

Local Treatment of Breast Cancer in *BRCA* Carriers

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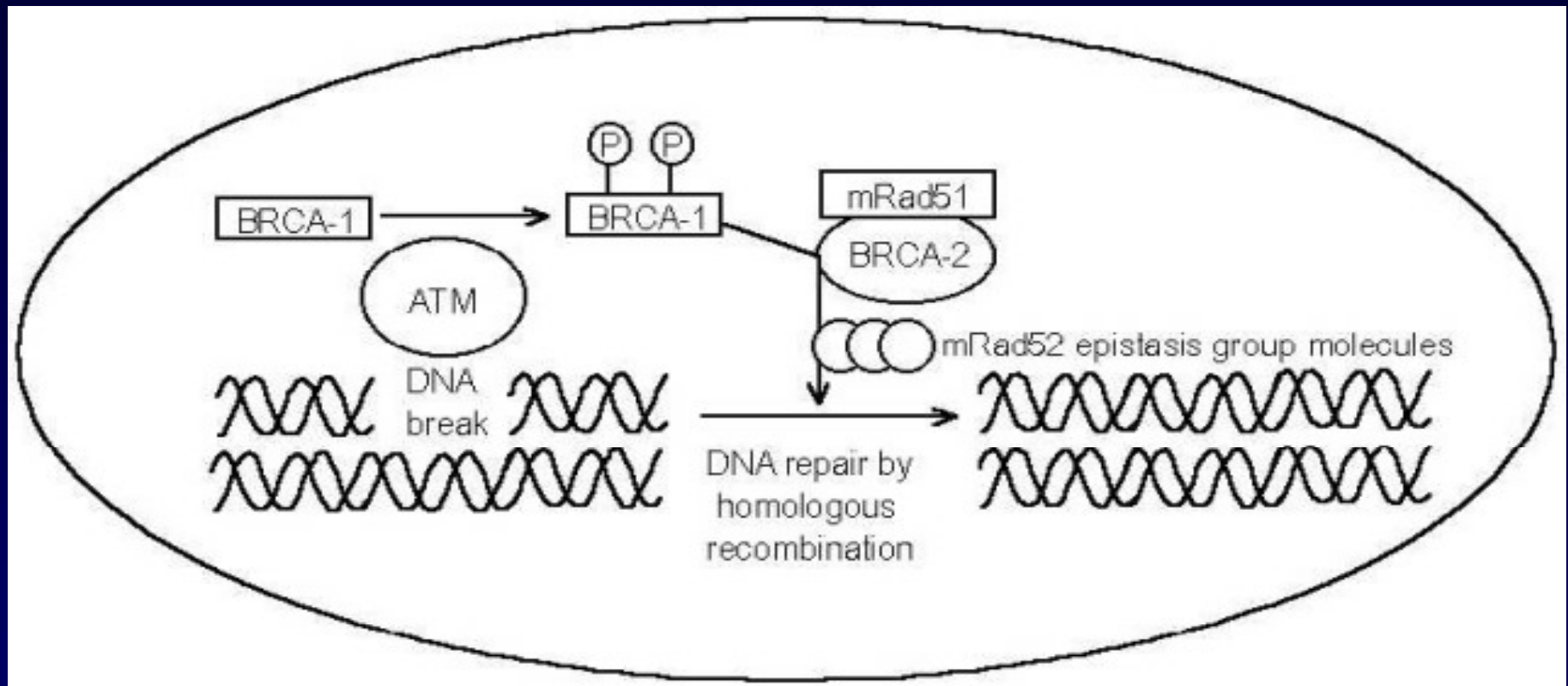
The BRCA Genes and Radiation

- Tumors arising in carriers express a truncated, inactive BRCA1/2 protein
- Both proteins are involved in the double strand break (DSB) repair of DNA, specifically through the BRCA1 / BRCA2 / RAD51 complex
- Both BRCA1 and BRCA2 have been shown to colocalize with RAD51 in damage-induced nuclear foci and to be required for normal levels of homologous recombination and DSB repair

The BRCA Genes and Radiation

- **Loss of either BRCA1/2 protein function has been shown to result in a reduction in the frequency of homologous recombination events in irradiated cells**
- **Homologous recombination holds a major role in DSB damage repair, and therefore maintaining genomic stability and integrity**
- **Radiation activity is mainly through double strand break**
- **BRCA1/2 have a role in other DNA damage repair mechanisms as well**

The BRCA Genes and Radiation



The BRCA Genes and Radiation

..... *BRCA* genes hold a valuable role in maintaining genomic integrity, a possible consequence of a defective protein in cancers of patients with *BRCA1/2* mutations could be the development of highly radiation-sensitive tumor...

