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14. ABSTRACT

Women with earlier stage breast cancer who receive breast conserving surgery and radiation therapy have a generally good prognosis. However, among 15-20% of these women, breast cancer recurs, and a similar proportion of women also experience severe toxicity with radiation therapy. It is possible that inter-individual differences in capabilities of both tumor and normal cells to protect themselves from radiation-induced damage, and to repair that damage if it does occur, will influence recurrence and toxicity. This variability results from common genetic polymorphisms. This study is conducted in a well-characterized cohort of women who had breast-conserving surgery followed by radiation therapy, and in whom skin reactions were measured and noted. We are extracting DNA from blood to determine genetic polymorphisms in a number of genes that may be important in response to treatment. By conducting follow-up on the women in the study, we will be able to determine how variability in genes that protect cells from damage and in those that repair DNA damage will affect both breast cancer recurrence and toxicity experienced. Follow-up is ongoing, through clinic visits, letters, and home visits, and in the next year, we will correlate genotyping results with toxicity.

15. SUBJECT TERMS
Radiation sensitivity, DNA repair, oxidative DNA damage, genetic

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INTRODUCTION: Women with earlier stage breast cancer who receive breast conserving surgery and radiation therapy have a generally good prognosis. However, among 15-20% of these women, breast cancer recurs, and a similar proportion of women also experience severe toxicity with radiation therapy. It is possible that inter-individual differences in capabilities of both tumour and normal cells to protect themselves from radiation-induced damage, and to repair that damage if it does occur, will influence recurrence and toxicity. Activity of many of the proteins involved in these processes are determined by common inborn genetic differences, termed genetic polymorphisms. We conducted a pilot study to determine if this were the case, and although the study population was mixed in stage at diagnosis and treatments received, we found that women with variant alleles that would allow more treatment-generated reactive intermediates to reach tumor cells had better survival.
We are conducting the present study in a well-characterized cohort of women who had breast-conserving surgery followed by radiation therapy, and in whom skin reactions were measured and noted. We are extracting DNA from blood to determine genetic polymorphisms in a number of genes that may be important in response to treatment. By conducting follow-up on the women in the study, we will be able to determine how variability in genes that protect cells from damage and in those that repair DNA damage will affect both breast cancer recurrence and toxicity experienced.

BODY: Research accomplishments associated with each Task outlined in the Statement of Work will be addressed within the context of each of the objectives.

Technical Objective 1 Follow-up of breast cancer patients of the parent study regarding therapy outcome and survival and data collection.

The fieldwork, which could only commence as of April 2003 due to delays in administering the subcontract to the collaborative partner in Germany as reported earlier, is running smoothly and will be completed by the end of June 2005. Details pertaining to follow-up are listed below.

Task 1: Months 1-2: Organization of recontact with patients through different sources, development of clinical data forms and questionnaire, and establishment of database.

This task has been completed as reported in 2003.

Task 2: Months 3-24: Recruitment of patients through different sources, perform follow-up examination, obtain informed consent, collect clinical data, complete questionnaire

For the follow-up we attempted to contact all 478 patients. By the end of March 2005 we reached 473 patients, 5 patients were lost to follow-up. Four patients refused any participation, so we have data available from 469 patients (98.1%).
The information provided by the patients was validated through clinical records or through contact with the attending physician in 455 cases. In 19 cases we could not get clinical information because the patients changed the attending physician, or the physician closed his office or the patients refused further participation or were lost to follow-up. In the 4 remaining cases the validity check is planned to be completed by the end of June 2005.

A total of 422 patients (90%) underwent physical examination to assess late toxicity by the project radiologist. 47 patients were not examined because they refused the examination or they were deceased before recontact. The interval between the postoperative radiation and the examination in the patients was

2.8 – 2.9 years: 6 patients
3.0 – 3.9 years: 193 patients
4.0 – 4.9 years: 204 patients
5.0 – 5.9 years: 19 patients

To achieve a minimal follow-up period of 3 years after the radiation, we plan to reexamine the 6 patients where possible until end of June.
Informed consent was obtained from the patients and the questionnaire was completed by 426 patients.

