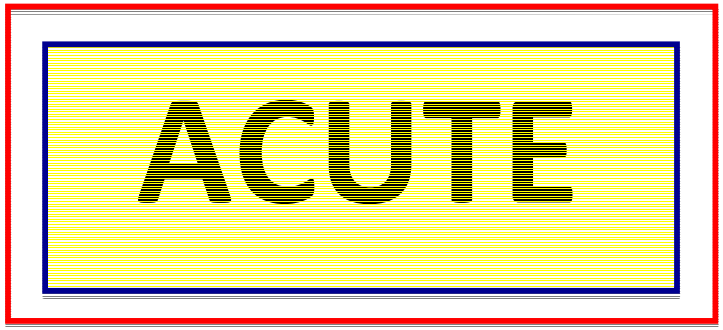
PREDICTORS OF TOXICITY: ACUTE AND LATE



M Mangoni

Università di Firenze

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Radiotherapy and Oncology 64 (2002) 131–140

RADIOTHERAPY & ONCOLOGY

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Does variability in normal tissue reactions after radiotherapy have a genetic basis – where and how to look for it?

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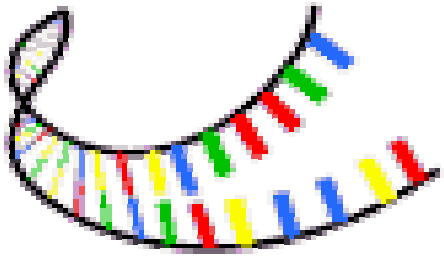
hyper-responsive clinical phenotype

Single Nucleotide Polymorphisms (SNPs)



