

# Mechanism underlying individual radiosensitivity of breast and head and neck cancer patients

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**DoReMi**

Integrating Low Dose Research

WP6 DoReMi  
**Individual variability in  
susceptibility to cancer  
(WP 6)**

# The overall objectives for WP6 are

- To provide the experimental evidence to incorporate the influence of genetic modifiers, age and gender on cancer risk ,at low doses and low dose rates, to radiation protection practices
- To coordinate activities with cross-workpackage programs in molecular epidemiology, dosimetry and systems biology.
- To integrate WP6 research with activities from national and EURATOM sponsored research into the HLEG roadmap through the preparation of open calls for scientific projects

## **Description of WP6 tasks**

*Task 6.1 Molecular epidemiological studies to address the role of individual genetic variation in determining susceptibility to low doses (Starting Year 1).*

*Task 6.2 Identification of genetic modifiers of individual cancer susceptibility and their mechanisms of action*

*Task 6.3 Modelling of the effects on risk prediction models due to changes in biological processes influenced by genetic variability*

*Task 6.4 The effect of genetic modifiers on carcinogenesis following low dose rate exposure*

*Task 6.5 Contribution of genetic and epigenetic mechanisms that indirectly influence susceptibility to radiation-induced cancer*

**Xxxx**

***Task 6.11: RADSENS***

## Task 6.8

Poster **2-PS2D-12** (Tuesday, May 26<sup>th</sup>)

Investigation of radiosensitivity in healthy controls, AT patients and prostate cancer patients. Presenter: **Lisa White**

Poster **4-PS1B-52** (Thursday May 28<sup>th</sup>)

Low dose effects in peripheral blood lymphocytes with Raman spectroscopy. Presenter: **Dr Jane Bryant**

# Aims of Radsens:

- What pathways triggered by low dose radiation (mGy range)
- What pathways differing sensitive/non sensitive patients

## Longterm aim:

- To have predictive assay to be able to distinguish between extreme sensitive normal normal sensitive patients

Cohorts?

Adverse effects of radiotherapy

Acute effects

Late effects

Ex. Osteoradionecrosis

Ex. Severe skin reaction

Occur in rapidly proliferating tissue  
Tend to cause inflammation  
Usually reversible