Task 3: Months 24-36: Data entry with ongoing quality control and plausibility checks
Study data were entered on an ongoing basis and were cleaned through plausibility checks at regular intervals. The final data quality control and plausibility checks will commence in July 2005.

Task 4: Months 30-36 Perform statistical data analysis; initial descriptive analyses, study of main effects of data derived from questionnaire.

The preliminary analysis of the data obtained by the beginning of June 2005 with respect to outcome, survival and toxicity yield the following results:

Table 1 Vital status and course of disease in 469 breast cancer patients

	Number	Percent
Vital status		
Alive	443	94.5%
Dead	26	5.5%
Cause of death		
Breast cancer	11	2.3%
Other causes	7	1.5%
Unknown	8	1.7%
Course of disease[a]		
Local relapse	10	2.1%
Regional relapse	5	1.1%
Metastases or second cancer	26	5.5%
Unknown	1	0.0%
Second cancer		
Second cancer ipsilateral breast	2	0.4%
Second cancer other location	20	4.3%

[a] counts of different outcomes are not exclusive

400 patients survived disease-free by end of follow-up and 7 patients were disease-free at death.

The focus of the examinations referring to late radiation induced side effects are the outcomes: skin reaction, fibrosis of the breast in the operation field, and fibrosis outside the operation field. The occurrence of late toxicity in this study population based on the EORTC-RTOG classification scale is shown in the following table.

Table 2 Occurrence of late side effects after radiation in 469 breast cancer patients

Late side effects	**Degree of severity**				
	0	1	2	3	4
Skin	203	77	133	1	
Fibrosis in the operation field	154	229	27	5	
Fibrosis outside the operation field	278	131	6		

So we have 143 patients (33.9 %) with an outcome at degree 2 or 3 for one of the side effects (late toxicity).
Additional information regarding chemotherapy during follow-up will be collected by the end of August 2005 to assess the effect of chemotherapy on the occurrence of late toxicity.

In the group of patients presenting with late toxicity (143 patients), 124 (86.7%) were disease free, 3 patients (2.1%) had local progression, 5 patients (3.5%) developed metastases and 12 patients (8.4%) developed a second tumor.

Table 3 Clinical course of 422 patients by occurrence of late toxicity

	Late toxicity (n=143)		Without late toxicity (n=279)	
disease free	124	29.4%	283	67.1%
local relapse	3	0.7%	7	1.7%
second tumor	12	2.8%	10	2.4%

<u>Technical Objective 2</u> Evaluation of the effect of genetic polymorphisms in certain candidate genes (i.e. alleles that confer reduced protection from ROS damage and variants in DNA repair genes) and outcomes; i.e., breast cancer recurrence and severe skin toxicity.

Task 1: Months 3-6 DNA extraction and shipment of aliquot
Completed as reported in 2003.

Task 2: Months 26-30 Perform DNA analysis for genetic polymorphisms in genes that confer reduced protection from ROS damage, e.g. *MnSOD, GPX1, CAT, GSTT1, GSTM1, GSTA1, GSTP1,* and in DNA repair genes, e.g. *XRCC1, XRCC2, XRCC3, XPD, APE1*

Genotyping has been completed for genetic polymorphisms in the following genes that confer reduced protection from ROS damage: *MnSOD, GPX1, CAT, GSTT1, GSTM1, GSTA1, GSTP1,* and in DNA repair genes: *XRCC1, XRCC2, XRCC3, NBS1, XPD, APE1,* and cell cycle control genes: *TP53, p21.*

Task 3: Months 31-36 Merge data from laboratory results with questionnaire database. Perform statistical analysis for main effects of polymorphisms on outcomes.

Data analysis to assess the effect of the genetic polymorphisms on occurrence of acute toxicity, has been completed for the majority of genetic variants studied.

