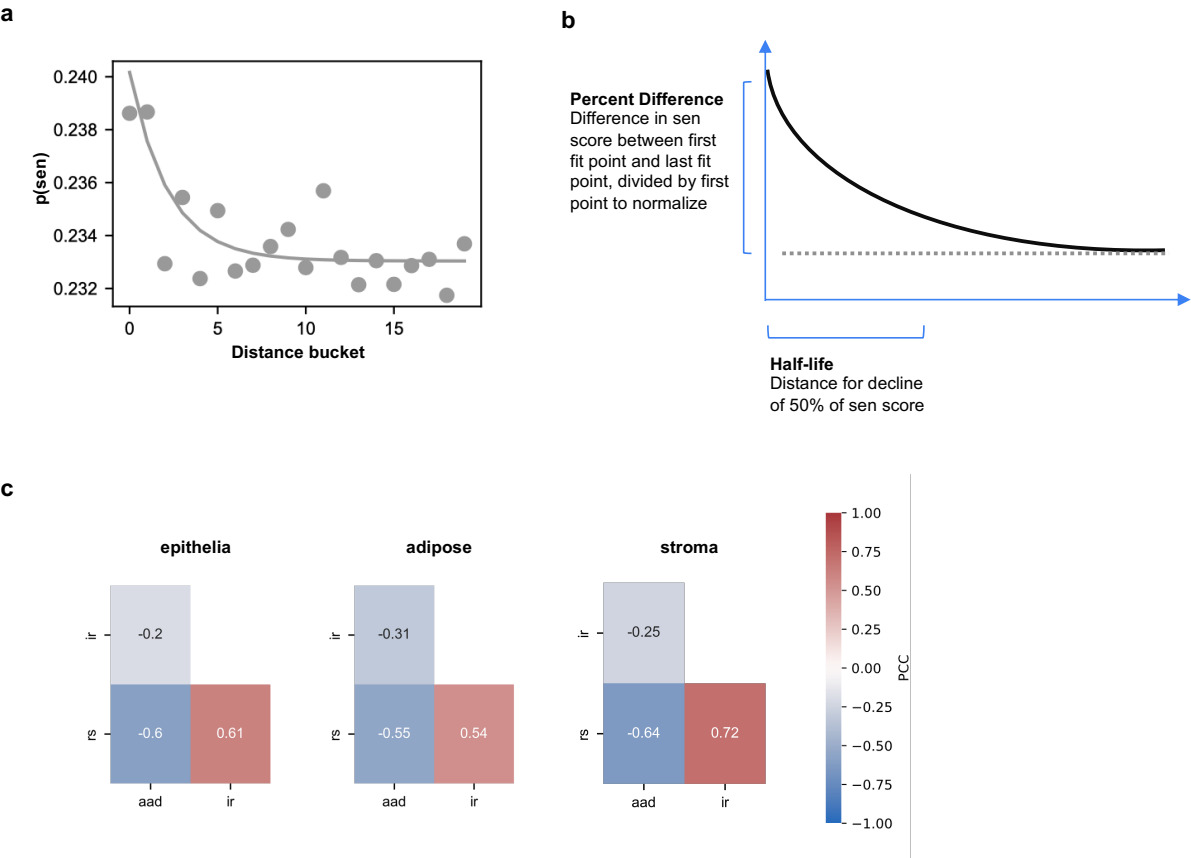


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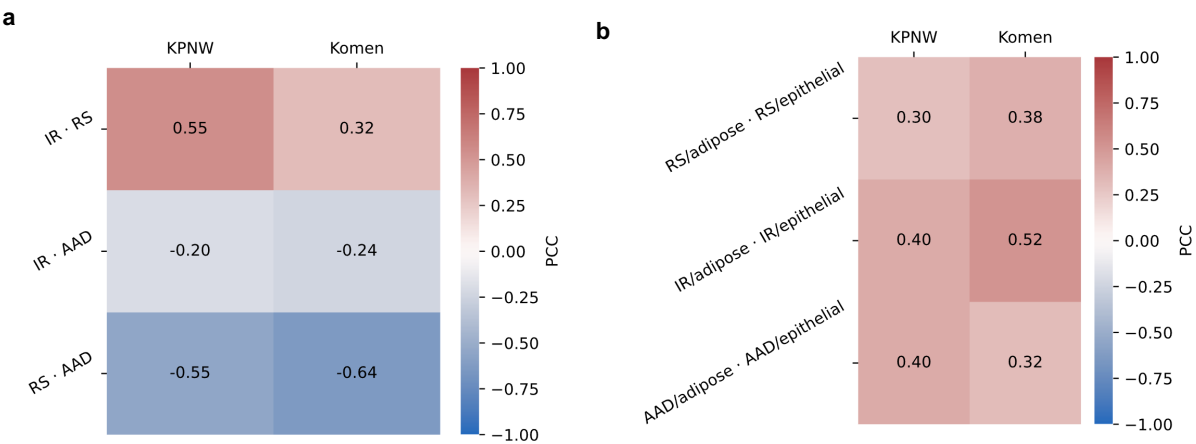
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Supplementary Figure 1. Spatial distribution of senescence near high scoring nuclei



Supplementary Figure 1: Spatial distribution of senescence near high scoring nuclei. **a**, Example of spatial distribution found relative to high scoring nuclei, showing mean senescence score per bucket. **b**, Schematic illustration of metrics used to characterize spatial effects of senescence. **c**, correlation between senescence scores per individual by tissue.

Supplementary Figure 2. Senescence model correlations for BBD patients and healthy women



Supplementary Figure 2: Senescence model correlations for BBD patients and healthy women. **a**, Heatmap of correlations between models for BBD and healthy cohorts (using average values for adipose and epithelia scores per individual). **b**, Heatmap of correlations between tissues by model for BBD and healthy cohorts.

