Ruolo dei polimorfismi del DNA nucleare nello sviluppo di tossicità cutanea e sottocutanea tardiva in pazienti affette da tumore mammario sottoposte a RT adiuvante ipofrazionata

Dr.ssa A.Podgornii

SC di Radioterapia Oncologica,
Dipartimento Oncologico e Tecnologie Avanzate,
ASMN-IRCCS, Reggio Emilia

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Association between Single Nucleotide Polymorphisms in XRCC3 and Radiation-Induced Adverse Effects on Normal Tissue: A Meta-Analysis.

Author, Year	Country	Ethnicity	Disease	SNP	Adverse Effect	Assessment Criteria	Sample Size (N)	Cases/N	Study Design	EBRT Dose, Gy	Chemotherapy Involved
Alsbeih 2010[30]	Saudi Arabia	Asian	HNC	rs861539	Late effect: fibrosis	RTOG/EORTC≥G2	60	50%	Case-control	66–70	Yes
Azria 2008[7]	France	Caucasian	Mixed[a]	rs861539	Late effect: fibrosis	CTCAE v3.0≥G3	34	47.06%	Case-control	NA	Yes
Burri 2008[31]	USA	Mixed	Prostate cancer	rs861539	Late effect: rectal bleeding, urinary morbidity, erectile dysfunction	RTOG/EORTC≥G1	135	9.36%	Cohort	45 Gy and/ OR brachytherapy	NA
Chang-Claude 2009[32]	Germany	Caucasian	Breast cancer	rs861539	Late effect: telangiectasia	RTOG/EORTC≥G2	401	31.67%	Cohort	55–70	No
Cheuk 2014[33]	China	Asian	HNC	rs861539, rs1799794	Late effect: fibrosis	RTOG≥G1	120	24.17%	Cohort	66–76	Yes
De Ruyck 2005 [8]	Belgium	Caucasian	Gynecologic cancer[b]	rs861539, rs1799794, rs1799796	Late effect: side effect in the pelvic area	CTCAE v3.0≥G2	62	35.48%	Cohort	45–66 and/or brachytherapy	Yes
Fachal 2012[34]	Spain	Caucasian	Prostate cancer	rs1799794	Early effect: gastrointestinal morbidity, genitourinary morbidity	CTCAE v3.0≥G2	698	4.87%	Cohort	70–76	NA
Falvo 2011[35]	Italy	Caucasian	Breast cancer	rs861539	Early effect: acute skin toxicity	CTCAE v3.0≥G1	57	33.33%	Cohort	18–21	Yes
Flavo 2012[36]	Italy	Caucasian	Breast cancer	rs1799794	Late effect: fibrosis or fat necrosis	CTCAE v3.0≥G2	57	45.61%	Cohort	18–21	Yes
Mangoni 2011 [37]	Italy	Caucasian	Breast cancer	rs861539	Early effect: acute skin toxicity	CTCAE v2.0≥G2c [c]	61	11.48%	Cohort	50–62.8	Yes
Popanda 2006[38]	Germany	Caucasian	Breast cancer	rs861539	Early effect: acute skin toxicity	CTCAE v2.0≥G2	444	17.12%	Cohort	49.2–58.8	NA
Pretasi 2011[39]	Italy	Caucasian	HNC	rs861539	Early effect: mucositis	CTCAE v3.0≥G2	101	67.33%	Cohort	54–70	Yes
Sakano 2010[40]	Japan	Asian	Bladder cancer	rs861539	Early effect: gastrointestinal morbidity	CTCAE v3.0≥G2	94	9.57%	Cohort	30.0–60.4	Yes
Tucker 2013[41]	USA	Caucasian	NSCLC	rs861539	Late effect: radiation pneumonitis	CTCAE v3.0≥G3	141	19.86%	Cohort	50.4–72	Yes
Werbrouck 2009 [42]	Belgium	Caucasian	HNC	rs861539, rs1799794, rs1799796	Early effect: mucositis, dysphagia	CTCAE v3.0≥G3	85	32.94%	Cohort	66–69	Yes
Yin 2011[43]	USA	Caucasian	NSCLC	rs861539	Late effect: radiation pneumonitis	CTCAE v3.0≥G1	196	69.90%	Cohort	60–70 (majority)	Yes
Zou 2014[11]	China	Asian	HNC	rs861539	Late effect: xerostomia	≥G 1 [d]	103	41.75%	Cohort	70	Yes