DNA repair and cell cycle control genes:

The genetic variants in the DNA repair genes as well as cell cycle control genes generally did not have a significant effect on the occurrence of acute toxicity in the complete series of patients (see Appendix, Table A1). Detailed analyses have been completed for some of the genes according to pathways and manuscripts are in preparation or in press (Chang-Claude et al. *Clin Cancer Res* 2005). In the paper on *XRCC1*, *APE1* and *XPD* to appear in the July 1 issue of *Clinical Cancer Research* (tables 4, 5, 6, 7), we reported that risk of acute toxicity was found to be differential by body mass index. Among normal weight patients only, both carriers of the *APE1* 148Glu and the *XRCC1* 399Gln allele had decreased risk of acute skin reactions after radiotherapy (HR 0.49, HR 0.51, respectively). The results for *XRCC1* were confirmed by haplotype analysis. When considering joint effects, we observed that, compared to homozygote carriers of the wild-type allele in both genes, the risk was most strongly reduced in carriers of both *APE1* 148Glu and *XRCC1* 399Gln alleles with normal weight (HR 0.19, 95% 0.06-0.56) but not in those with overweight (HR 1.39, 95% CI 0.56-3.45) (p for interaction 0.009). We conclude that the *XRCC1*-399Gln or *APE1* 148Glu alleles may be protective against the development of acute side effects after radiotherapy in patients with normal weight.

Table 4. Association of XRCC1, APE1 and XPD polymorphisms with risk of acute skin reaction after radiotherapy in breast cancer patients.

Gene/SNP	Genotypes	All patients	Radiosensitive patients	Adjusted HR (95% CI) [a]
XRCC1				
Arg194Trp	Arg/Trp (CC)	396	70	1.00
	Arg/Trp (CT)	45	7	0.77 (0.35-1.70)
	Trp/Trp (TT)	2	0	NC b
Arg280His	Arg/Arg (GG)	395	71	1.00
	Arg/His (GA)	48	5	0.51 (0.20-1.31)
	His/His (AA)	2	1	3.53 (0.48-26.02)
Arg399Gln	Arg/Arg (GG)	181	31	1.00
	Arg/Gln (GA)	204	36	0.96 (0.58-1.57)
	Gln/Gln (AA)	61	10	0.89 (0.43-1.84)
APE1				
Asp148Glu	Asp/Asp (TT)	121	23	1.00
	Asp/Glu (TG)	220	38	0.88 (0.52-1.49)
	Glu/Glu (GG)	104	16	0.79 (0.41-1.51)

XPD				
Asp312Asn	Asp/Asp (GG)	173	33	1.00
	Asp/Asn (GA)	213	38	0.87 (0.54-1.41)
	Asn/Asn (AA)	56	5	0.39 (0.15-1.01)
Lys751Gln	Lys/Lys (AA)	165	33	1.00
	Lys/Gln (AC)	219	33	0.66 (0.40-1.08)
	Gln/Gln (CC)	57	10	0.83 (0.40-1.70)

[a]Adjusted for BMI, hospital (four clinics), photon beam quality for whole breast (two categories) and for boost irradiation (no boost and four categories);
CI, confidence interval.
[b]NC, not calculated

Table 5 Association of *XRCC1* and *APE1* polymorphisms with risk of acute skin reaction after radiotherapy in breast cancer patients stratified by BMI.