Supplementary Table 1. Characteristic of the study subjects by case-control status

		Controls	Cases	p-value
		N (%)	N (%)	
Age ^a (yrs)		491(49.0)	512 (51.0)	
		52.1 (12.2)	52.3 (12.5)	0.771
Time between BBD and IBC diagnosis ^b (yrs)		-	8.9 (4.5-15.7)	
BMI (kg/m ²)				
	<18.5	12 (2.4)	6 (1.2)	
	18.5 -<25.0	192 (39.1)	202 (39.5)	
	25.0-<30.0	129 (26.3)	143 (28.0)	
	≥30.0	111 (22.6)	108 (21.0)	
	missing	47 (9.6)	53 (10.3)	0.568
Menopausal status				
	Premenopausal	199 (40.7)	206 (40.7)	
	Postmenopausal	278 (56.4)	287 (55.6)	
	missing	14 (2.9)	19 (3.7)	0.899
Bilateral oophorectomy				
	No	372 (75.9)	409 (79.9)	
	Yes	78 (15.9)	52 (10.2)	
	missing	40 (8.2)	51 (10.0)	0.020
Family history of IBC				
	No	388 (79.0)	385 (75.2)	
	Yes	69 (14.1)	92 (18.0)	
	missing	34 (6.9)	35 (6.8)	0.238
Menopausal hormone therapy				
	No	256 (52.1)	239 (46.7)	
	Yes	51 (10.4)	11 (2.1)	
	missing	184 (37.5)	262 (51.2)	<0.001
Ever smoked				
	No	190 (38.7)	181 (35.4)	
	Yes	215 (43.8)	206 (40.2)	
	missing	86 (17.5)	125 (24.4)	0.028
Number of pregnancies				
	0	56 (11.4)	73 (14.3)	
	1	69 (14.1)	58 (11.3)	
	2-3	268 (54.6)	262 (51.2)	
	≥4	76 (15.5)	88 (17.2)	
	missing	22 (4.5)	31 (6.0)	0.265
Age at first live birth (yrs)				
	≤19	116 (23.6)	139 (27.2)	
	20-24	180 (36.7)	161 (31.5)	
	25-29	93 (18.9)	68 (13.3)	
	≥30	33 (6.7)	56 (10.9)	
	missing	69 (14.1)	88 (17.2)	0.005

Age at menarche (yrs)				
	≤11	73 (14.9)	78 (15.2)	
	12-13	230 (46.8)	219 (42.8)	
	≥14	96 (19.6)	103 (20.1)	
	missing	92 (18.7)	112 (21.9)	0.531
BBD histopathology				
	No lesions/non-proliferative lesions	116 (23.6)	86 (16.8)	
	Epithelial hyperplasia with/without atypia	374 (76.2)	425 (83.0)	
	missing	1 (0.20)	1 (0.20)	0.025

Sample comprises cases and controls whose senescence scores in the epithelial tissue were calculated on >100 cells.

^a Mean values (standard deviations).

^b Median value (interquartile range).

Abbreviations: IBC, invasive breast cancer; BBD, benign breast disease.

Supplementary Table 2. Age-adjusted association between senescence measurements by tissue type and risk of breast cancer

Tissue	Epithelium	Adipose tissue	Stroma	Tdlu
N	1,003	712	1,006	937
Quartiles ^a				
RS				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.49 (1.02-2.17)	1.44 (0.90-2.33)	1.01 (0.69-1.47)	1.26 (0.83-1.91)
3	1.64 (1.11-2.44)	1.54 (0.91-2.62)	1.24 (0.86-1.80)	1.20 (0.80-1.81)
4	1.74 (1.17-2.60)	2.09 (1.16-3.78)	1.47 (1.00-2.16)	0.85 (0.55-1.34)
<i>p-trend</i>	<i>0.014</i>	<i>0.052</i>	<i>0.068</i>	<i>0.385</i>
IR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.24 (0.85-1.81)	1.43 (0.90-2.28)	1.13 (0.78-1.64)	0.89 (0.59-1.33)
3	1.73 (1.18-2.55)	1.22 (0.73-2.04)	1.07 (0.74-1.54)	1.20 (0.79-1.81)
4	1.46 (0.98-2.18)	2.53 (1.35-4.71)	1.26 (0.84-1.88)	1.26 (0.81-1.95)
<i>p-trend</i>	<i>0.090</i>	<i>0.065</i>	<i>0.770</i>	<i>0.408</i>
AAD				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.19 (0.81-1.76)	1.09 (0.66-1.79)	1.48 (1.02-2.14)	0.84 (0.58-1.24)
3	1.11 (0.75-1.65)	1.21 (0.74-1.98)	1.08 (0.72-1.61)	1.00 (0.66-1.52)
4	0.95 (0.64-1.40)	1.19 (0.66-2.14)	0.99 (0.67-1.47)	0.78 (0.51-1.19)
<i>p-trend</i>	<i>0.662</i>	<i>0.388</i>	<i>0.698</i>	<i>0.719</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age.

^a Quartiles of senescence scores.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin Tdlu, terminal duct lobular units.

Supplementary Table 3. Association between senescence measurements by tissue type and risk of breast cancer

Tissue	Epithelium	Adipose tissue	Stroma	Tdlu
N	1,003	712	1,006	937
Quartiles ^a				
RS				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.44 (0.99-2.06)	1.43 (0.92-2.21)	1.09 (0.76-1.58)	1.12 (0.77-1.65)
3	1.78 (1.22-2.58)	1.34 (0.86-2.08)	1.23 (0.85-1.78)	1.06 (0.72-1.56)
4	1.53 (1.05-2.22)	1.69 (1.03-2.77)	1.29 (0.89-1.88)	0.80 (0.54-1.19)
<i>p-trend</i>	<i>0.015</i>	<i>0.067</i>	<i>0.143</i>	<i>0.319</i>
IR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.17 (0.81-1.68)	1.57 (1.03-2.41)	1.08 (0.75-1.56)	0.91 (0.62-1.35)
3	1.70 (1.17-2.46)	1.27 (0.82-1.97)	1.00 (0.69-1.45)	1.22 (0.83-1.80)
4	1.18 (0.81-1.71)	1.73 (1.06-2.82)	0.98 (0.68-1.42)	1.04 (0.70-1.53)
<i>p-trend</i>	<i>0.144</i>	<i>0.083</i>	<i>0.803</i>	<i>0.509</i>
AAD				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.08 (0.75-1.56)	0.93 (0.60-1.42)	1.63 (1.12-2.36)	0.86 (0.60-1.25)
3	1.20 (0.84-1.72)	1.14 (0.74-1.76)	1.09 (0.75-1.57)	1.08 (0.75-1.57)
4	0.87 (0.60-1.27)	1.06 (0.65-1.72)	1.03 (0.71-1.48)	0.86 (0.59-1.25)
<i>p-trend</i>	<i>0.751</i>	<i>0.557</i>	<i>0.559</i>	<i>0.937</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

^a Quartiles of senescence scores.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin Tdlu, terminal duct lobular units.