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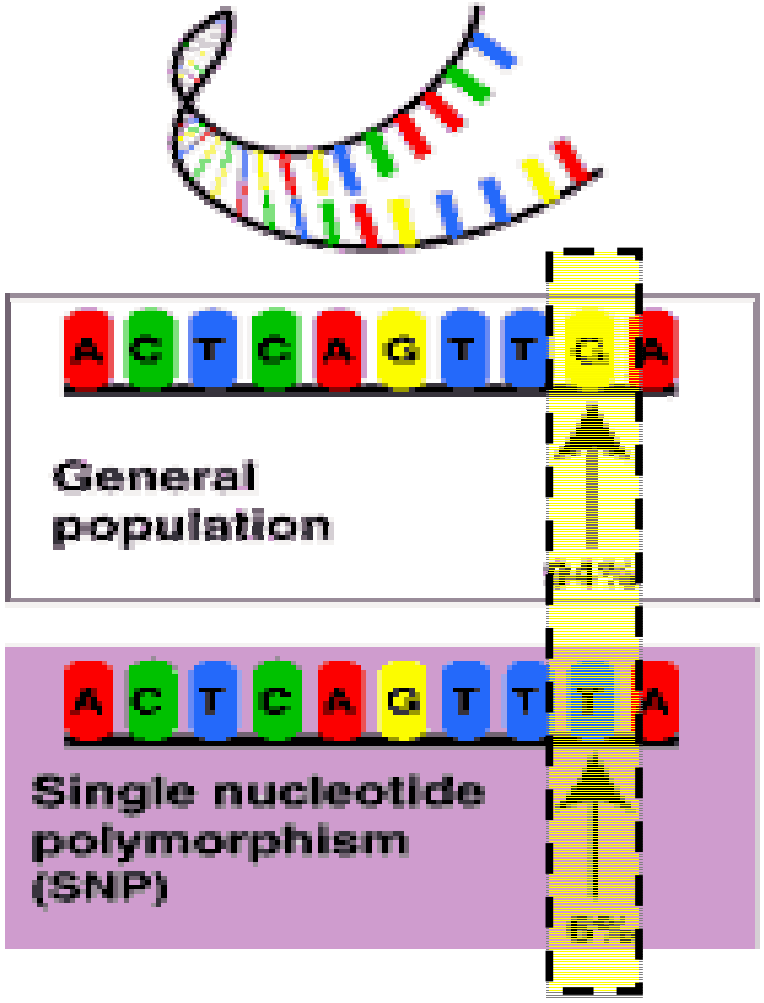
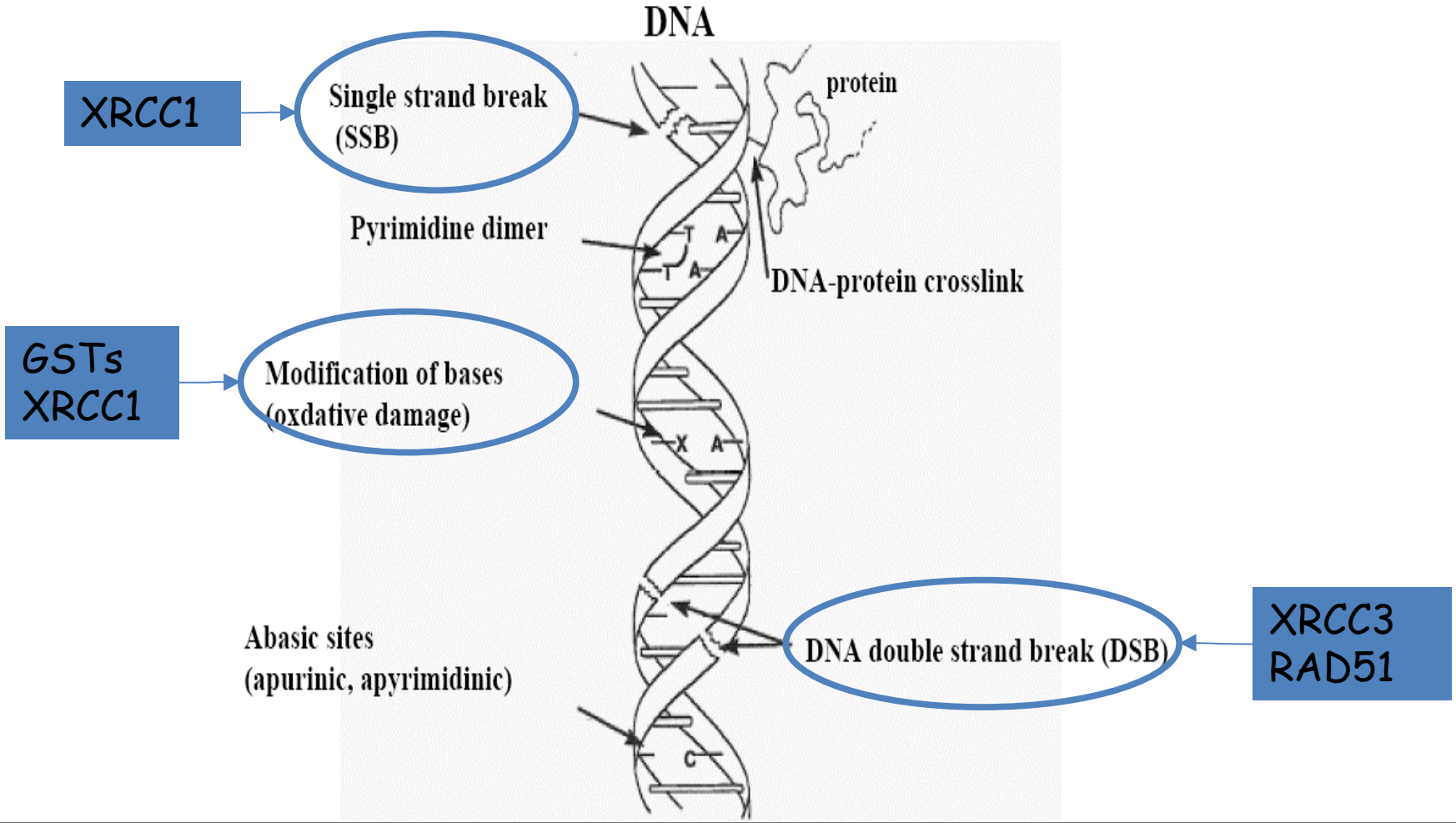


Genetic variants in which an alternate base pair is present at a particular nucleotide location

where to look for it?

candidate gene approach



where to look for it?

candidate gene approach

- ✓ Endogenous oxidative stress defence
  - GSTM1, GSTT1, GSTA1, GSTP1
  - SOD2, MPO, eNOS

Ambrosone CB. Breast Cancer Res. 8 (2006) R40.