	Normal weight (BMI≤25)			Overweight (BMI>25)		
Gene/SNP	No. of patients	RS-patients	Hazard ratio (95% CI) [a]	No. of patients	RS-patients	Hazard ratio (95% CI) [a]
XRCC1						
Arg194Trp						
Arg/Arg	202	21	1.00	194	49	1.00
Arg/Trp	24	2	0.70 (0.16-3.13)	21	5	0.84 (0.32-2.19)
Trp / Trp	1	0	NC [b]	1	0	NC [b]
Trp carrier	25	2	0.69 (0.16-3.11)	22	5	0.81 (0.31-2.11)
Arg280His						
Arg/Arg	204	22	1.00	191	49	1.00
Arg/His	24	1	0.42 (0.05-3.21)	24	4	0.69 (0.24-1.99)
His/His	0	0	NC [b]	2	1	2.54 (0.34-19.04)
His carrier	24	1	0.42 (0.05-3.21)	26	5	0.82 (0.31-2.13)
Arg399Gln						
Arg/Arg	85	11	1.00	96	20	1.00
Arg/Gln	115	10	0.55 (0.23-1.34)	89	26	1.30 (0.71-2.38)
Gln/Gln	29	2	0.37 (0.08-1.71)	32	8	1.23 (0.53-2.85)
Gln carrier	144	12	0.51 (0.22-1.19)	121	34	1.28 (0.72-2.27)
APE1						
Asp148Glu						
Asp/Asp	60	10	1.00	61	13	1.00
Asp/Glu	110	7	0.48 (0.17-1.20)	110	31	1.12 (0.58-2.20)
Glu/Glu	58	6	0.55 (0.19-1.60)	46	10	0.88 (0.38-2.04)
Glu carrier	168	13	0.49 (0.21-1.15)	156	41	1.05 (0.55-2.00)
XPD						
Asp312Asn						
Asp/Asp	92	10	1.00	81	23	1.00
Asp/Asn	107	12	0.97 (0.41-2.28)	106	26	0.81 (0.46-1.43)
Asn/Asn	28	0	NC [b]	28	5	0.53 (0.19-1.44)
Asn carrier	135	12	0.77 (0.33-1.81)	134	31	0.75 (0.43-1.30)

Lys751Gln						
Lys/ Lys	92	13	1.00	73	20	1.00
Lys/Gln	108	9	0.56 (0.24-1.34)	111	24	0.62 (0.34-1.14)
Gln/Gln	25	0	NC [b]	32	10	1.06 (0.48-2.35)
Gln carrier	133	9	0.48 (0.20-1.14)	143	34	0.70 (0.40-1.24)

[a]Adjusted for BMI, hospital (four clinics), photon beam quality for whole breast (two categories) and for boost irradiation (no boost and four categories); CI, confidence interval.
[b]NC, not calculated

Table 6 Association of XRCC1 and XPD haplotypes with risk of acute skin reaction after radiotherapy in breast cancer patients stratified by BMI.

Haplotypes	All patients	Normal weight (BMI≤25)			Overweight (BMI>25)		
		No. of patients	RS-patients	Hazard ratio (95% CI) [a]	No. of patients	RS-patients	Hazard ratio (95% CI) [a]
XRCC1							
CGG	466	235	29	1.00	231	55	1.00
CGA	325	173	14	0.55 (0.29-1.05)	152	42	1.14 (0.76-1.72)
CAG	51	24	1	0.34 (0.05-2.54)	27	6	1.01 (0.42-2.41)
CAA	1	0	0	NC [b]	1	0	NC [b]
TGG	49	26	2	0.55 (0.13-2.37)	23	6	0.85(0.33-2.17)
XPD							
GA	501	265	33	1.00	236	62	1.00
GC	66	31	1	0.36 (0.05-2.68)	35	10	0.93 (0.47-1.84)
AA	52	30	3	0.83 (0.25-2.75)	22	2	0.28 (0.07-1.17)
AC	273	132	9	0.55 (0.26-1.16)	141	34	0.85 (0.55-1.31)

[a]Adjusted for BMI, hospital (four clinics), photon beam quality for whole breast (two categories) and for boost irradiation (no boost and four categories);
CI, confidence interval.
[b]NC, not calculated
[c]P<0.05

Table 7. The combined genotypes and clinical radiosensitivity investigated by Cox proportional hazard model stratified by BMI.