Supplementary Table 4. Association between individual components of the AAD senescence score and risk of breast cancer

Tissue	Epithelium	Adipose tissue	Stroma	Tdlu
N	1,003	712	1,006	934
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ANTI				
Quartiles				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.07 (0.75-1.52) ^b	1.46 (0.95-2.22) ^b	1.40 (0.98-1.98) ^b	1.19 (0.83-1.71) ^v
	1.08 (0.75-1.55) ^b	1.42 (0.92-2.21) ^b	1.46 (1.01-2.11) ^b	1.23 (0.84-1.80) ^b
3	1.45 (1.02-2.07) ^b	1.46 (0.95-2.23) ^b	1.41 (0.99-2.00) ^b	1.13 (0.79-1.63) ^b
	1.55 (1.07-2.26) ^b	1.49 (0.96-2.31) ^b	1.34 (0.93-1.94) ^b	1.24 (0.85-1.82) ^b
4	1.26 (0.89-1.80) ^b	1.38 (0.87-2.19) ^b	1.15 (0.81-1.63) ^b	1.14 (0.78-1.65) ^b
	1.28 (0.88-1.85) ^b	1.46 (0.90-2.37) ^b	1.10 (0.76-1.59) ^b	1.18 (0.80-1.75) ^b
<i>p-trend^c</i>	0.070	0.121	0.701	0.669
AVTR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.14 (0.80-1.62) ^b	0.86 (0.57-1.29) ^b	1.15 (0.81-1.63) ^b	0.93 (0.65-1.35) ^b
	1.16 (0.80-1.67) ^c	0.91 (0.59-1.38) ^c	1.16 (0.80-1.67) ^c	0.98 (0.67-1.45) ^c
3	1.53 (1.08-2.18) ^b	0.99 (0.65-1.49) ^b	1.07 (0.72-1.52) ^b	1.04 (0.72-1.50) ^b
	1.87 (1.08-2.28) ^c	1.05 (0.68-1.61) ^c	1.06 (0.74-1.53) ^c	1.04 (0.71-1.53) ^c
4	1.22 (0.86-1.74) ^b	0.89 (0.55-1.44) ^b	1.38 (0.89-1.82) ^b	0.99 (0.68-1.43) ^b
	1.17 (0.81-1.69) ^c	0.92 (0.55-1.53) ^c	1.19 (0.82-1.73) ^c	1.02 (0.69-1.51) ^c
<i>p-trend^c</i>	0.201	0.999	0.924	0.809
DOXO				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.84 (0.59-1.20) ^b	0.98 (0.63-1.53) ^b	1.28 (0.90-1.82) ^b	1.15 (0.79-1.65) ^b
	0.90 (0.62-1.30) ^c	1.03 (0.65-1.64) ^c	1.18 (0.83-1.71) ^c	1.14 (0.78-1.67) ^c
3	0.90 (0.63-1.28) ^b	1.23 (0.79-1.92) ^b	1.01 (0.71-1.43) ^b	1.07 (0.75-1.54) ^b
	0.90 (0.72-1.70) ^c	1.05 (0.67-1.67) ^c	1.00 (0.69-1.45) ^c	1.08 (0.74-1.57) ^c

4	0.98 (0.69-1.39) ^b	1.13 (0.71-1.78) ^b	1.11 (0.78-1.59) ^b	0.77 (0.53-1.32) ^b
	1.02 (0.71-1.49) ^c	1.14 (0.70-1.84) ^c	1.06 (0.73-1.55) ^c	0.79 (0.54-1.17) ^c
<i>p-trend^c</i>	0.902	0.582	0.995	0.964

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression.

^a Quartiles of senescence marker measurements.

^b Analysis adjusted for age.

^c Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

Abbreviations: ANTI, antimycin-A; ATVR, atazanavir-ritonavir treatment; DOXO, doxorubicin; and tdlu, terminal duct lobular units.

Supplementary Table 5. Association between senescence measurements and risk of developing ipsilateral or contralateral breast cancer

Tissue	Risk of ipsilateral breast cancer			
	Epithelial	Adipose tissue	Stroma	Tdlu
Breast cancer cases	276	187	277	260
RS				
Quartiles ^a	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.64 (1.06-2.53) ^b	1.44 (0.86-2.41) ^b	1.05 (0.69-1.60) ^b	1.55 (1.00-2.40) ^b
	1.71 (1.09-2.69) ^c	1.48 (0.87-2.53) ^c	1.04 (0.67-1.61) ^c	1.48 (0.94-2.33) ^c
3	2.09 (1.36-3.22) ^b	1.40 (0.84-2.36) ^b	1.17 (0.77-1.78) ^b	1.37 (0.88-2.13) ^b
	2.23 (1.43-3.49) ^c	1.44 (0.84-2.48) ^c	1.16 (0.75-1.78) ^c	1.40 (0.88-2.21) ^c
4	1.68 (1.09-2.61) ^b	1.88 (1.07-3.31) ^b	1.30 (0.85-1.97) ^b	0.96 (0.60-1.53) ^b
	1.71 (1.08-2.70) ^c	1.86 (1.03-3.36) ^c	1.19 (0.76-1.84) ^c	0.91 (0.59-1.48) ^c
<i>p-trend</i> ^c	0.011	0.058	0.379	0.577
IR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.26 (0.82-1.94) ^b	1.52 (0.93-2.49) ^b	1.17 (0.76-1.78) ^b	0.85 (0.55-1.32) ^b
	1.24 (0.79-1.94) ^c	1.64 (0.98-2.76) ^c	1.13 (0.73-1.77) ^c	0.85 (0.54-1.34) ^c
3	2.02 (1.33-3.08) ^b	1.32 (0.80-2.18) ^b	1.05 (0.68-1.60) ^b	1.01 (0.65-1.56) ^b
	2.05 (1.32-3.18) ^c	1.27 (0.75-2.15) ^c	1.00 (0.65-1.58) ^c	1.10 (0.69-1.73) ^c
4	1.35 (0.88-2.08) ^b	1.80 (1.03-3.15) ^b	1.30 (0.85-1.96) ^b	1.05 (0.68-1.62) ^b
	1.27 (0.82-1.99) ^c	1.83 (1.02-3.29) ^c	1.17 (0.76-1.80) ^c	1.02 (0.65-1.61) ^c
<i>p-trend</i> ^c	0.091	0.127	0.598	0.639
AAD				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.50 (0.98-2.27) ^b	0.84 (0.52-1.37) ^b	1.63 (1.08-2.46) ^b	0.83 (0.54-1.27) ^b
	1.43 (0.93-2.21) ^c	0.78 (0.47-1.30) ^c	1.60 (1.04-2.46) ^c	0.90 (0.57-1.41) ^c
3	1.50 (0.99-2.29) ^b	1.14 (0.70-1.85) ^b	1.10 (0.72-1.67) ^b	1.18 (0.76-1.83) ^b