**Fibrosis**  
Proliferation of surviving fibrocytes owing to growth factors released as a result of injury

**Atrophy**  
Loss of fibrocytes and collagen reabsorption

**Vascular damage**  
Either small vessel dilation or constriction

**Infertility**

**Hormone deficiencies**

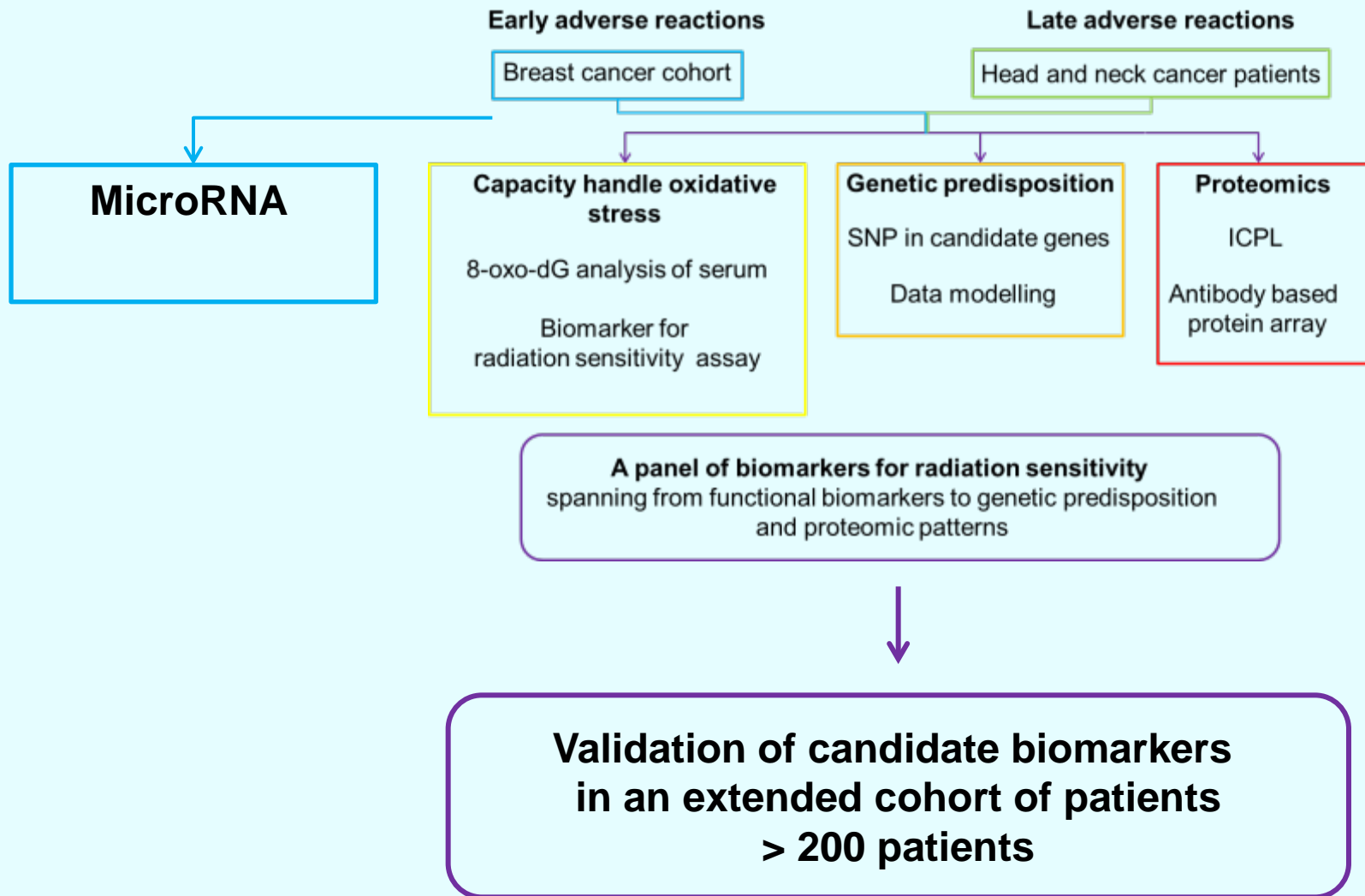
**Second malignancies**

- Examples:**  
 Dermatitis  
 Mucositis  
 Cystitis  
 Proctitis  
 Hair loss  
 Bone marrow suppression

- Examples:**  
 Hardening and shrinkage of an irradiated breast  
 Strictures and malabsorption of irradiated small bowel

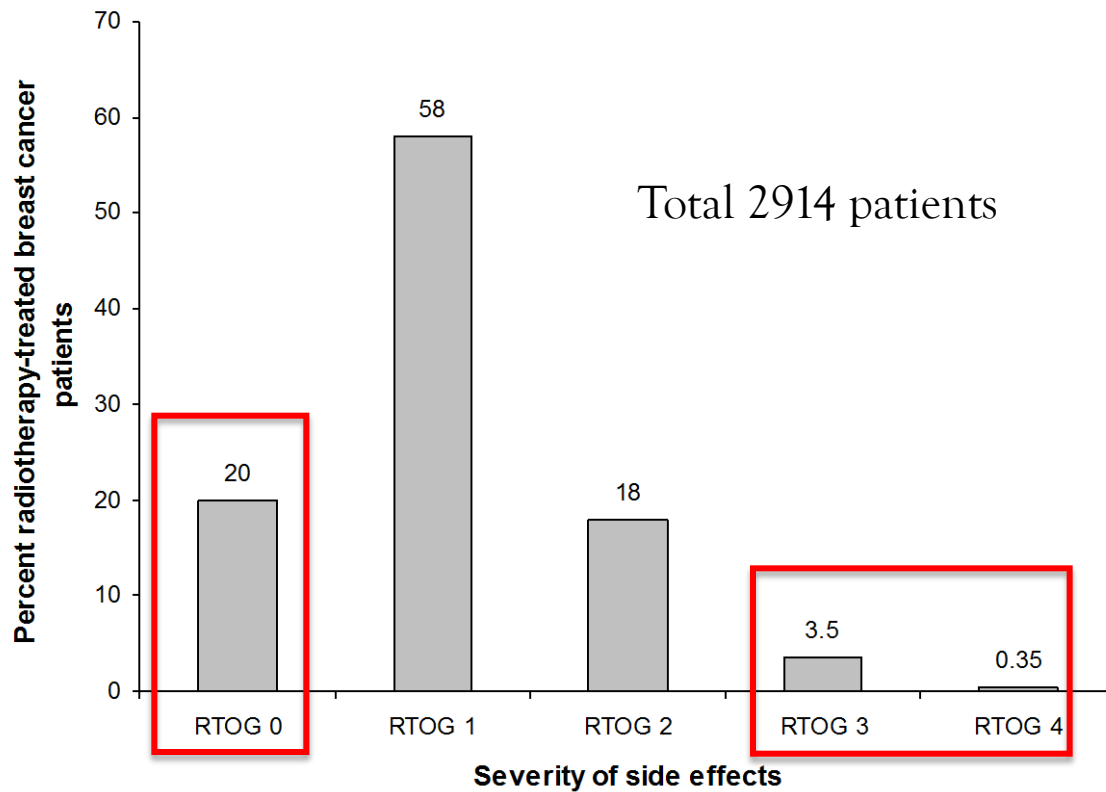
- Examples:**  
 Telangiectasia in the skin  
 Bleeding, e.g. haematuria  
 Ischaemia resulting in bowel perforation and formation of fistulae

# Experimental design





# Breast cancer cohort



S Skiöld et.al. 2013 Mut. Res. 30; 756 (1-2): 152-7



0-1



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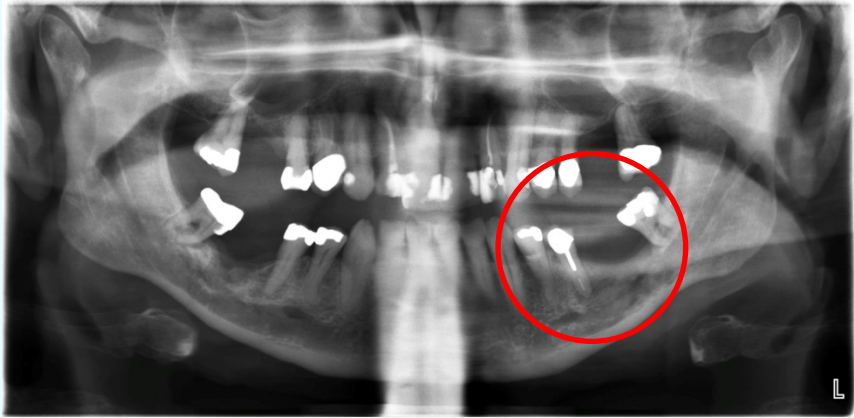