Background

- ✓ The aim of this study was to examine the effect of polymorphisms on the acute and late radiation-induced toxicity in early breast cancer survivors treated with a HF-WBI

- ✓ ICAM1 (intercellular adhesion molecule) gene, located on the 19th chromosome
  VCAM1 (vascular adhesion molecule) gene, located on the 1st chromosome

- ✓ Selected 2 SNP (single nucleotide polymorphism) in coding regions:
  - rs1041163 for VCAM1 gene
  - rs5498 for ICAM1 gene

ala.podgornii@asmn.re.it

Methods and Materials

January 2009 – December 2012

- ✓ FU median 34 mths (range 0-44)
- ✓ 160 patients
- ✓ mean age 63 yr (range 38-88)
- ✓ 53% of the patients ≥ 65 yr

Factors	Number	%
No Age (38-88, mean 63)	160	
Breast side right left	 76 84	 47.5 52.5
Breast quadrant SE SC II IE IC EE SI	 77 31 8 12 8 8 16	 48.1 19.4 5 7.5 5 5 10
Histological type IDC ILC Intraductal other	 113 15 31 1	 70.6 9.4 19.4 0.6
T stage Tis T1a T1b T1c T2	 31 6 30 67 26	 19.3 3.8 18.8 41.9 16.2
N stage Nx N0 N1	 10 122 28	 6.3 76.2 17.5
Grading G1 G2 G3 NA	 23 88 47 2	 14.4 55 29.4 1.2
Chemotherapy Yes No	 37 123	 23.1 76.9

ala.podgornii@asmn.re.it

Methods and Materials

DNA extraction and SNP genotyping

Genomic DNA was isolated from competitive allele-specific PCR method

rs5498 (ICAM1) major allele A (57.2%)

rs1041163 (VCAM1) of major allele T (83.4%)