	1.44 (0.93-2.23) ^c	1.07 (0.64-1.79) ^c	1.01 (0.65-1.56) ^c	1.23 (0.80-1.42) ^c
4	1.00 (0.64-1.55) ^b	0.94 (0.53-1.66) ^b	1.00 (0.66-1.53) ^b	0.77 (0.49-1.22) ^b
	0.99 (0.62-1.57) ^c	0.96 (0.53-1.74) ^c	0.98 (0.63-1.52) ^c	0.80 (0.50-1.29) ^c
<i>p-trend^c</i>	0.981	0.751	0.459	0.687
Risk of contralateral breast cancer				
Tissue	Epithelial	Adipose tissue	Stroma	Tdlu
Breast cancer cases	212	152	212	188
RS				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.19 (0.76-1.87) ^b	1.46 (0.85-2.52) ^b	1.09 (0.68-1.73) ^b	0.96 (0.60-1.54) ^b
	1.24 (0.78-1.99) ^c	1.47 (0.83-2.58) ^c	1.07 (0.66-1.73) ^c	0.89 (0.55-1.45) ^c
3	1.19 (0.75-1.90) ^b	1.33 (0.75-2.36) ^b	1.25 (0.79-1.99) ^b	0.83 (0.51-1.34) ^b
	1.31 (0.80-2.12) ^c	1.36 (0.77-2.37) ^c	1.28 (0.79-2.05) ^c	0.76 (0.46-1.26) ^c
4	1.34 (0.85-2.10) ^b	1.54 (0.81-2.93) ^b	1.47 (0.93-2.32) ^b	0.84 (0.52-1.35) ^b
	1.39 (0.87-2.23) ^c	1.58 (0.83-2.99) ^c	1.45 (0.89-2.35) ^c	0.76 (0.47-1.25) ^c
<i>p-trend^c</i>	0.166	0.262	0.095	0.152
IR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.03 (0.65-1.62) ^b	1.58 (0.93-2.68) ^b	1.00 (0.64-1.56) ^b	0.89 (0.54-1.46) ^b
	1.03 (0.64-1.63) ^c	1/67 (0.97-2.88) ^c	0.97 (0.61-1.54) ^c	0.86 (0.51-1.44) ^c
3	1.30 (0.82-2.05) ^b	1.31 (0.76-2.24) ^b	0.93 (0.60-1.46) ^b	1.33(0.83-2.15) ^b
	1.31 (0.81-2.09) ^c	1.37 (0.78-2.42) ^c	0.94 (0.59-1.49) ^c	1.36 (0.83-2.25) ^c
4	1.12 (0.72-1.76) ^b	1.69 (0.92-3.09) ^b	0.82 (0.52-1.30) ^b	0.95 (0.58-1.57) ^b
	1.07 (0.67-1.71) ^c	1.76 (0.94-3.29) ^c	0.76 (0.47-1.23) ^c	0.92 (0.55-1.56) ^c
<i>p-trend^c</i>	0.493	0.197	0.275	0.747
AAD				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.78 (0.49-1.23) ^b	1.15 (0.67-1.96) ^b	1.50 (0.94-2.38) ^b	0.95 (0.60-1.54) ^b
	0.74 (0.46-1.19) ^c	0.99 (0.57-1.73) ^c	1.49 (0.92-2.42) ^c	1.03 (0.63-1.68) ^c
3	1.05 (0.68-1.63) ^b	1.30 (0.75-2.25) ^b	1.39 (0.88-2.17) ^b	0.85 (0.52-1.39) ^b

	0.99 (0.63-1.56) ^c	1.18 (0.67-2.08) ^c	1.26 (0.79-2.01) ^c	0.84 (0.50-1.40) ^c
4	0.80 (0.51-1.26) ^b	1.37 (0.74-2.52) ^b	1.05 (0.65-1.67) ^b	1.01 (0.62-1.65) ^b
	0.72 (0.45-1.15) ^c	1.26 (0.67-2.38) ^c	1.00 (0.61-1.64) ^c	1.09 (0.65-1.81) ^c
<i>p-trend^c</i>	0.347	0.370	0.862	0.972

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression.

^a Quartiles of senescence measurements.

^b Analysis adjusted for age.

^c Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin; Tdlu, terminal duct lobular units.

Supplementary Table 6. Age-adjusted association between combinations of RS- and IR-derived senescence scores in epithelial and adipose tissues and risk of breast cancer

Quartiles ^{a, b}		1	2-4
IR Epithelial tissue			
RS Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	87/64	53/44
	2-4	50/51	301/353
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.13 (0.68-1.89)
	2-4	1.39 (0.84-2.31)	1.60 (1.12-2.29)
IR Adipose tissue			
RS Adipose tissue		Controls/Cases N	Controls/Cases N
	1	51/34	37/31
	2-4	48/39	221/249
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.24 (0.58-2.22)
	2-4	1.21 (0.66-2.22)	1.69 (1.05-2.70)
RS Adipose tissue			
RS Epithelial		Controls/Cases N	Controls/Cases N
	1	48/32	73/56
	2-4	40/33	195/232
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.14 (0.65-2.01)
	2-4	1.24 (0.65-2.36)	1.80 (1.10-2.93)
IR Adipose tissue			
RS Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	51/35	70/53
	2-4	48/38	188/227
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.09 (0.62-1.90)
	2-4	1.15 (0.63-2.10)	1.77 (1.10-2.83)
IR Adipose tissue			

IR Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	53/33	70/56
	2-4	46/40	288/224
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.28 (0.73-2.24)
	2-4	1.40 (0.76-2.57)	1.92 (1.19-3.09)

RS Adipose tissue			
IR Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	28/16	70/56
	2-4	46/40	188/224
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.39 (0.69-2.83)
	2-4	1.53 (0.72-3.22)	2.10 (1.10-4.01)

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age.

^b The quartiles with the lowest risk (the lowest quartile of RT-Epithelial, IR-Epithelial, RT-Adipose tissue and IR-Adipose tissue) were used as the reference category.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin

Supplementary Table 7. Association between combinations of RS- and IR-derived senescence scores in epithelial and adipose tissue and risk of breast cancer

Quartiles ^{a, b}		1	2-4
IR Epithelial tissue			
RS Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	87/64	53/44
	2-4	50/51	301/353
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.13 (0.66-1.92)
	2-4	1.53 (0.90-2.60)	1.64 (1.13-2.38)
IR Adipose tissue			
RS Adipose tissue		Controls/Cases N	Controls/Cases N
	1	51/34	37/31
	2-4	48/39	221/249
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.13 (0.58-2.22)
	2-4	1.05 (0.56-1.98)	1.66 (1.02-2.71)
RS Adipose tissue			
RS Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	48/32	73/56
	2-4	40/33	196/232
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.05 (0.58-1.88)
	2-4	1.19 (0.61-2.32)	1.81 (1.09-2.99)
IR Adipose tissue			
RS Epithelial tissue		Controls/Cases N	Controls/Cases N
	1	51/35	70/53
	2-4	48/38	188/227
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref)	1.07 (0.60-1.91)
	2-4	1.13 (0.61-2.12)	1.88 (1.15-3.07)
IR Adipose tissue			

IR Epithelial tissue		Controls/Cases N	Controls/Cases N
1		53/33	70/56
2-4		46/40	288/224
		OR (95% CI)	OR (95% CI)
1		1.00 (ref)	1.57 (0.87-2.82)
2-4		1.67 (0.89-3.14)	2.14 (1.30-3.51)

RS Adipose tissue			
IR Epithelial tissue		Controls/Cases N	Controls/Cases N
1		28/16	70/56
2-4		46/40	188/224
		OR (95% CI)	OR (95% CI)
1		1.00 (ref)	1.65 (0.79-3.42)
2-4		1.71 (0.79-3.72)	2.24 (1.15-4.35)

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

^a Quartiles of senescence scores.

