'induced' number of γ-H2AX foci
- Preparation of the microcope slides
  - T-lymphocyte isolation
  - Double immunostaining
  - Manual scoring of γ-H2AX foci
- Calculation of patient-specific blood dose
  - Monte Carlo simulation

19

Adult patients – contrast CT



Beels et al. EJRadiology. 2011.

20

Adult patients – contrast CT

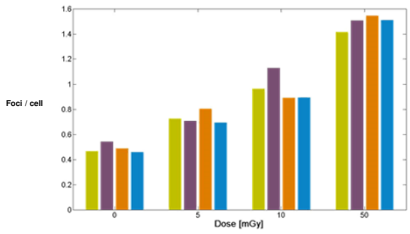
- Lifetime attributable risk for cancer mortality
  - Monte Carlo organ doses
  - Age dependance
  - LNT hypothesis
- LAR for the study population = 0,040% (~1/2500)

→ might be underestimated!!

https://riskmanagement365.wordpress.com

21

Adult patients – contrast CT - contrast agent effect?

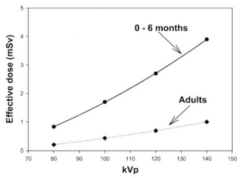


Beels et al. EJRadiology. 2011.

22

Paediatric patients – multicenter CT study

- Concern about radiation dose
  - (very) young patients
    - Children are 3 times more radiosensitive for cancer compared to adults
  - Higher radiation doses compared to conventional RX
  - Increasing number of CT procedures
    - Belgium: 1-2 % of CT procedures are in children < 12 y



Huda et al. Ped Rad. 2002.

23

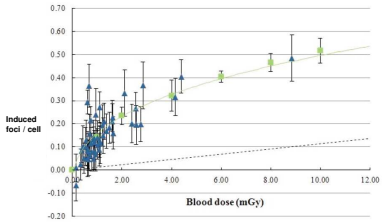
Paediatric patients – multicenter CT study

- Study population
  - 51 children (scanned in 5 hospitals)
    - CT chest: 41
    - CT abdomen: 10
  - Median age = 3,8 y
- CT system
  - Siemens (Somatom Definition Flash / Sensation 64)
  - Toshiba Aquilion
  - GE Discovery CT750 HD
- Collection of blood sample (+/- 2 ml)
  - 1 sample before the use of x-rays
  - 1 sample after the x-ray procedure
  - → calculation of 'induced' number of γ-H2AX foci
- Preparation of the microcope slides
  - T-lymphocyte isolation
  - Double immunostaining
  - Manual scoring of γ-H2AX foci
- Calculation of patient-specific blood dose
  - Monte Carlo simulation

https://www.boredpanda.com

24

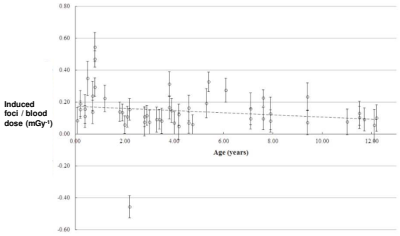
Paediatric patients – multicenter CT study



Vandevoorde et al. Eur Radiol. 2015.

25

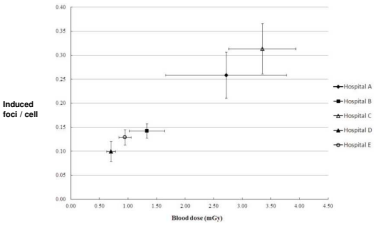
Paediatric patients – multicenter CT study



Vandevoorde et al. Eur Radiol. 2015.

26

Paediatric patients – multicenter CT study



Vandevoorde et al. Eur Radiol. 2015.

27

Paediatric patients – multicenter CT study

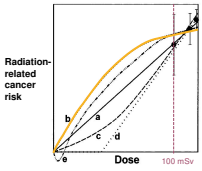
- Lifetime attributable risk for cancer mortality
  - Monte Carlo organ doses
  - Age dependance
  - LNT hypothesis
- LAR for the study population
  - CT chest = 0,008% (~1/12500)
  - CT abdomen = 0,013% (~1/7500)
- → might be underestimated!!

https://riskmanagement365.wordpress.com

28

Low-dose cancer risks?

- Discussion
  - Patient studies point to a low-dose hypersensitivity, bystander effect?
  - Necessity of dose reduction in diagnostic x-rays

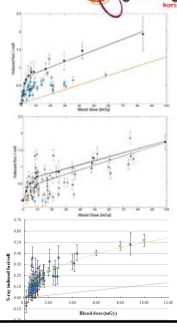


Brenner et al. Proc Natl Acad Sci USA. 2003.

29

Patient studies point to a low-dose hypersensitivity

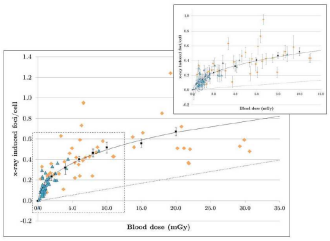
- Biphasic dose response
  - Steep increase at very low doses
  - Followed by a more linear increase at higher doses (> 5 – 10 mGy)
- More DNA DSB's than expected according to the LNT hypothesis
  - Cancer risk underestimated?
- Possibly related to a bystander effect
  - Signalling to non-targeted neighbouring cells
  - Not fully understood and complex



30

Necessity of dose reduction in diagnostic x-rays

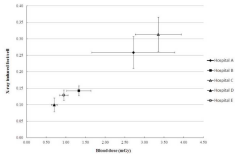
- LAR based on γ-H2AX foci data
  - +/- 10 times higher than based on the LNT model
  - Although small risks, public health concern when multiplying with the procedures performed each year
- ! Especially in children!



31

Necessity of dose reduction in diagnostic x-rays

- Importance of justification of an x-ray exam
- Importance of optimisation → ALARA
  - ! For children: age and biometry dependent protocols



https://www.imagewisely.org – https://www.imagegently.org

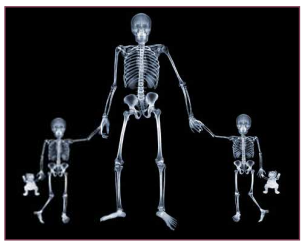
Vandevoorde et al. Eur Radiol. 2015.

32

Life is dangerous, keep radiation risks in perspective!

Volg ons:

www.twitter.com/azgroeninge
www.facebook.com/azgroeningekortrijk
www.instagram.com/azgroeninge
www.linkedin.com/company/azgroeninge/



Adapted from Vassey Nick's Photo – Take my hand. Parent and child (and teddy bear) take a stroll.

33