Genotypes		Normal weight (BMI≤25)			Overweight (BMI>25)		
		No. of patients	RS-patients	Adjusted HR (95% CI) [a]	No. of patients	RS-patients	Adjusted HR (95% CI) [a]
XRCC1 Arg399Gln	APE1 Asp148Glu						
Arg/Arg	Asp/Asp	20	6	1.00	32	6	1.00
Arg/Arg	Glu carrier	64	5	0.20 (0.06-0.71) [b]	64	14	1.17 (0.44-3.16)
Gln carrier	Asp/Asp	40	4	0.19 (0.05-0.73) [c]	29	7	1.57 (0.51-4.84)

Gln carrier	Glu carrier	104	8	0.19 (0.06-0.56)[c]	92	27	1.39 (0.56-3.45)

[a] Adjusted for BMI, hospital (four clinics), photon beam quality for whole breast (two categories) and for boost irradiation (no boost and four categories); HR, hazard ratio; CI, confidence interval.
[b] P for interaction =0.05
[c] P for interaction <0.05

We have also completed analysis for the genes related to oxidative stress, including the glutathione S-transferases M1, T1, P1, A1 as well as CAT, MnSOD, MPO, and NOS. Glutathione-associated metabolism is a major mechanism for cellular protection against reactive oxygen species (ROS) and their toxic products, and GSTs α, μ, π, and θ are active in detoxification of organic epoxides, hydroperoxides, and unsaturated aldehydes, including reactive bases and lipid peroxides produced by reactive oxidant damage to DNA and lipids, respectively. *GSTM1* and *GSTT1* both contain gene deletions, resulting in no enzymatic activity for that isozyme. The *GSTA1**A and *GSTA1**B genetic polymorphism (RS3957357), containing 3 linked base substitutions in the promoter at positions – 567, -69, and –52, results in differential expression, with lower transcriptional activation of *GSTA1**B (variant) than that of *GSTA1**A (common) allele *in vitro*.. The GSTP1 isoleucine^{105}valine substitution is also associated with reduced activity. Reduced detoxification of ROS and their products resulting from polymorphisms in the GSTs could be responsible for greater acute toxicities among women receiving radiation therapy.

In a prospective study of genetic and non-genetic factors that could impact effects of radiation therapy on normal tissue, we evaluated the role of polymorphisms in the glutathione S-transferases, *GSTM1*, *GSTT1, GSTA1* and *GSTP1* in predicting acute side effects. As shown in Table 8, the *GSTP1* genotype associated with lower activity was associated with grade 2c and above skin toxicities, with women having *GSTP1 GG* genotypes having more than 2 times the likelihood of severe side effects than those with AA genotypes. There were no significant relationships noted for the other GST genotypes. Furthermore, when 'at-risk' alleles were counted, there was no significant increase in risk for greater amounts of low activity alleles compared to women with 0 or 1 low activity alleles (Table 9).

Table 8. Associations of *GSTA1*, *GSTP1*, *GSTM1* and *GSTT1* Polymorphisms with Toxicity (n=447)

Genotypes		No. patients (toxicities)		Hazard Ratio (95% C.I.)	p-value
GSTA1					
	GG	149	(29)	Reference	
	GA	194	(35)	1.21 (0.71-2.07)	
	AA	87	(12)	0.88 (0.42-1.84)	
GSTP1					
	AA	176	(27)	Reference	
	AG	213	(39)	1.29 (0.76-2.20)	
	GG	38	(10)	2.52 (1.15-5.55)	

GSTT1			
Positive	384	(69)	Reference
Null	55	(6)	0.74 (0.29-1.90)
GSTM1			
Positive	215	(36)	Reference
Null	213	(39)	1.25 (0.73-2.11)

Cox model used to estimate hazard ratio adjusted for BMI, Smoking status, Alcohol, HRT, clinic, photon field, beam energy and boost method; unknown group not considered for analysis.