^b The quartiles with the lowest risk (the lowest quartile of RT-Epithelial, IR-Epithelial, RT-Adipose tissue and IR-Adipose tissue) were used as the reference category.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin.

Supplementary table 8. Age-adjusted association between senescence measurements and risk of breast cancer by menopausal status

Tissue	Epithelial	Adipose tissue	Stroma	Tdlu
Premenopausal women				
N	409	388	417	396
Quartiles ^a				
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.15 (0.65-2.03)	2.74 (1.35-5.58)	0.95 (0.54-1.66)	0.95 (0.52-1.11)
3	1.47 (0.84-2.57)	1.80 (0.92-3.51)	0.90 (0.51-1.57)	0.98 (0.55-1.77)
4	0.97 (0.55-1.70)	1.85 (0.88-3.87)	0.72 (0.41-1.25)	0.4 (0.29-0.99)
<i>p-trend</i>	<i>0.904</i>	<i>0.294</i>	<i>0.233</i>	<i>0.053</i>
	IR			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.79 (0.45-1.39)	1.27 (0.65-2.47)	0.93 (0.53-1.63)	1.16 (0.65-2.08)
3	1.14 (0.65-1.97)	1.11 (0.57-2.16)	0.92 (0.54-1.57)	1.05 (0.60-1.84)
4	1.16 (0.66-2.02)	1.40 (0.68-2.87)	0.86 (0.49-1.50)	1.08 (0.60-1.94)
<i>p-trend</i>	<i>0.346</i>	<i>0.490</i>	<i>0.606</i>	<i>0.908</i>
	AAD			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.26 (0.73-2.15)	1.64 (0.85-3.19)	1.60 (0.94-2.69)	0.85 (0.49-1.47)
3	1.71 (1.00-2.90)	1.83 (0.96-3.49)	1.44 (0.82-2.52)	1.28 (0.72-2.27)
4	1.49 (0.83-2.66)	0.93 (0.46-1.89)	1.70 (0.97-2.98)	1.07 (0.59-1.94)
<i>p-trend</i>	<i>0.078</i>	<i>0.940</i>	<i>0.097</i>	<i>0.470</i>
Postmenopausal women				
N	561	406	563	509
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

2	1.42 (0.90-2.24)	0.90 (0.53-1.54)	1.23 (0.79-1.95)	1.30 (0.81-2.10)
3	1.59 (1.00-2.54)	1.04 (0.59-1.84)	1.43 (0.90-2.27)	1.05 (0.65-1.69)
4	1.72 (1.07-2.77)	1.55 (0.82-2.95)	1.96 (1.21-3.17)	1.15 (0.71-1.90)
<i>p-trend</i>	<i>0.019</i>	<i>0.166</i>	<i>0.006</i>	<i>0.933</i>
IR				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.36 (0.86-2.15)	1.78 (1.06-3.00)	1.14 (0.73-1.80)	0.80 (0.49-1.31)
3	2.15 (1.33-3.47)	1.48 (0.87-2.54)	1.10 (0.68-1.76)	1.26 (0.76-2.10)
4	1.10 (0.69-1.75)	1.86 (0.98-3.50)	1.09 (0.68-1.75)	1.10 (0.67-1.81)
<i>p-trend</i>	<i>0.305</i>	<i>0.088</i>	<i>0.757</i>	<i>0.335</i>
AAD				
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.03 (0.63-1.68)	0.80 (0.47-1.36)	1.75 (1.07-2.89)	0.99 (0.60-1.65)
3	1.03 (0.63-1.67)	1.01 (0.58-1.75)	1.07 (0.67-1.71)	0.99 (0.60-1.61)
4	0.72 (0.45-1.15)	1.43 (0.76-2.69)	0.89 (0.55-1.42)	0.82 (0.50-1.34)
<i>p-trend</i>	<i>0.155</i>	<i>0.223</i>	<i>0.243</i>	<i>0.447</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression.

^a Quartiles of senescence marker measurements.

Analysis adjusted for age.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin

Supplementary Table 9. Association between senescence measurements and risk of breast cancer by menopausal status

Tissue	Epithelial	Adipose tissue	Stroma	Tdlu
Premenopausal women				
N	409	388	417	396
Quartiles ^a				
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.27 (0.68-2.36)	2.66 (1.21-5.85)	1.00 (0.55-1.82)	0.79 (0.42-1.50)
3	1.78 (0.95-3.34)	1.77 (0.84-3.74)	1.06 (0.58-1.93)	1.23 (0.64-2.35)
4	1.02 (0.55-1.91)	1.76 (0.74-4.02)	0.78 (0.43-1.43)	0.43 (0.22-0.84)
<i>p-trend</i>	<i>0.760</i>	<i>0.439</i>	<i>0.486</i>	<i>0.051</i>
	IR			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.67 (0.36-1.26)	1.06 (0.50-2.26)	1.06 (0.57-1.97)	1.10 (0.57-2.09)
3	1.16 (0.63-2.16)	0.85 (0.40-1.81)	0.99 (0.54-1.80)	1.15 (0.62-2.14)
4	1.08 (0.58-2.01)	1.22 (0.55-2.74)	0.85 (0.47-1.56)	1.11 (0.58-2.13)
<i>p-trend</i>	<i>0.408</i>	<i>0.793</i>	<i>0.582</i>	<i>0.731</i>
	AAD			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.17 (0.63-2.16)	1.32 (0.61-2.82)	1.53 (0.84-2.79)	0.90 (0.49-1.67)
3	1.64 (0.90-3.00)	1.47 (0.69-3.12)	1.25 (0.66-2.36)	1.50 (0.78-2.88)
4	1.67 (0.85-3.28)	0.85 (0.37-1.97)	1.48 (0.78-2.80)	1.37 (0.70-2.71)
<i>p-trend</i>	<i>0.067</i>	<i>0.895</i>	<i>0.348</i>	<i>0.199</i>
Postmenopausal women				
N	561	406	563	509
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

2	1.55 (0.96-2.48)	0.89 (0.51-1.54)	1.21 (0.75-1.93)	1.34 (0.82-2.19)
3	1.69 (1.04-2.76)	1.01 (0.56-1.81)	1.43 (0.89-2.30)	0.94 (0.57-1.56)
4	1.84 (1.11-3.02)	1.57 (0.80-3.09)	1.84 (1.12-3.04)	1.17 (0.70-1.96)
<i>p-trend</i>	<i>0.017</i>	<i>0.196</i>	<i>0.013</i>	<i>0.853</i>