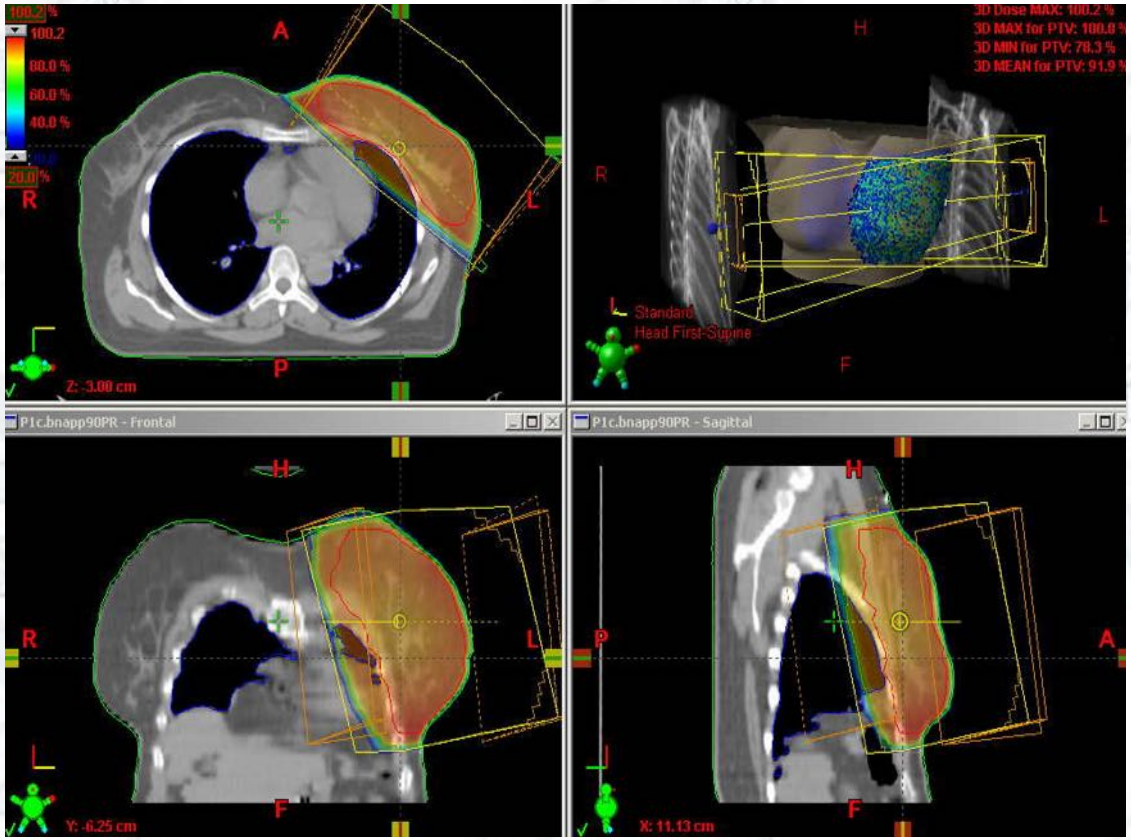
ala.podgornii@asmn.re.it

Planning

- ✓ HF-WBI
- ✓ Daily dose: 2.67 Gy/die
- ✓ Total dose: 40.05 Gy

28 % of the patient received a tumor bed boost

(3 Gy/die x 3fr)*

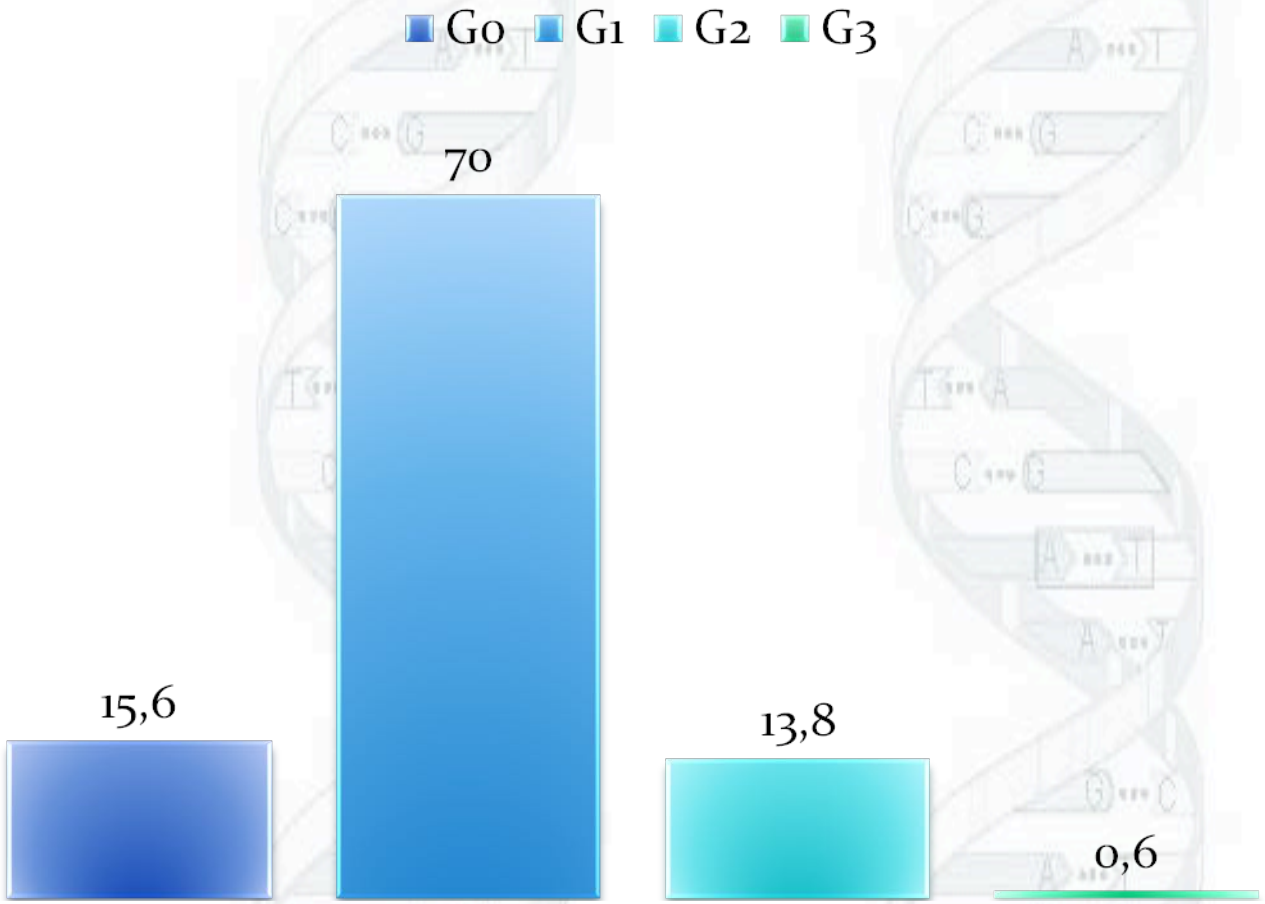


•Indications for a tumor bed boost:

- age ≤ 50 years
- positive margins
- other factors of risk

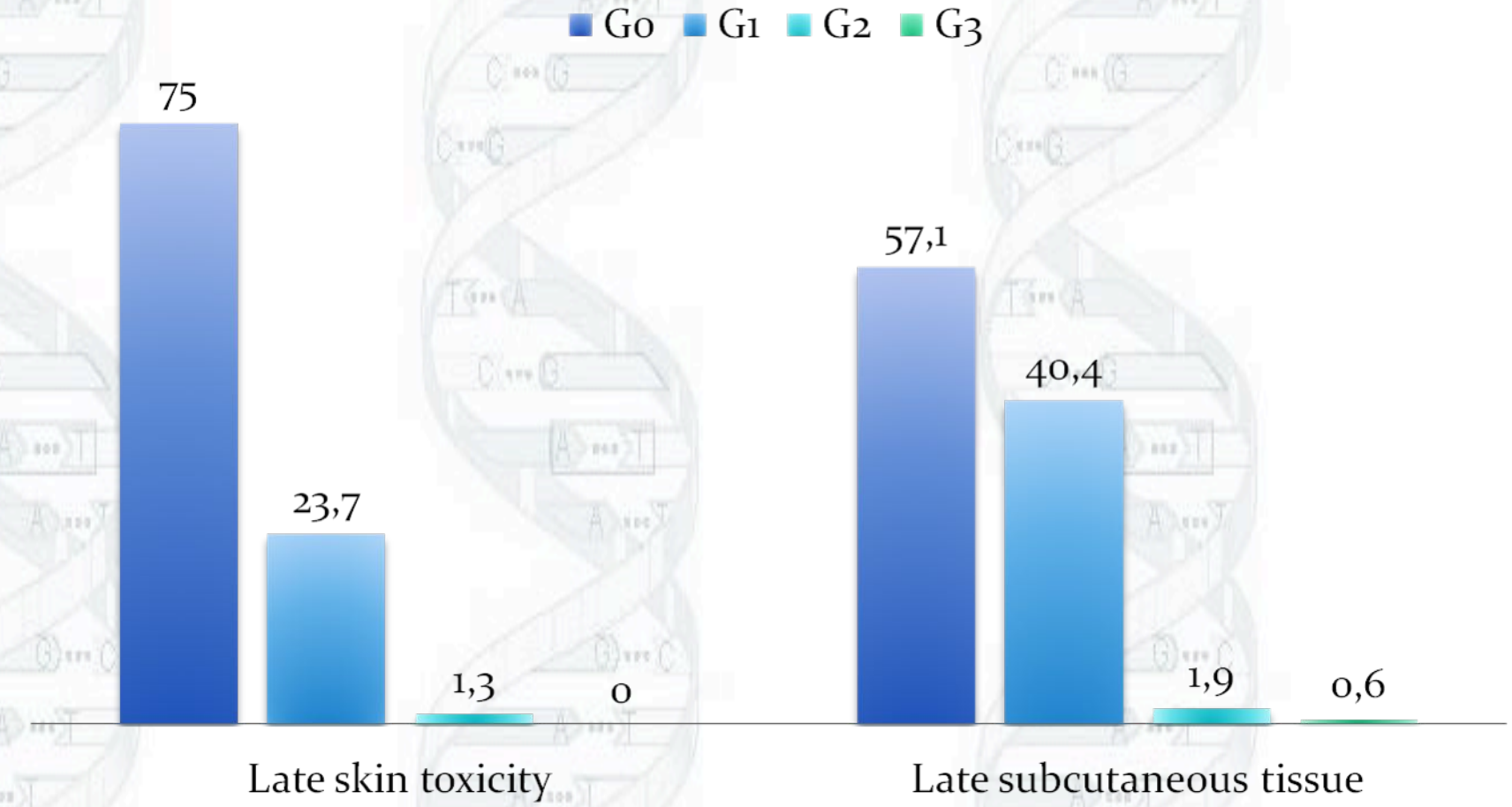
ala.podgornii@asmn.re.it

Acute skin toxicity



http://www.rtog.org

Late toxicity



http://www.rtog.org

Results

Acute Skin toxicity

Predictive factors of radiation-induced toxicity in breast cancer patients

Acute Skin Toxicity									
				Univariate Analysis			Multivariate Analysis		
	Patients (n, 100%)	No (n,%)	Yes (n,%)	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	160	25 (15.6)	135 (84.4)						
Age									
≤64	81	14 (17.3)	67 (82.7)	-					
> 64	79	11 (13.9)	68 (86.1)	1.29	0.55-3.11	0.559	1.72	0.65-4.71	0.278
Diabetes									
No	144	22 (15.3)	122 (84.7)	-					
Yes	16	3 (18.8)	13 (81.2)	0.78	0.22-3.60	0.717	0.94	0.25-4.62	0.936
Ipertension									
No	139	22 (15.8)	117 (84.2)	-					
Yes	21	3 (14.3)	18 (85.7)	1.13	0.34-5.10	0.856	1.03	0.26-5.18	0.962
Boost									
No	119	23 (19.3)	96 (80.7)	-					
Yes	41	2 (4.9)	39 (95.1)	1.17	1.29-30.0	0.043*	5.35	1.38-35.7	0.033*

Results

Predictive factors of radiation-induced toxicity in breast cancer patients

Late Skin toxicity

Chronic Skin Toxicity									
				Univariate Analysis			Multivariate Analysis		
	Patients (n, 100%)	No (n,%)	Yes (n,%)	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	156	117(75.0)	39 (25.0)						