- ✓ DNA repair systems
  - **BER**: XRCC1, APEX1, OGG1, LIG3
  - **NER**: ERCC2/XPD, ERCC4/XPF, RAD9A
  - **HR and NHEJ**: RAD51, RAD52, XRCC3, XRCC2,NBN, LIG4, BRCA1, BRCA2

Moullan N.Cancer Epidemiol. Biomarkers Prev. 12 (2003) 1168–1174.

- ✓ DNA damage signalling and cell cycle control
  - ATM

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 52–58, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.04.023

CLINICAL INVESTIGATION **Breast**

ASSOCIATION BETWEEN GENETIC POLYMORPHISMS IN THE XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, AND MGMT GENES AND RADIOSENSITIVITY IN BREAST CANCER PATIENTS

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- Prospective study: 87 breast cancer patients receiving RT after a breast conserving surgery

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- Prospective study: 87 breast cancer patients receiving RT after a breast conserving surgery

- severe acute skin reactions (moist desquamation or interruption of RT due to toxicity) were associated with SNPs, using Cox proportional hazards accounting for biologically effective dose (BED)

$$BED = nd\left(1 + \frac{\alpha}{\alpha/\beta}\right) - \frac{\gamma}{\alpha}(T - T_\circ)$$

where: *n: number of fractions; d: fraction size*
α/β ratio: 10 for acute skin reaction
γ/α: time factor of 0,7Gy/day
T: overall treatment time
$T_\circ$:starting time for compensatory proliferation of 21 days

(Fowler JF. IJROBP 1991, 21: 1451-6)

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- Prospective study: 87 breast cancer patients receiving RT after a breast conserving surgery
- severe acute skin reactions (moist desquamation or interruption of RT due to toxicity) were associated with SNPs, using biologically effective dose (BED)
- polymorphic regions analyzed:

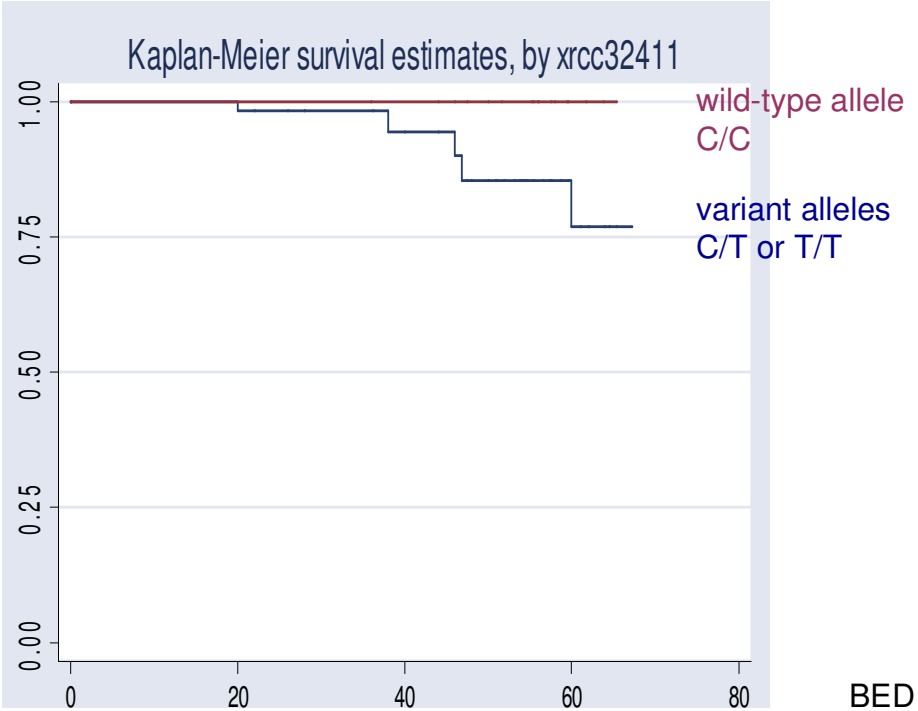
DNA repair genes	XRCC1-Arg399Gln XRCC1-Arg194Trp
	XRCC3-Thr241Met
	XPD-Asp312Asn XPD-Lys751Gln
Glutathione S-transferase genes	GSTM1 GSTT1
DNA mismatch repair genes	hMSH2 gIVS12-6T>C MLH1 I219V MSH3 T1045A MGMT L84F