IR

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.46 (0.92-2.34)	1.99 (1.15-3.45)	1.22 (0.75-1.97)	0.83 (0.50-1.39)
3	2.15 (1.32-3.51)	1.56 (0.88-2.78)	1.01 (0.62-1.64)	1.28 (0.75-2.18)
4	1.06 (0.65-1.71)	1.96 (1.00-3.83)	1.05 (0.64-1.71)	1.03 (0.61-1.73)
<i>p-trend</i>	<i>0.382</i>	<i>0.084</i>	<i>0.972</i>	<i>0.357</i>

AAD

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.98 (0.59-1.63)	0.75 (0.43-1.33)	1.87 (1.10-3.17)	1.01 (0.59-1.73)
3	1.00 (0.60-1.66)	0.98 (0.54-1.75)	1.05 (0.64-1.72)	0.91 (0.54-1.52)
4	0.71 (0.43-1.15)	1.32 (0.67-2.60)	0.93 (0.56-1.53)	0.80 (0.48-1.36)
<i>p-trend</i>	<i>0.163</i>	<i>0.334</i>	<i>0.277</i>	<i>0.368</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

^a Quartiles of senescence scores.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin Tdlu, terminal duct lobular units.

Supplementary Table 10. Age-adjusted association between senescence measurements and risk of breast cancer by histological characteristics

Tissue	Epithelial	Adipose tissue	Stroma	Tdlu
No lesions or non-proliferative lesions				
N	202	145	205	168
Quartiles				
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.87 (0.41-1.84)	3.12 (1.18-8.16)	1.59 (0.74-3.41)	0.82 (0.32-2.08)
3	1.21 (0.57-2.56)	2.18 (0.78-6.11)	1.26 (0.59-2.69)	0.92 (0.39-2.20)
4	1.05 (0.46-2.36)	2.46 (0.86-7.02)	0.93 (0.42-2.09)	1.00 (0.44-2.25)
<i>p-trend</i>	<i>0.586</i>	<i>0.432</i>	<i>0.921</i>	<i>0.883</i>
	IR			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.87 (0.35-2.13)	0.87 (0.35-2.13)	1.78 (0.81-3.89)	0.97 (0.42-2.24)
3	1.53 (0.70-3.31)	1.42 (0.56-3.60)	1.14 (0.52-2.49)	1.33 (0.57-3.12)
4	0.80 (0.36-1.81)	1.30 (0.44-3.82)	1.60 (0.75-3.41)	1.39 (0.52-3.71)
<i>p-trend</i>	<i>0.964</i>	<i>0.396</i>	<i>0.387</i>	<i>0.379</i>
	AAD			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.65 (0.26-1.63)	0.99 (0.38-2.54)	1.60 (0.65-3.92)	0.61 (0.24-1.56)
3	2.29 (0.96-5.45)	0.81 (0.34-1.94)	1.36 (0.57-3.22)	1.07 (0.43-2.65)
4	1.17 (0.54-2.56)	0.65 (0.22-1.95)	1.50 (0.65-3.46)	0.67 (0.30-1.52)
<i>p-trend</i>	<i>0.336</i>	<i>0.355</i>	<i>0.483</i>	<i>0.526</i>
Epithelial hyperplasia (with/without atypia)				
N	799	566	798	764
	RS			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.51 (1.01-2.26)	1.14 (0.71-1.82)	0.99 (0.66-1.47)	1.18 (0.79-1.77)

3	1.70 (1.13-2.55)	1.16 (0.72-1.85)	1.15 (0.77-1.72)	1.05 (0.70-1.58)
4	1.58 (1.06-2.37)	1.56 (0.91-2.67)	1.39 (0.93-2.08)	0.83 (0.54-1.27)
<i>p-trend</i>	<i>0.026</i>	<i>0.132</i>	<i>0.071</i>	<i>0.269</i>

IR

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.13 (0.75-1.69)	1.83 (1.16-2.90)	0.91 (0.62-1.36)	0.88 (0.58-1.33)
3	1.61 (1.07-2.41)	1.23 (0.78-1.95)	0.95 (0.65-1.42)	1.09 (0.72-1.65)
4	1.28 (0.85-1.91)	1.83 (1.09-3.07)	0.93 (0.62-1.39)	0.95 (0.63-1.43)
<i>p-trend</i>	<i>0.102</i>	<i>0.125</i>	<i>0.789</i>	<i>0.909</i>

AAD

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.22 (0.83-1.80)	1.06 (0.67-1.66)	1.64 (1.11-2.42)	0.91 (0.61-1.35)
3	1.07 (0.73-1.57)	1.49 (0.93-2.39)	1.21 (0.82-1.68)	1.01 (0.68-1.51)
4	0.88 (0.59-1.32)	1.28 (0.76-2.13)	1.01 (0.68-1.50)	0.96 (0.62-1.48)
<i>p-trend</i>	<i>0.496</i>	<i>0.144</i>	<i>0.770</i>	<i>0.842</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression.

^a Quartiles of senescence marker measurements.

Analysis adjusted for age.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin.

Supplementary Table 11. Association between senescence measurements and risk of breast cancer by histological characteristics

Tissue	Epithelial	Adipose tissue	Stroma	Tdlu
No lesions or non-proliferative lesions				
N	202	145	205	168
Quartiles				
	RS			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.71 (0.30-1.64)	4.03 (1.32-12.27)	1.37 (0.59-3.19)	0.92 (0.33-2.53)
3	0.92 (0.40-2.10)	2.01 (0.62-6.54)	0.98 (0.43-2.23)	1.01 (0.39-2.63)
4	0.87 (0.36-2.09)	2.68 (0.79-9.13)	0.75 (0.32-1.78)	1.05 (0.43-2.57)
<i>p-trend</i>	<i>0.857</i>	<i>0.301</i>	<i>0.450</i>	<i>0.883</i>
	IR			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.87 (0.35-2.13)	0.88 (0.32-2.40)	1.74 (0.73-4.12)	0.92 (0.36-2.37)
3	1.28 (0.54-3.00)	1.15 (0.40-3.28)	0.83 (0.35-1.95)	1.46 (0.57-3.76)
4	0.69 (0.29-1.66)	1.16 (0.36-3.79)	1.33 (0.59-3.01)	1.31 (0.45-3.780)
<i>p-trend</i>	<i>0.629</i>	<i>0.330</i>	<i>0.797</i>	<i>0.404</i>
	AAD			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	0.69 (0.25-1.88)	0.69 (0.22-2.10)	1.68 (0.65-4.39)	0.88 (0.31-2.50)
3	2.68 (1.05-6.86)	0.59 (0.22-1.56)	1.37 (0.55-3.42)	1.68 (0.60-4.70)
4	1.33 (0.57-3.13)	0.57 (0.16-2.01)	1.62 (0.67-3.92)	0.85 (0.34-2.13)
<i>p-trend</i>	<i>0.160</i>	<i>0.289</i>	<i>0.439</i>	<i>0.994</i>
Epithelial hyperplasia (with/without atypia)				
N	799	566	798	764
	RS			
1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.70 (1.11-2.59)	1.12 (0.69-1.83)	0.96 (0.63-1.46)	1.16 (0.78-1.78)