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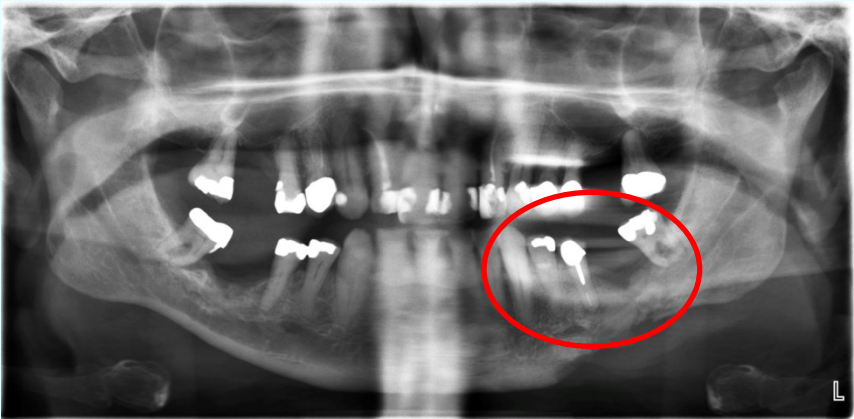
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# Head and neck cancer cohort



The incidence for ORN is ~5%

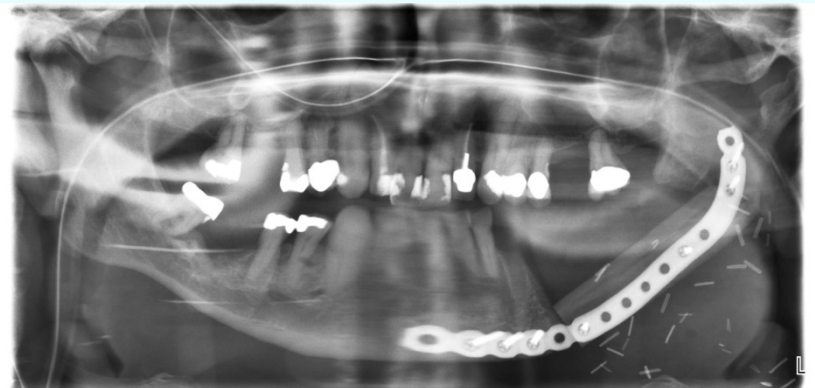
It is a late adverse effect to radiotherapy occurring 1-10 years after the end of the treatment.



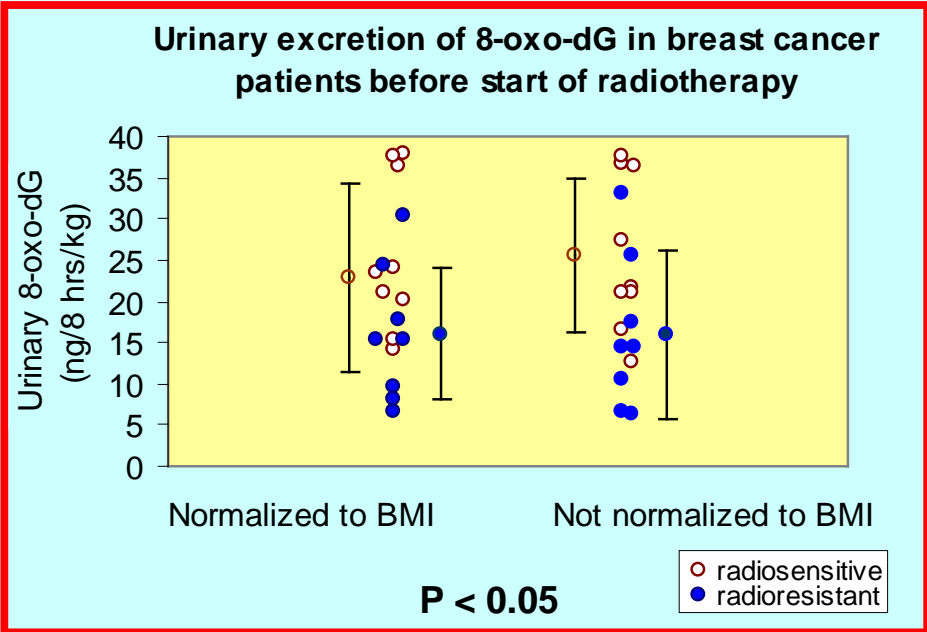
There are ~280 new cases/year of head and neck cancer in Stockholm, Sweden

Available:

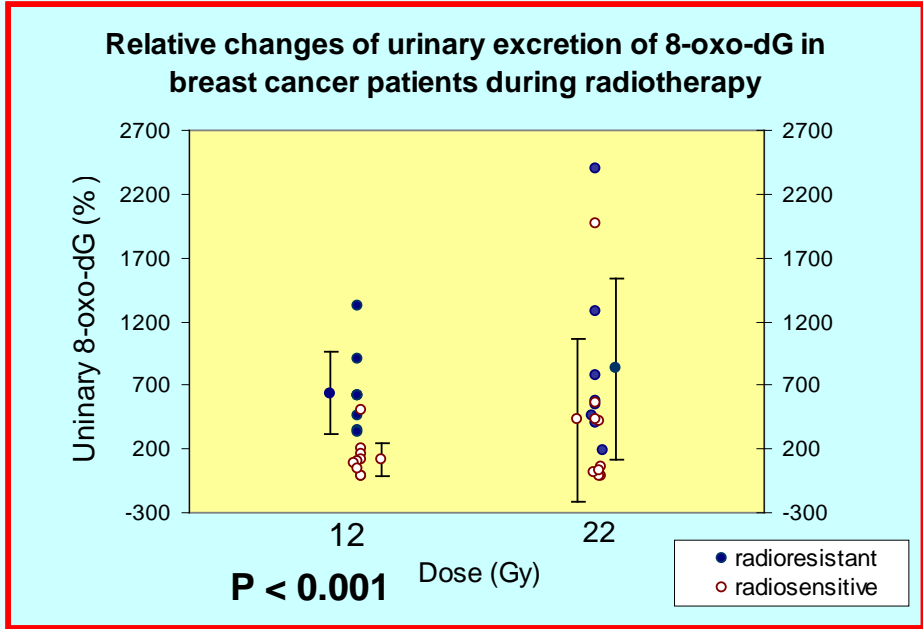
37 patients with osteoradionecrosis (ORN) and 37 matched controls.

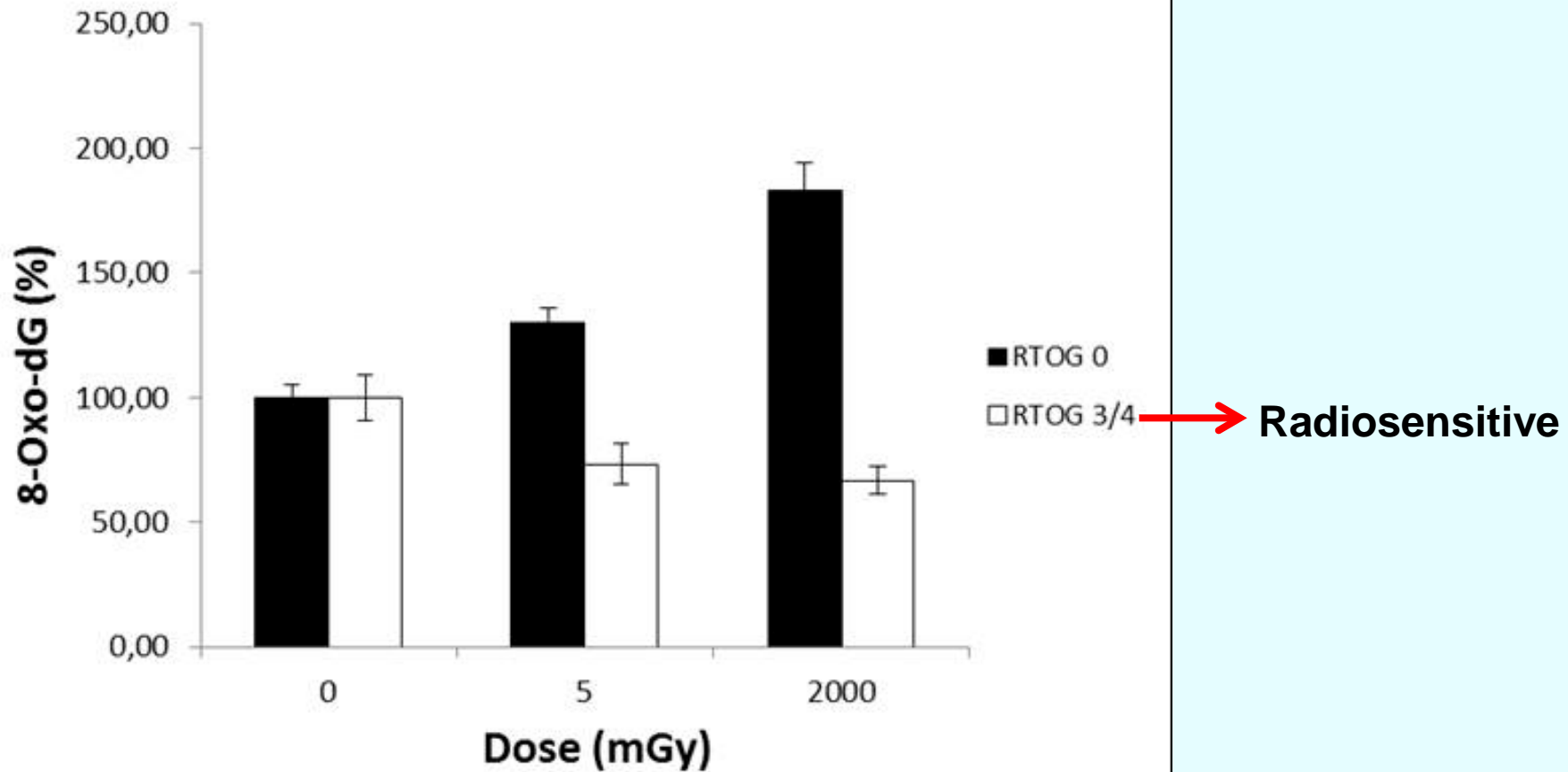


Radiosensitive group:  
 High background levels and  
 low therapy related increase  
 of urinary 8-oxo-dG