8 out of 87 patients → severe acute skin toxicity

1) Carriers of the **variants of the XRCC3-Thr241Met gene** have an increased risk of severe acute toxicity

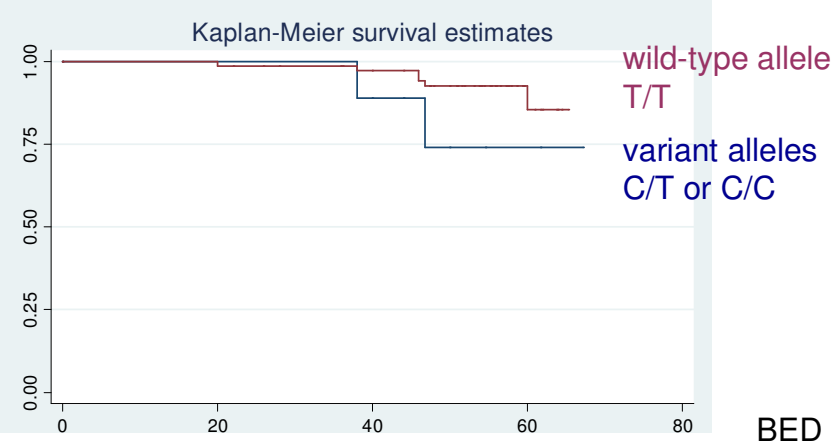
hazard ratio (HR) unquantifiably high

	HR (95% CI)	All patients	Severe toxicity
C/C (wt)	1.00	29	0
C/T or T/T	∞	58	8



2) Carriers of the **variants of the hMSH2 gIVS12-6T>C gene** have an increased risk of severe acute toxicity

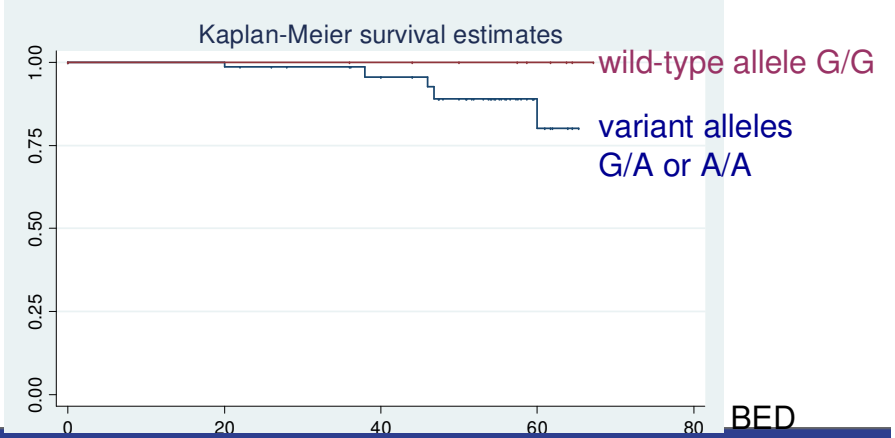
	HR (95% CI)	All patients	Severe toxicity
T/T(wt)	1.00	78	6
C/T or C/C	10.92 (1.61-73.89)	9	2



3) Carriers of the **variants of the MSH3 T1045A gene** have an increased risk of severe acute toxicity

hazard ratio (HR) unquantifiably high

	HR (95% CI)	All patients	Severe toxicity
G/G(wt)	1.00	11	0
G/A or A/A	∞	76	8



4) when considering joint effects of different SNPs,
carriers of the **XRCC1-Arg194Trp variant allele** and **XRCC1-Arg399Gln wild-type allele** have un increased risk of severe acute toxicity

Arg194Trp	**Arg399Gln**	HR (95% CI)	All patients	Severe toxicity
C/C (wt)	G/G (wt)	1.00	36	1
C/C (wt)	A/A o G/A	7.14 (0.77-66.34)	41	6
C/T o T/T	G/G (wt)	23.12 (0.94-567.75)	5	1
C/T o T/T	A/A o G/A	0.00	5	0