3	1.98 (1.29-3.05)	1.16 (0.70-1.89)	1.22 (0.80-1.86)	1.04 (0.67-1.60)
4	1.70 (1.11-2.60)	1.77 (1.00-3.12)	1.39 (0.90-2.12)	0.78 (0.50-1.22)
<i>p-trend</i>	<i>0.015</i>	<i>0.069</i>	<i>0.073</i>	<i>0.229</i>

IR

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.18 (0.77-1.80)	1.90 (1.17-3.09)	0.91 (0.60-1.39)	0.90 (0.58-1.39)
3	1.70 (1.11-2.60)	1.22 (0.75-2.00)	0.94 (0.61-1.43)	1.20 (0.77-1.86)
4	1.26 (0.83-1.93)	1.98 (1.14-3.42)	0.86 (0.56-1.31)	0.97 (0.63-1.49)
<i>p-trend</i>	<i>0.131</i>	<i>0.101</i>	<i>0.521</i>	<i>0.797</i>

AAD

1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2	1.12 (0.74-1.67)	0.95 (0.59-1.53)	1.50 (0.99-2.27)	1.01 (0.66-1.54)
3	0.97 (0.65-1.46)	1.39 (0.84-2.28)	1.01 (0.67-1.52)	1.06 (0.70-1.61)
4	0.82 (0.54-1.26)	1.27 (0.73-2.19)	0.92 (0.61-1.39)	1.03 (0.66-1.60)
<i>p-trend</i>	<i>0.313</i>	<i>0.212</i>	<i>0.356</i>	<i>0.842</i>

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression. Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

^a Quartiles of senescence scores.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin Tdlu, terminal duct lobular units.

Supplementary Table 12. Association between RS and IR senescence measurements in epithelial and adipose tissues among women with epithelial hyperplasia (with/without atypia) and risk of breast cancer

Quartiles ^a		1	2-4
Predictive model – Tissue		IR Epithelial	
RS Epithelial		Controls/Cases N	Controls/Cases N
	1	58/45	42/34
	2-4	35/39	239/307
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref) ^b	1.04 (0.57-1.89) ^b
		1.00 (ref) ^c	1.05 (0.56-1.96) ^c
	2-4	1.43 (0.78-2.61) ^b	1.65 (1.08-2.53) ^b
		1.76 (0.93-3.31) ^c	1.84 (1.18-2.89) ^c
Predictive model – Tissue		IR Adipose	
RS Adipose		Controls/Cases N	Controls/Cases N
	1	36/30	25/26
	2-4	40/28	171/210
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref) ^b	1.24 (0.60-2.59) ^b
		1.00 (ref) ^c	1.07 (0.49-2.31) ^c
	2-4	0.84 (0.42-1.66) ^b	1.47 (0.87-2.49) ^b
		0.73 (0.35-1.52) ^c	1.43 (0.82-2.51) ^c
Predictive model – Tissue		RS Adipose	
RS Epithelial		Controls/Cases N	Controls/Cases N
	1	32/29	54/37
	2-4	29/27	157/201
		OR (95% CI)	OR (95% CI)
	1	1.00 (ref) ^b	0.75 (0.39-1.45) ^b
		1.00 (ref) ^c	0.60 (0.30-1.18) ^c
	2-4	1.03 (0.50-2.12) ^b	1.42 (0.82-2.44) ^b
		0.93 (0.43-2.00) ^c	1.47 (0.83-2.59) ^c
Predictive model – Tissue		IR Adipose	
RS Epithelial		Controls/Cases	Controls/Cases

	N	N
1	38/27	48/39
2-4	38/31	148/197
	OR (95% CI)	OR (95% CI)
1	1.00 (ref) ^b	1.13 (0.59-2.17) ^b
	1.00 (ref) ^c	1.01 (0.50-2.01) ^c
2-4	1.15 (0.58-2.27) ^b	1.87 (1.09-3.20) ^b
	1.20 (0.58-2.47) ^c	2.05 (1.16-3.62) ^c
Predictive model – Tissue	IR Adipose	
IR Epithelial	Controls/Cases N	Controls/Cases N
1	39/23	48/45
2-4	37/35	148/191
	OR (95% CI)	OR (95% CI)
1	1.00 (ref) ^b	1.58 (0.82-3.06) ^b
	1.00 (ref) ^c	1.96 (0.97-3.95) ^c
2-4	1.60 (0.80-3.20) ^b	2.19 (1.25-3.82) ^b
	2.10 (1.00-4.41) ^c	2.54 (1.40-4.58) ^c
Predictive model – Tissue	RS Adipose	
IR Epithelial	Controls/Cases N	Controls/Cases N
1	18/13	48/45
2-4	37/35	148/191
	OR (95% CI)	OR (95% CI)
1	1.00 (ref) ^b	1.29 (0.56-2.93) ^b
	1.00 (ref) ^c	1.61 (0.68-3.83) ^c
2-4	1.31 (0.56-3.06) ^b	1.78 (0.85-3.76) ^b
	1.71 (0.70-4.21) ^c	2.09 (0.96-4.56) ^c

Results are odds ratios (OR) and 95% confidence intervals (CI) obtained using unconditional logistic regression.

^a Quartiles of senescence marker measurements.

^b Analysis adjusted for age.

^c Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, history of bilateral oophorectomy, and ever use of postmenopausal hormone therapy.

Abbreviations: RS, replicative senescence; IR, ionizing radiation.