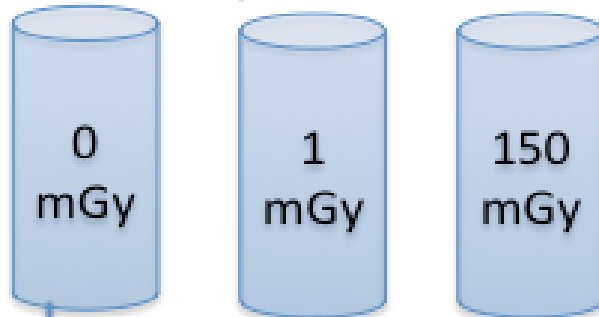
Non-sensitive group:  
 Low background levels and  
 high therapy related increase  
 of urinary 8-oxo-dG





## RTOG 0

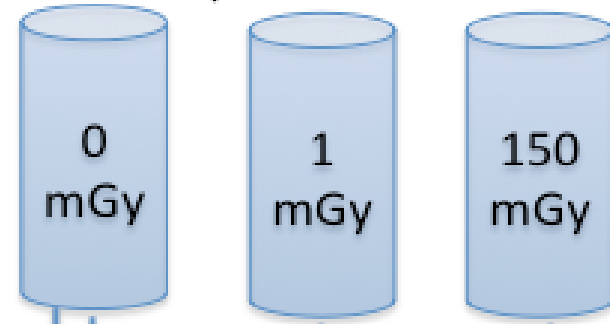
Pooled from 9 donors after IR  
and protein isolation



Triplex ICPL labelling  
comparing the control  
to the irradiated samples.

## RTOG 4

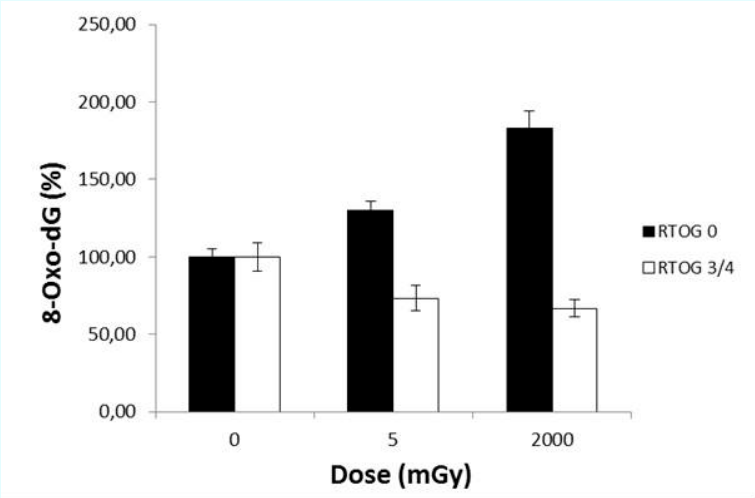
Pooled from 8 donors after IR  
and protein isolation