Age									
≤64	80	60 (75.0)	20 (25.0)						
> 64	76	57 (75.0)	19 (25.0)	1	0.48-2.07	0.999	0.88	0.37-2.06	0.768
Diabetes									
No	141	108 (76.6)	33 (23.4)						
Yes	15	9 (60.0)	6 (40.0)	2.18	0.68-6.51	0.166	2.50	0.73-8.20	0.130
Ipertension									
No	135	102 (75.6)	33 (24.4)						
Yes	21	15 (71.4)	6 (28.6)	1.24	0.41-3.32	0.685	1.34	0.38-4.32	0.631
Boost									
No	115	90 (78.3)	25 (21.7)						
Yes	41	27 (65.9)	14 (34.1)	1.87	0.84-4.06	0.118	2.20	0.92-5.28	0.072

Late Subcutaneous tissue toxicity

Chronic Soft-Tissues Toxicity									
				Univariate Analysis			Multivariate Analysis		
	Patients (n, 100%)	No (n,%)	Yes (n,%)	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	156	89 (57.1)	67 (42.9)						
Age									
≤64	80	44 (55.0)	36 (45.0)						
> 64	76	45 (59.2)	31 (40.8)	0.84	0.44-1.59	0.596	0.73	0.34-1.53	0.411
Diabetes									
No	141	84 (59.6)	57 (40.4)						
Yes	15	5 (33.3)	10 (66.7)	2.95	0.99-9.88	0.060	3.27	1.04-11.5	0.049*
Ipertension									
No	135	77 (57.0)	58 (43.0)						
Yes	21	12 (57.1)	9 (42.9)	0.99	0.38-2.51	0.993	1.10	0.37-3.17	0.856
Boost									
No	115	69 (60.0)	46 (40.0)						
Yes	41	20 (48.8)	21 (51.2)	1.58	0.77-3.24	0.214	1.75	0.80-3.90	0.164