Table 9. Effects of combined genotypes for reduced GST activity on toxicity

Number of Alleles	Number of patients	Toxicities	Hazard Ratio	(95% C.I.)
0 or 1	149	22	Reference	
2	148	33	1.34	0.76-2.38
3 or 4	102	17	1.37	0.69-2.73

P trend= 0.54

We also evaluated the role of polymorphisms in *MnSOD, MPO, CAT, GPX1,* and *NOS* in greater skin toxicities. As shown in Table 10, none of the genotypes were associated with increased risk of adverse side effects.

Table 10. Associations of CAT, MnSOD, MPO and NOS Polymorphisms with Toxicity (n=447)

Genotypes	N	Toxicities	Minimally-adjusted HR	95% CI	Fully-adjusted HR	95% CI
CAT						
CC	233	43	1		1	
CT	162	31	0.92	0.56-1.51	0.90	0.55-1.50
TT	22	1	0.33	0.05-2.47	0.33	0.05-2.48
CC	233	43	1		1	
CT+TT	184	32	0.86	0.53-1.40	0.85	0.52-1.39
MnSOD						
TT	113	24	1		1	
TC	204	34	0.75	0.43-1.31	0.74	0.43-1.30
CC	111	17	0.71	0.36-1.38	0.67	0.33-1.34
TT	113	24	1		1	
TC+CC	315	51	0.74	0.44-1.24	0.72	0.43-1.22

MPO						
GG	251	44	1		1	
AG	133	22	0.89	0.52-1.51	0.88	0.51-1.50
AA	13	3	1.26	0.38-4.19	1.48	0.44-4.98
GG	251	44	1		1	
AG+AA	146	25	0.92	0.55-1.53	0.92	0.55-1.54
NOS						
GG	187	33	1	1	1	
GT	174	32	0.95	0.57-1.59	0.87	0.51-1.49
TT	65	9	0.72	0.34-1.53	0.66	0.31-1.41
GG	187	33	1		1	
GT+TT	239	41	0.89	0.55-1.44	0.81	0.50-1.32

Minimally adjusted model: adjusted for clinic, photon field, beam energy and boost method. Fully adjusted model: adjusted for clinic, photon field, beam energy and boost method; BMI, Current smoking status, alcohol consumption, Hormone therapy use.

Because of the delays in beginning follow-up of patients, we were not able to complete the analysis of genetic polymorphisms in relation to late toxicities and to recurrence status. Because of this, we have requested a no-cost extension, and will complete the study in June, 2006. The final report will be submitted at that time.

REPORTABLE OUTCOMES:

Posters:

Poster presented at American Association for Cancer Research 96th Annual Meeting:

Chang-Claude J, Popanda O, Tan X-L, Kropp S, Schmezer P, Ambrosone CB. Polymorphisms in DNA repair gene XRCC1, APE1 and XPD and risk fo acute side effects of radiotherapy in breast cancer patients. Proc Amer Assoc Cancer Res 2005;46:113.

Poster presented at DOD Era of Hope meeting, 2005:

Chang-Claude J, Popanda O, Tan X-L, Kropp S, Schmezer P, Tian C, Ahn J, Ambrosone CB. Oxidative stress, DNA repair, and acute side effects of radiotherapy in breast cancer patients.

Paper in press:

Chang-Claude J, Popanda O, Tan X-L, Kropp S, von Fournier D, Haase W, Sautter-Bihl ML, Wnez F, Schmezer P, Ambrosone. CB Association between polymorphisms in the DNA repair genes, *XRCC1, APE1* and *XPD*, and acute side effects of radiotherapy in breast cancer patients. *Clin Cancer Res* (in press)

Papers in preparation:

Ahn J, Ambrosone CB, Tian C, Kanetsky PA, Popanda O, Tan X-L, Kropp S, Helmbold I, von Fournier D, Haase W, Sautter-Bihl, Wenz F, Schmezer P, Chang-Claude J. Polymorphisms in genes related to oxidative stress (*CAT, MnSOD, MPO,* and *NOS*) and acute toxicities related to radiation therapy following lumpectomy for breast cancer: a prospective cohort study.