Triplex ICPL labelling  
comparing the control  
to the irradiated samples

Duplex labelling comparing the non irradiated  
controls of the two groups

# Pooled samples



Normo-sensitive patients

Radiosensitive patients

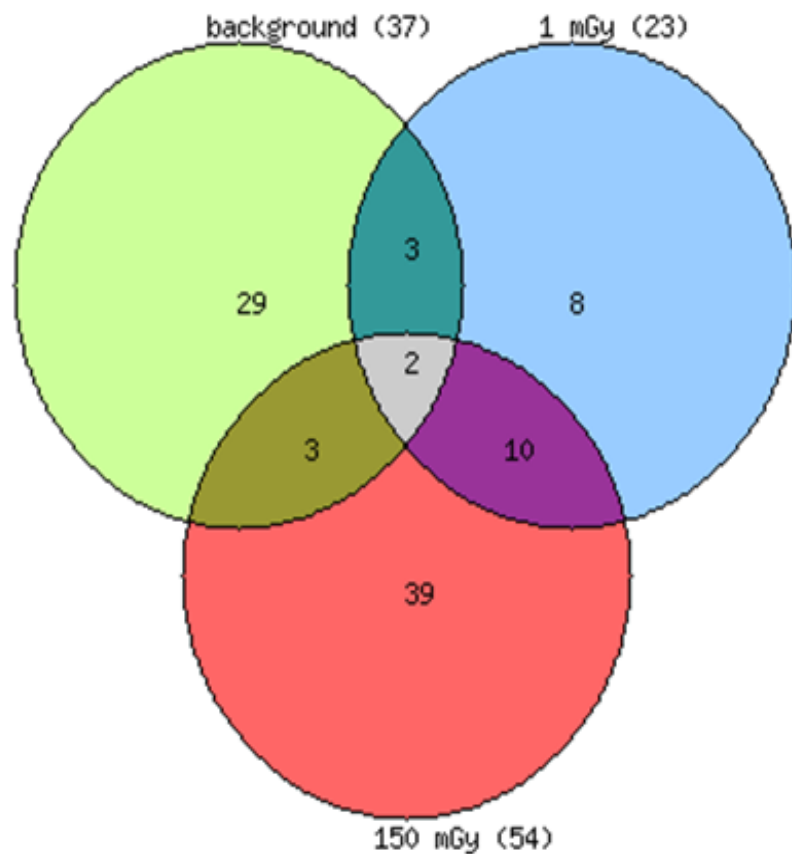


8-oxo-dG level

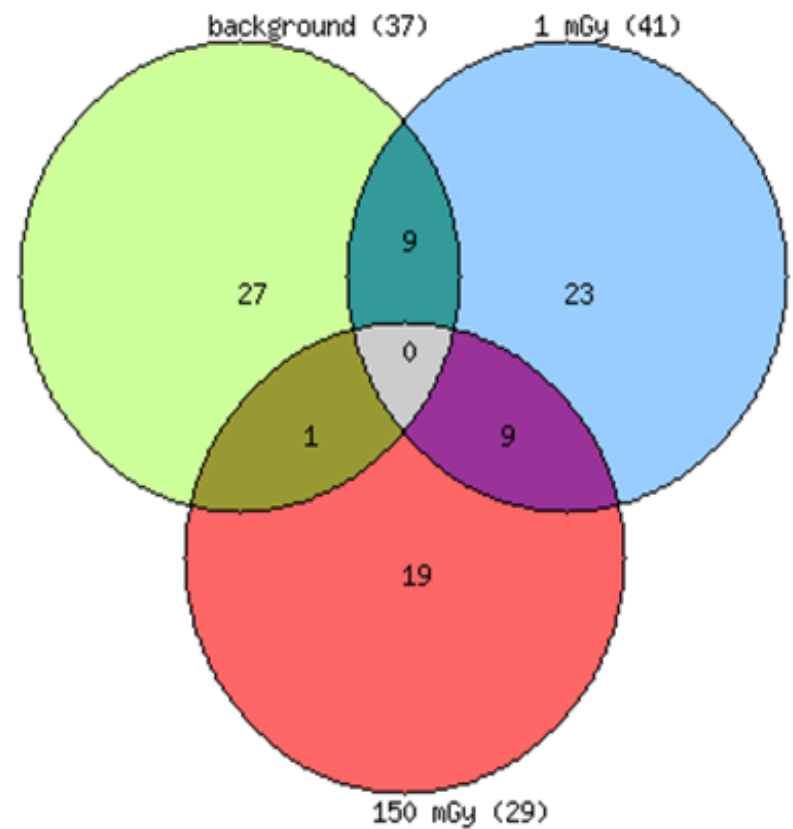
- SOD1
- CA1
- PARK7
- PRDX2
- SH3BGRL3

- BLVRB
- PRDX2

Sensitive patients (RTOG 4)



Normo-sensitive patients (RTOG 0)



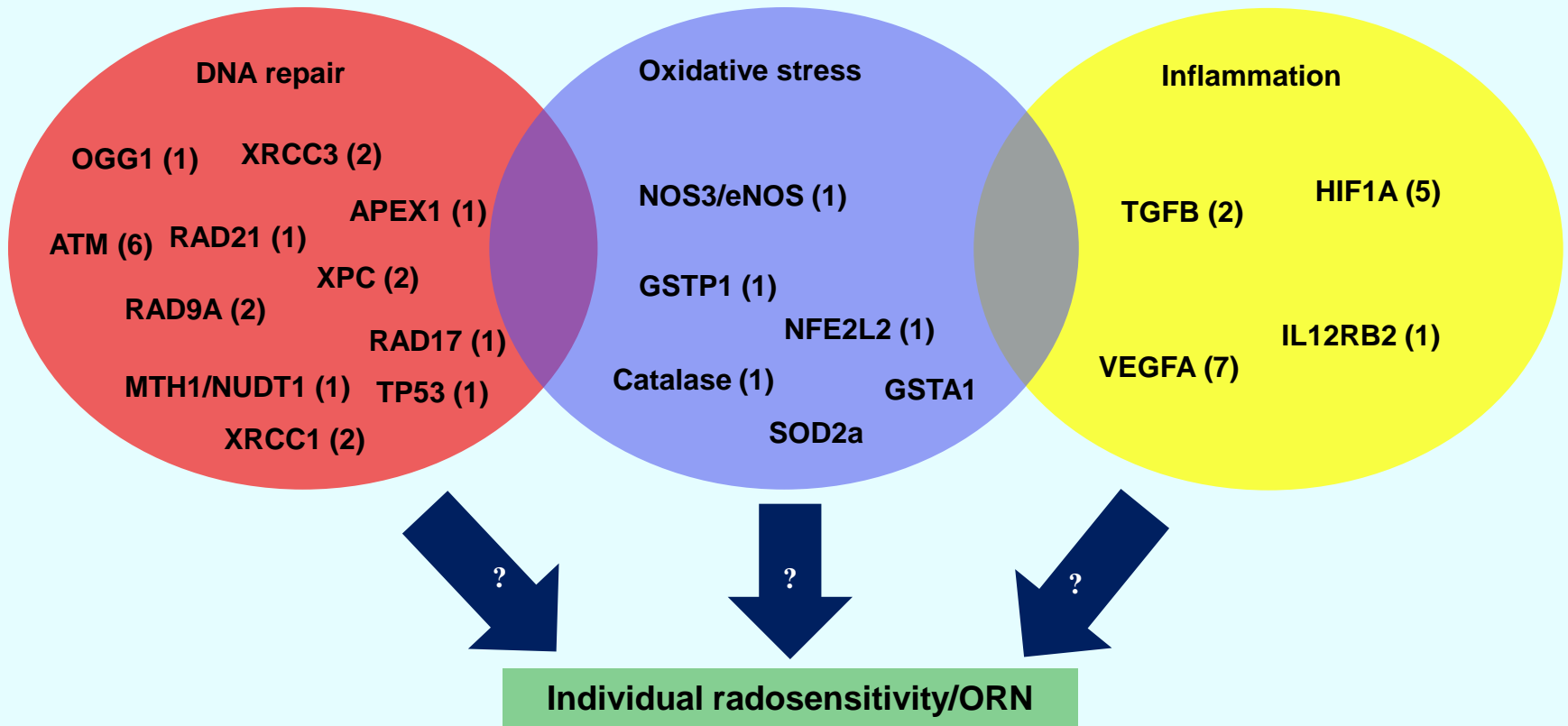
1 mGy gamma radiation affects several protein expression in cells from normosensitive related to:

- Oxidative stress / NRF2-mediated oxidative stress response,
- Decreased transmembrane potential of mitochondria and mitochondrial membrane

**Unique proteomic signature for radiation sensitive patients; a comparative study between normo-sensitive and radiation sensitive breast cancer patients**

[Sara Skiöld<sup>a</sup>](#), [Omid Azimzadeh<sup>b</sup>](#), [Juliane Merl-Pham<sup>c</sup>](#), [Ingemar Naslund<sup>d</sup>](#), [Peter Wersall<sup>d</sup>](#), [Elisabet Lidbrink<sup>d</sup>](#), [Soile Tapio<sup>b</sup>](#), [Mats Harms-Ringdahl<sup>a</sup>](#), [Siamak Haghdoost<sup>a</sup>](#), Mutation Research. 2014,

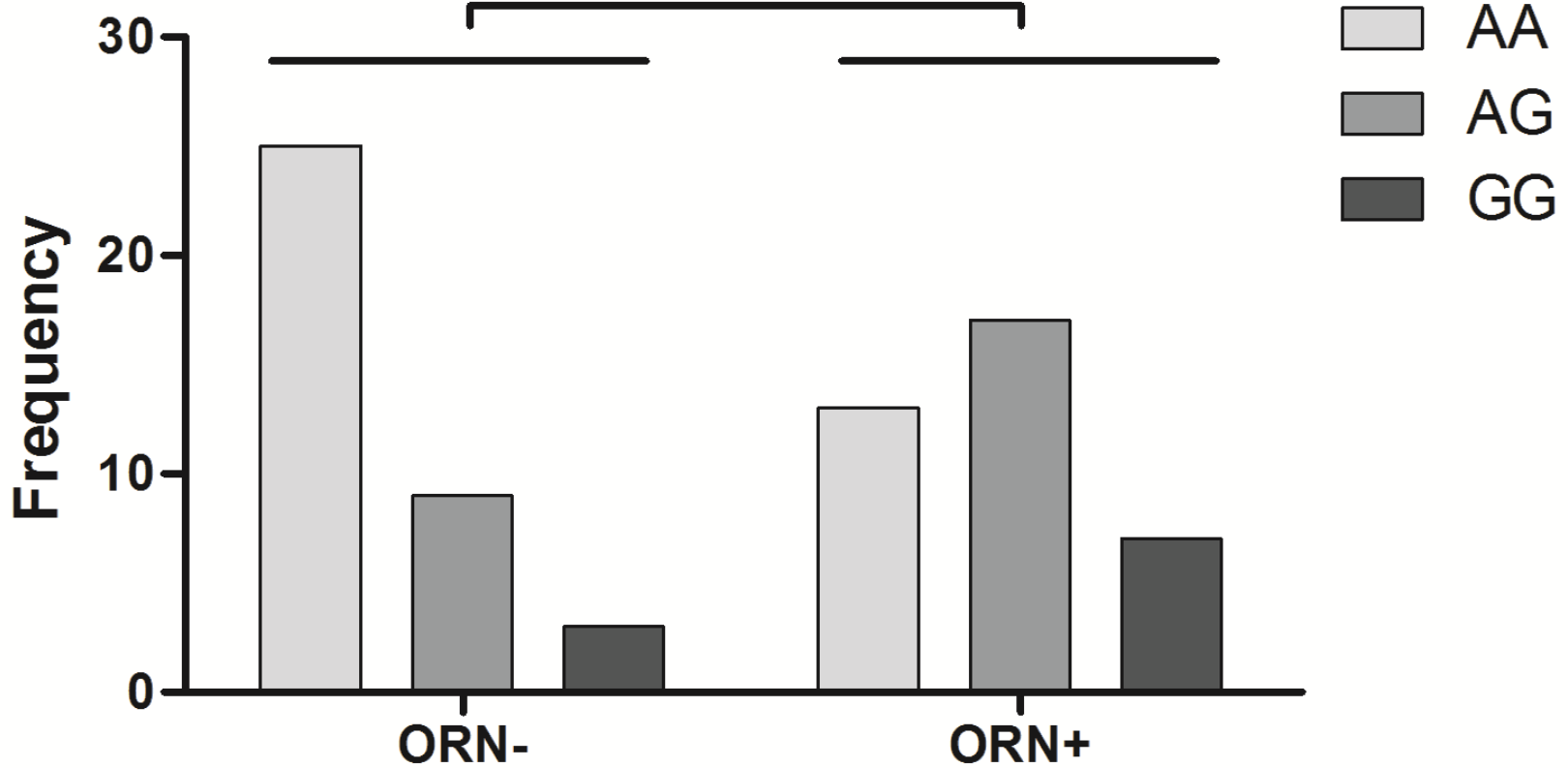




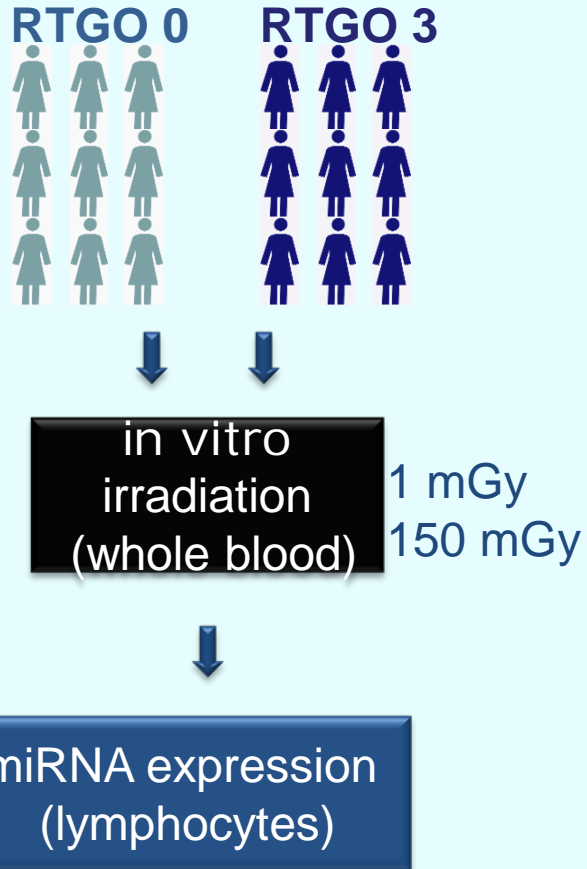
Investigating 58 point mutations (SNPs) previously implicated in side effects to RT

**B****rs1695 (GSTP1)**

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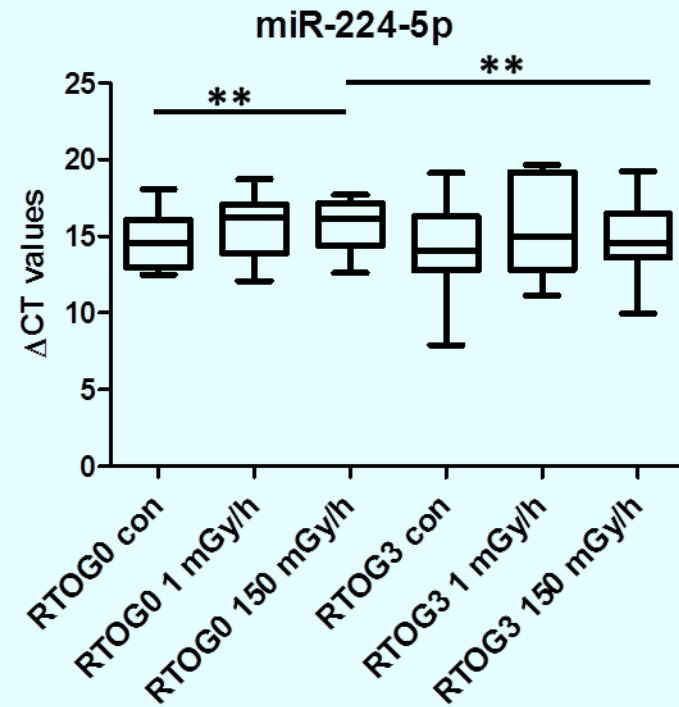