Supplementary Table 13. Age-adjusted association of spatial patterns of cellular senescence and risk of breast cancer

RS			
Tissue	Half-life		Percentage difference ^d
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Epithelial			
Quartiles ^a			
N	737 ^b	1,003	1,003
1	1.00 (ref)	1.00 (ref) ^c	1.00 (ref)
2	0.85 (0.57-1.29)		0.76 (0.53-1.08)
3	0.91 (0.60-1.36)		0.78 (0.55-1.11)
4	0.84 (0.56-1.27)		0.71 (0.50-1.02)
		1.31 (1.03-1.81)	
<i>p-value</i>	0.495		0.088
Adipose			
N	344 ^b	712	709
1	1.00 (ref)	1.00 (ref) ^c	1.00 (ref) e
2	1.21 (0.66-2.22)		
3	1.21 (0.66-2.20)		1.25 (0.86-1.80)
4	1.39 (0.76-2.53)		0.90 (0.62-1.32)
		0.92 (0.68-1.23)	
<i>p-value</i>	0.310		0.820
Stroma			
N	769 ^a	1,006	1,006
1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
2	1.31 (0.88-1.95)		1.10 (0.77-1.56)
3	1.07 (0.72-1.59)		1.23 (0.87-1.75)
4	1.26 (0.84-1.88)		0.89 (0.62-1.23)
		0.90 (0.67-1.21)	

<i>p-value</i>		0.345	0.668	
IR				
		Half-life	Percentage difference	
Tissue		Epithelial		
	N	922 ^a	1,003	1,003
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	0.94 (0.65-1.36)		0.89 (0.63-1.27)
	3	0.87 (0.61-1.26)		1.04 (0.74-1.48)
	4	1.08 (0.75-1.56)		1.22 (0.86-1.73)
			0.93 (0.59-1.47)	
	<i>p-value</i>	0.786	0.185	
Tissue		Adipose		
	N	352 ^a	712	712
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	0.90 (0.50-1.64)		
	3	1.09 (0.60-1.97)		1.08 (0.75-1.56)
	4	0.82 (0.46-1.49)		1.14 (0.80-1.63)
			0.90 (0.67-1.21)	
	<i>p-value</i>	0.684	0.458	
Tissue		Stroma		
	N	755 ^a	1,006	1,006
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	1.44 (0.96-2.16)		0.72 (0.51-1.03)
	3	1.41 (0.94-2.11)		0.65 (0.46-0.92)
	4	1.42 (0.95-2.14)		0.75 (0.53-1.07)
			1.43 (1.07-1.91)	
	<i>p-value</i>	0.114	0.092	

Cross-analysis RS senescence score and RS percent difference in the epithelial tissue

RS percent difference		
Quartiles ^d	2-4	1
RS senescence	Controls/Cases N	Controls/Cases N
1	116/88	24/20
2-4	270/286	81/118
	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.10 (0.57-2.12)

2-4	1.40 (1.01-1.93)	1.92 (1.29-2.86)
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Analyses adjusted for age.

^a Quartiles of senescence decay measurements.

^b Excluding women whose data did not fit a negative exponential curve.

^c All data that fit a negative exponential curve were combined into a single group and used as the reference category and compared to a group consisting of subjects whose data that did not fit a negative exponential curve.

^d Percent difference calculated based on a negative exponential curve fit.

^e The quartiles of senescence scores with the lowest risk (1st quartile of RT-Epithelial and 2nd-4th quartiles of the percent difference) were used as reference category.

Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin.

Supplementary Table 14. Association of spatial patterns of cellular senescence and risk of breast cancer

		RS		
		Half-life		Percentage difference ^d
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Tissue		Epithelial		
	Quartiles ^a			
	N	737 ^b	1,003	1,003
	1	1.00 (ref)	1.00 (ref) ^c	1.00 (ref)
	2	0.85 (0.55-1.30)		0.75 (0.52-1.10)
	3	0.90 (0.59-1.39)		0.85 (0.59-1.22)
	4	0.83 (0.54-1.27)		0.65 (0.45-0.93)
			1.34 (1.00-1.81)	
	<i>p-value</i>	0.481		0.039
Tissue		Adipose		
	N	344 ^b	712	709
	1	1.00 (ref)	1.00 (ref) ^c	1.00 (ref) ^e
	2	1.01 (0.53-1.93)		
	3	1.14 (0.59-2.18)		1.21 (0.83-1.78)
	4	1.31 (0.69-2.49)		0.90 (0.62-1.32)
			0.96 (0.71-1.31)	
	<i>p-value</i>	0.415		0.311
Tissue		Stroma		
	N	769 ^a	1,006	1,006
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	1.44 (0.94-2.20)		1.17 (0.81-1.69)
	3	1.19 (0.78-1.83)		1.25 (0.87-1.81)
	4	1.37 (0.90-2.09)		0.90 (0.62-1.29)
			0.86 (0.63-1.17)	

<i>p-value</i>		0.261	0.655	
IR				
		Half-life		Percentage difference
Tissue		Epithelial		
	N	922 ^a	1,003	1,003
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	0.96 (0.65-1.42)		0.93 (0.64-1.35)
	3	0.83 (0.56-1.22)		0.98 (0.68-1.42)
	4	1.00 (0.68-1.48)		1.14 (0.79-1.65)
			1.01 (0.62-1.63)	
	<i>p-value</i>	0.826	0.439	
Tissue		Adipose		
	N	352 ^a	712	712
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref) ^e
	2	0.88 (0.47-1.64)		
	3	1.00 (0.54-1.86)		1.13 (0.77-1.67)
	4	0.81 (0.43-1.53)		1.18 (0.81-1.71)
			0.86 (0.63-1.18)	
	<i>p-value</i>	0.636	0.354	
Tissue		Stroma		
	N	755 ^a	1,006	1,006
	1	1.00 (ref)	1.00 (ref) ^b	1.00 (ref)
	2	1.49 (0.98-2.29)		0.80 (0.55-1.15)
	3	1.46 (0.96-2.22)		0.70 (0.49-1.01)
	4	1.43 (0.93-2.18)		0.82 (0.57-1.18)
			1.31 (0.97-1.77)	
	<i>p-value</i>	0.126	0.212	

Cross-analysis RS senescence score and RS percent difference in the epithelial tissue

RS percent difference		
Quartiles ^f	2-4	1
RS senescence	Controls/Cases N	Controls/Cases N
1	116/88	24/20
2-4	270/286	81/118
	OR (95% CI)	OR (95% CI)
1	1.00 (ref)	1.06 (0.53-2.10)

2-4	1.44 (1.02-2.02)	2.01 (1.32-3.04)
Analyses adjusted for age, body mass index, menopausal status, ever smoked, number of pregnancies, age at first pregnancy, history of breast cancer in first degree relatives, and ever use of postmenopausal hormone therapy.		
^a Quartiles of senescence decay measurements.		
^b Excluding women whose data did not fit a negative exponential curve.		
^c All data that fit a negative exponential curve were combined into a single group and used as the reference category and compared to a group consisting of subjects whose data that did not fit a negative exponential curve.		
^d Percent difference calculated based on a negative exponential curve fit.		
^e Quartiles 1 and 2 were combined as 50% of the sample has a percent-difference value of 0 in the adipose tissue.		
^f The quartiles of senescence scores with the lowest risk (1 st quartile of RT-Epithelial and 2 nd -4 th quartiles of the percent difference) were used as reference category.		
Abbreviations: RS, replicative senescence; IR, ionizing radiation; AAD, antimycin-A, atazanavir-ritonavir treatment, and doxorubicin.		