Ambrosone CB, Tian C, Ahn J, Popanda O, Tan X-L, Kropp S, Helmbold I, von Fournier D, Haase W, Sautter-Bihl, Wenz F, Schmezer P, Chang-Claude J. Acute toxicities related to radiation therapy following lumpectomy for breast cancer: role of glutathione *S*-transferase polymorphisms.

CONCLUSIONS: The re-contacting and recruitment for participation of the patients has been extremely successful. We expect to achieve around 83 % full participation and to be able to obtain information on clinical course without re-examination from another 8% and permission from all these patients to use the blood samples collected in the parent study for genotyping in this project. Analysis is near completion for the relationship between genotypes and acute toxicities, and results infer that low activity *GSTP1* genotypes are associated with increased risk of skin side effects. While genotypes associated with reduced protection from oxidative stress and reduced DNA repair were not significantly associated with toxicities, body mass index modified associations, with associations between genotype and side effects greatest among women with heavier BMI.

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Chang-Claude J, Popanda O, Tanhttp://www.sciencedirect.com/ - aff1 XL, Kropp S, Helmboldhttp://www.sciencedirect.com/ - aff1 I, von Fournier D, Haase W, Sautter-Bihl ML, Wenz F, Schmezer Phttp://www.sciencedirect.com/ - aff2, Ambrosone CB. Association between polymorphisms in the DNA repair genes, *XRCC1*, *APE1* and *XPD*, and acute side effects of radiotherapy in breast cancer patients. *Clin Cancer Res* 2005, in press.

APPENDICES:

Table 1 Distribution of DNA repair gene polymorphisms and results of the Cox proportional analysis.