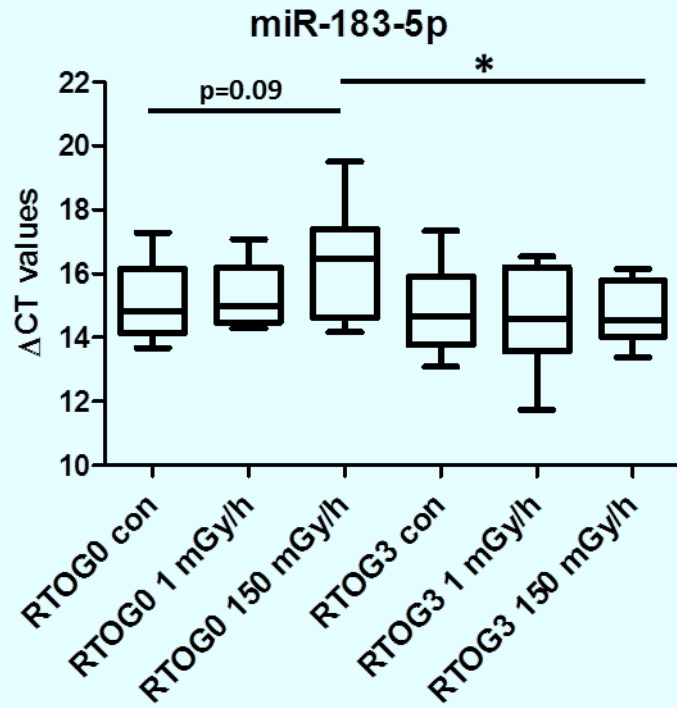
# miRNAs as biomarker for individual radiosensitivity (RADSENS)



miRnome analysis: 1152 miRNAs

sample	
RTOG 3/ RTGO 0	20 down, 11 up
RTOG 3, 150 mGy	23 down, 24 up
RTOG 0, 150 mGy	18 down, 15 up
RTOG 3, 1 mGy	61 up
RTOG 0, 1 mGy	41 down, 24 up

# miRNA expression changes after low dose irradiation



# General conclusion

- Patients individual ability to handle oxidative is related to individual response to radiotherapy
- miRNA biomarkers: validation is ongoing in cellular model system using miRNA inhibitors
- Oxidative stress response, coagulation properties and acute phase response are hallmarks of radiation sensitivity supporting our previous study on oxidative stress response.
  - 8-oxo-dG levels
  - proteomic approach
  - SNP in GSTP1



## HelmholtzZentrum münchen

Deutsches Forschungszentrum für Gesundheit und Umwelt

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