Analysis of different genotypes and acute and late toxicity

Acute Skin Toxicity									
				Univariate Analysis			Multivariate Analysis		
	# Patients	No	Yes	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	160	25	135						
s5498_ICAM1									
AA	50	4	46	-					
AG	83	17	66	0.34	0.09-0.98	0.065	0.36	0.10-1.10	0.094
GG	27	4	23	0.50	0.11-2.29	0.356	0.47	0.10-2.23	0.328
1163_VCAM1									
TT	110	14	96	-					
TC	47	11	36	0.48	0.20-1.16	0.099	0.49	0.19-1.24	0.124
CC	3	0	3	nd	nd	nd	nd	nd	nd

Chronic Skin Toxicity									
				Univariate Analysis			Multivariate Analysis		
	# Patients	No	Yes	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	156	117	39						
s5498_ICAM1									
AA	49	30	19						
AG	80	66	14	0.33	0.15-0.75	*0.009 **	0.32	0.13-0.74	*0.009 **
GG	27	21	6	0.45	0.14-1.27	0.146	0.46	0.14-1.34	0.176
1163_VCAM1									
TT	107	76	31						
TC	46	38	8	0.52	0.20-1.18	0.136	0.49	0.18-1.18	0.126
CC	3	3	0	nd	nd	nd	nd	nd	nd

Chronic Soft-Tissues Toxicity									
				Univariate Analysis			Multivariate Analysis		
	# Patients	No	Yes	OR	C.I (95%)	P Value	OR	C.I (95%)	P Value
	156	89	67						
s5498_ICAM1									
AA	49	22	27						
AG	80	50	30	0.49	0.23-1.00	0.052	0.46	0.21-0.98	*0.045 **
GG	27	17	10	0.48	0.18-1.24	0.134	0.49	0.17-1.32	0.164
1163_VCAM1									
TT	107	55	52						
TC	46	31	15	0.51	0.24-1.04	0.069	tab	0.21-1.01	0.058
CC	3	3	0	nd	nd	nd	nd	nd	nd

Results

ameno un allele C del rs1041163
di VCAM1
rischio minore di sviluppare tox.
cronica dei tessuti molli

Chronic Soft Tissues Toxicity				
	No	Yes	OR (95%CI)	*P value*
Rs5498_ICAMI				
Single Genotype				
A/A	22	27		
A/G	50	30	0.46(0.21-0.98)	*0.045**
G/G	17	10	0.49(0.17-1.32)	0.164
Dominant Model				
A/A	22	27		
G/A+G/G	67	40	0.47 (0.22-0.96)	*0.041**
Recessive Model				
A/A+G/A	72	57		
G/G	17	10	0.77 (0.31-1.86)	0.573
Rs1041163_VCAMI				
Single Genotype				
T/T	55	52		
C/T	31	15	0.48 (0.21-1.01)	0.058
C/C	3	0	nd	nd
Dominant Model				
T/T	55	52		
C/T+C/C	34	15	0.43 (0.20-0.89)	*0.026**
Recessive Model				
T/T+C/T	86	67		
C/C	3	0	nd	nd

Chronic Skin Toxicity				
	No	Yes	OR (95%CI)	*P value*
Rs5498_ICAMI				
Single Genotype				
A/A	30	19		
A/G	66	14	0.32 (0.13-0.74)	*0.009**
G/G	21	6	0.46 (0.14-1.34)	0.176
Dominant Model				
A/A	30	19		
G/A+G/G	87	20	0.35 (0.16-0.78)	*0.010**
Recessive Model				
A/A+G/A	96	33		
G/G	21	6	0.87 (0.29-2.32)	0.787
Rs1041163_VCAMI				
Single Genotype				
T/T	76	31		
C/T	38	8	0.49 (0.18-1.18)	0.126
C/C	3	0	nd	nd
Dominant Model				
T/T	76	31		
C/T+C/C	41	8	0.44 (0.17-1.04)	0.075
Recessive Model				
T/T+C/T	114	39		
C/C	3	0	nd	nd