Gene/SNP	genotypes	Number (%)	No. of events	Hazard ratio (95% CI)[#]	P value	Adjusted hazard ratio (95%CI)[##]	P value
XRCC1-399	G	566	98	1.00		1.00	
G28152A	A	326	56	0.95 (0.68-1.32)	0.76	0.95 (0.68-1.32)	0.75
	GG	181 (40.58)	31	1.00		1.00	
	GA	204 (45.74)	36	0.95 (0.59-1.55)	0.85	0.96 (0.58-1.57)	0.86
	AA	61 (13.68)	10	0.90 (0.44-1.84)	0.77	0.89 (0.43-1.84)	0.75
XRCC1-280	G	838	147	1.00		1.00	
G27466A	A	52	7	0.80 (0.37-1.70)	0.56	0.72 (0.33-1.57)	0.41
	GG	395 (88.76)	71	1.00		1.00	
	GA	48 (10.79)	5	0.60 (0.24-1.49)	0.27	0.51 (0.20-1.31)	0.18
	AA	2 (0.45)	1	2.93 (0.41-21.26)	0.29	3.53 (0.48-26.02)	0.16
XRCC1-194	C	837	147	1.00		1.00	
C26304T	T	49	7	0.79 (0.37-1.68)	0.54	0.76 (0.35-1.62)	0.47
	CC	396 (89.39)	70	1.00		1.00	
	CT	45 (10.16)	7	0.82 (0.37-1.78)	0.61	0.77 (0.35-1.70)	0.52
	TT	2 (0.45)	0	---	---	---	---
APE1	T	462	84	1.00		1.00	
T2197G	G	428	70	0.88 (0.64-1.22)	0.45	0.89 (0.64-1.22)	0.46
	TT	121 (27.19)	23	1.00		1.00	
	TG	220 (49.44)	38	0.94 (0.56-1.59)	0.83	0.88 (0.52-1.49)	0.63
	GG	104 (23.37)	16	0.78 (0.41-1.48)	0.44	0.79 (0.41-1.51)	0.47
XPD312	G	559	104	1.00		1.00	
G23591A	A	325	48	0.72 (0.51-1.02)	0.06	0.73 (0.52-1.04)	0.08
	GG	173 (39.14)	33	1.00		1.00	
	GA	213 (48.19)	38	0.86 (0.54-1.38)	0.53	0.87 (0.54-1.41)	0.58
	AA	56 (12.67)	5	0.38 (0.15-0.98)	0.04	0.39 (0.15-1.01)	0.05
XPD751	A	549	99	1.00		1.00	
A35931C	C	332	53	0.84 (0.60-1.18)	0.31	0.84 (0.60-1.17)	0.30
	AA	165 (37.41)	33	1.00		1.00	
	AC	219 (49.66)	33	0.70 (0.43-1.14)	0.16	0.66 (0.40-1.08)	0.10
	CC	57 (12.93)	10	0.80 (0.39-1.63)	0.54	0.83 (0.40-1.70)	0.60
XRCC3	C	524	83	1.00		1.00	
Thr241Met	T	364	69	1.22 (0.89-1.69)	0.22	1.15 (0.83-1.59)	0.39
C18067T	CC	156 (35.14)	21	1.00		1.00	
	CT	212 (47.75)	41	1.41 (0.83-2.39)	0.20	1.34 (0.79-2.29)	0.28
	TT	76 (17.12)	14	1.46 (0.74-2.88)	0.27	1.28 (0.64-2.56)	0.48
XRCC2	G	829	147	1.00		1.00	
Arg188His	A	61	7	0.59 (0.28-1.27)	0.18	0.65 (0.30-1.40)	0.27
	GG	387 (86.97)	71	1.00		1.00	
	GA	55 (12.36)	5	0.47 (0.19-1.16)	0.10	0.56 (0.22-1.39)	0.22
	AA	3 (0.07)	1	1.25 (0.17-9.07)	0.83	0.95 (0.13-7.02)	0.96
NBS1	G	602	107	1.00		1.00	
Glu185Gln	C	288	47	0.93 (0.66-1.31)	0.67	0.95 (0.67-1.35)	0.79
	GG	196 (44.05)	36	1.00		1.00	
	GC	210 (47.19)	35	0.90 (0.56-1.43)	0.65	0.94 (0.58-1.52)	0.80
	CC	39 (8.76)	6	0.88 (0.37-2.01)	0.78	0.90 (0.37-2.22)	0.83
P53	C	676	118	1.00		1.00	
Arg72Pro	G	214	36	0.99 (0.68-1.44)	0.96	0.85 (0.58-1.25)	0.41
	CC	256 (57.53)	46	1.00		1.00	
	CG	164 (36.85)	26	0.93 (0.57-1.50)	0.76	0.73 (0.44-1.21)	0.22
	GG	25 (5.62)	5	1.13 (0.45-2.84)	0.80	0.94 (0.37-2.41)	0.90

P53	A	763	136	1.00		1.00	
PIN3	B	127	18	0.85 (0.52-1.39)	0.52	0.81 (0.49-1.33)	0.40
	AA	326	60	1.00		1.00	
	AB	111	16	0.83 (0.48-1.45)	0.52	0.79 (0.45-1.39)	0.41
	BB	8	1	0.81 (0.11-5.83)	0.83	0.72 (0.10-5.34)	0.74
P21	C	829	144	1.00		1.00	
Ser31Arg	A	61	10	0.98 (0.52-1.87)	0.96	1.10 (0.58-2.10)	0.78
	CC	387 (86.97)	68	1.00		1.00	
	CA	55 (12.36)	8	0.88 (0.42-1.83)	0.73	0.94 (0.45-1.96)	0.86
	AA	3 (0.67)	1	1.73 (0.23-12.59)	0.59	3.34 (0.45-25.05)	0.24

[#]95% confidence interval

[##]Adjusted for BMI, hospital (four clinics), photon beam quality for whole breast (tree categories) and for boost irradiation (no boost and five categories).