Conclusions

The variant alleles of the **XRCC3-Thr241Met**, **hMSH2 gIVS12-6T>C**, **MSH3 T1045A**, **XRCC1-Arg194Trp** may increase the risk of severe acute skin toxicity after RT

Conclusions

The variant alleles of the **XRCC3-Thr241Met**, **hMSH2 gIVS12-6T>C**, **MSH3 T1045A**, **XRCC1-Arg194Trp** may increase the risk of severe acute skin toxicity after RT

Comparison with other studies

•No association between GSTM1 or GSTT1 and skin reaction,

= Ambrosone CB, *Breast Cancer Res* 2006; 8: R40

•XRCC1-194 Trp in combination with XRCC1-399 Gln alleles more frequent in radiosensitive pts

= Moullan N, *Cancer Epidemiol Biomarkers Prev* 2003; 12: 1168-74

•Association between XRCC3 241 Met and acute skin reactions

≠ in other reports

Chang-Claude J, *Clin cancer Res* 2005; 11: 4802-9

Popanda O, *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1048-50

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S145–S150, 2010

0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.08.076

QUANTEC

QUANTEC: VISION PAPER

BIOMARKERS AND SURROGATE ENDPOINTS FOR NORMAL-TISSUE EFFECTS OF RADIATION THERAPY: THE IMPORTANCE OF DOSE–VOLUME EFFECTS

Søren M. Bentzen, Ph.D., D.Sc.,*† Matthew Parliament, M.D.,‡ Josepi Adam Dicker, M.D., Ph.D.,†¶ Walter J. Curran, M.D.,¶‖ Jacqueline P. and Barry S. Rosenstein, Ph.D.††

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1295–1296, 2010

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doi:10.1016/j.ijrobp.2009.12.017

GENEPI
Europe

REPORT

ESTABLISHMENT OF A RADIOGENOMICS CONSORTIUM

Catharine West* and Barry S. Rosenstein† On behalf of: Jan Alsner, David Azria, Gillian Barnett, Adrian Begg, Søren Bentzen, Neil Burnet, Jenny Chang-Claude, Eric Chuang, Charlotte Coles, Kim De Ruyck, Dirk De Ruysscher, Alison Dunning, Rebecca Elliott, Laura Fachal, Janet Hall, Karin Haustermans, Carsten Herskind, Tobias Hoelscher, Takashi Imai, Mayumi Iwakawa, Don Jones, Cecilia Kulich on behalf of EQUAL-ESTRO, Jan-Hans Langendijk, Peter O'Neill, Mahmut Ozsahin, Matthew Parliament, Andrzej Polanski, Barry Rosenstein, ds, Chris Talbot, Hubert Thierens, Ana Vega, Catharine West, & John Yarnold.

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 3, pp. 646–655, 2006

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ELSEVIER

doi:10.1016/j.ijrobp.2006.03.006

REPORT

*GENE*TIC *P*REDICTORS OF *A*DVERSE *R*ADIOTHERAPY *E*FFECTS: THE GENE-PARE PROJECT

Alice Y. Ho, M.D.,* David P. Atencio, Ph.D.,* Sheila Peters, B.A.,* Richard G. Stock, M.D.,* Silvia C. Formenti, M.D.,§ Jamie A. Cesaretti, M.D.,* Sheryl Green, M.D.,* Bruce Haffty, M.D.,¶ Karen Drumea, M.D.,‖ Larisa Leitzin, M.D.,‖ Abraham Kuten, M.D.,‖ David Azria, M.D., Ph.D.,# Mahmut Ozsahin, M.D., Ph.D.,** Jens Overgaard, M.D., D.M.Sc., F.A.C.R., F.R.C.R.,†† Christian N. Andreassen, M.D.,†† Cynthia S. Trop, M.D.,‡‡ Janelle Park, M.D.,§§ and Barry S. Rosenstein, Ph.D.*†‡§

GENEPARE
USA

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L Livi

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A Seniori Costantini

S Bisanzi

F Carozzi

C Sani