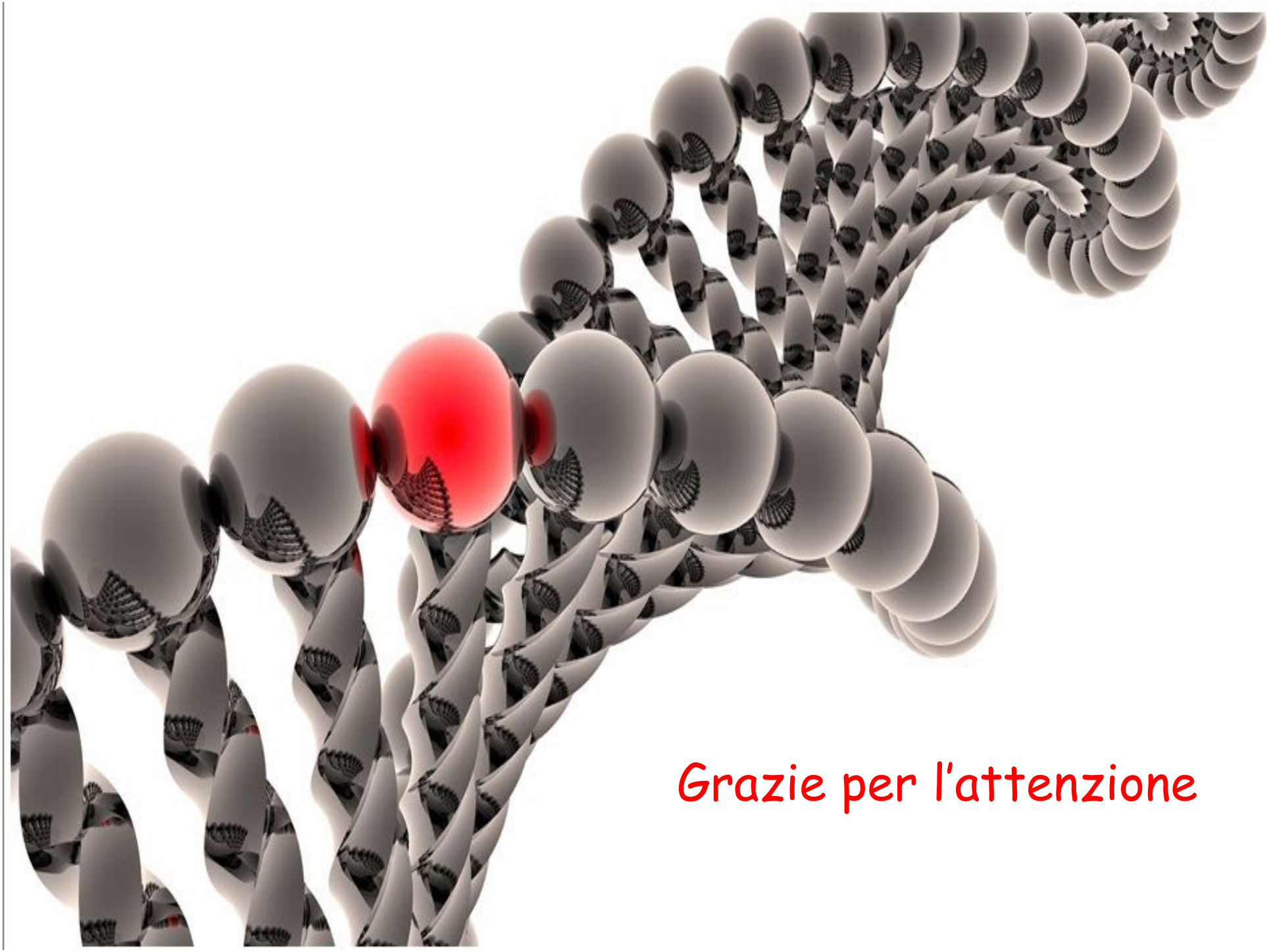
paziente portatrici allele G del
rs5498 di ICAM1
hanno un rischio minore di
sviluppare tox. cute e tessuti molli
cronica

Conclusions

✓le molecole di adesione ICAM1 e VCAM1 possono modulare lo sviluppo della fibrosi in pazienti affette da tumore mammario sottoposte a RT adiuvante HF

✓gli studi prospettici successivi potrebbero fornire informazioni più complete sulle basi genetiche della risposta dei tessuti sani alla radioterapia

✓l' identificazione di un sottogruppo di pazienti geneticamente predisposte ad un danno tardivo da RT, potrebbe indirizzare verso l' impiego di un diverso frazionamento della dose e/o tecniche di trattamento



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