The BRCA Genes and Radiation

Moreover, since *BRCA1/2* are both tumor suppressor genes and the somatic cells of mutation carriers are already lacking one normal copy of the gene, it has been suggested that:

1. Radiotherapy could increase the rate of second cancers in the treated breast from direct radiation exposure
2. Further increase the rates of contralateral breast cancers (beyond the elevated baseline risk) as a consequence of scattered low dose radiation

The BRCA Genes and Radiation

- What is the effectiveness of radiation therapy for *BRCA* carriers as adjuvant therapy after BCS?
- Is there higher radiation sensitivity (toxicity) in *BRCA* carriers?
- Do carriers have more contralateral breast cancers from radiation?

Local Control Results in
Carriers with Early-Stage
Breast Cancer

Rates of IBTR Following BCS and RT

Author	Patients, n		IBTR, %		P Value	F/U, years
	BRCA1/2	Sporadic	BRCA1/2	Sporadic		
Hafftey*	22	105	49	21	0.007	12
Metcalfe	188	---	11.5	---	---	10
Pierce	160	445	12	9	0.19	10
Robson	87	---	14	---	---	10
Robson, Chappuis	56	440	12	8	0.68	10
Delaloge	53	43	9BRCA1 37BRCA2	12	0.07	10
Eccles	36	83	17	24	0.63	10

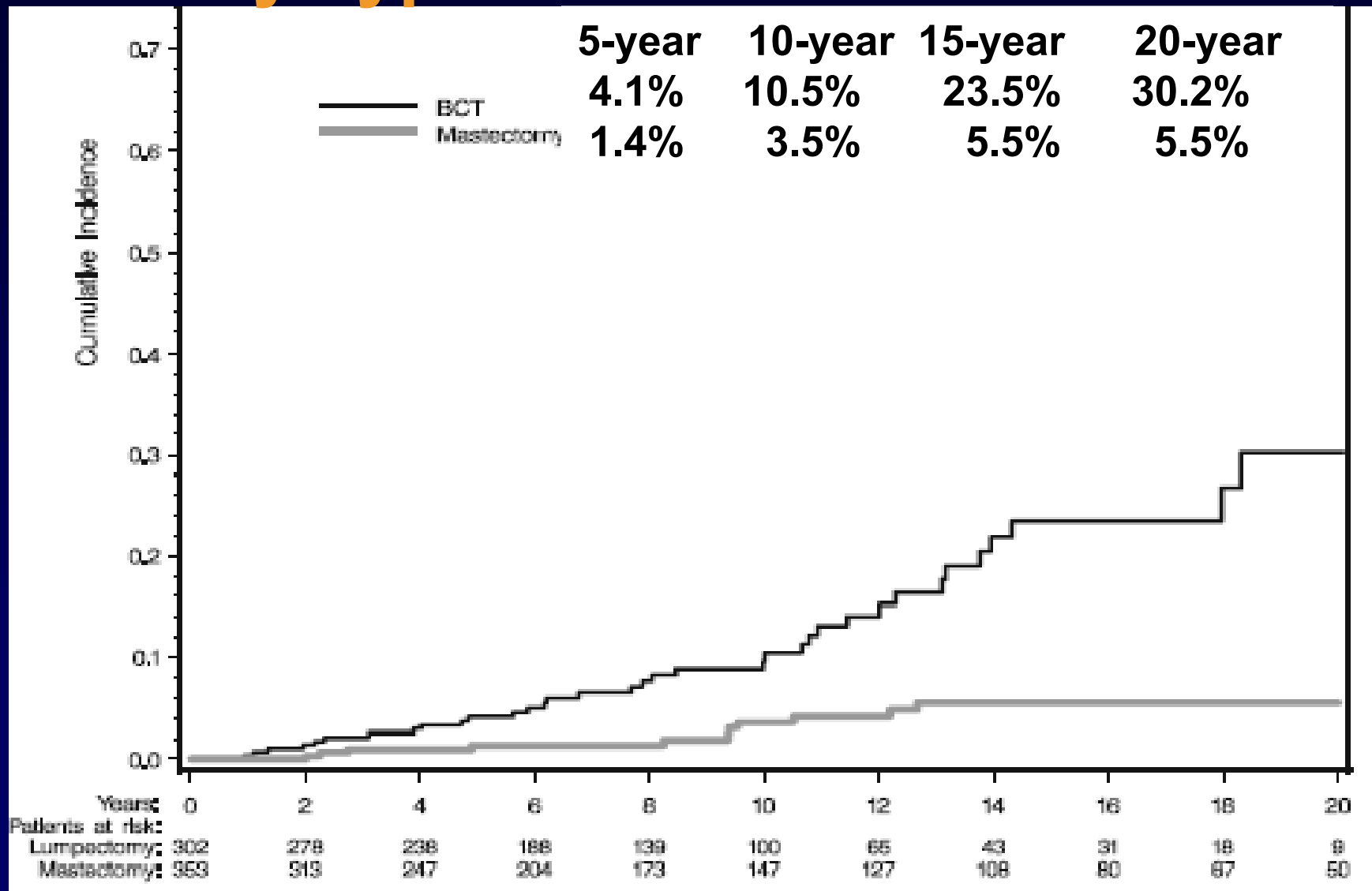
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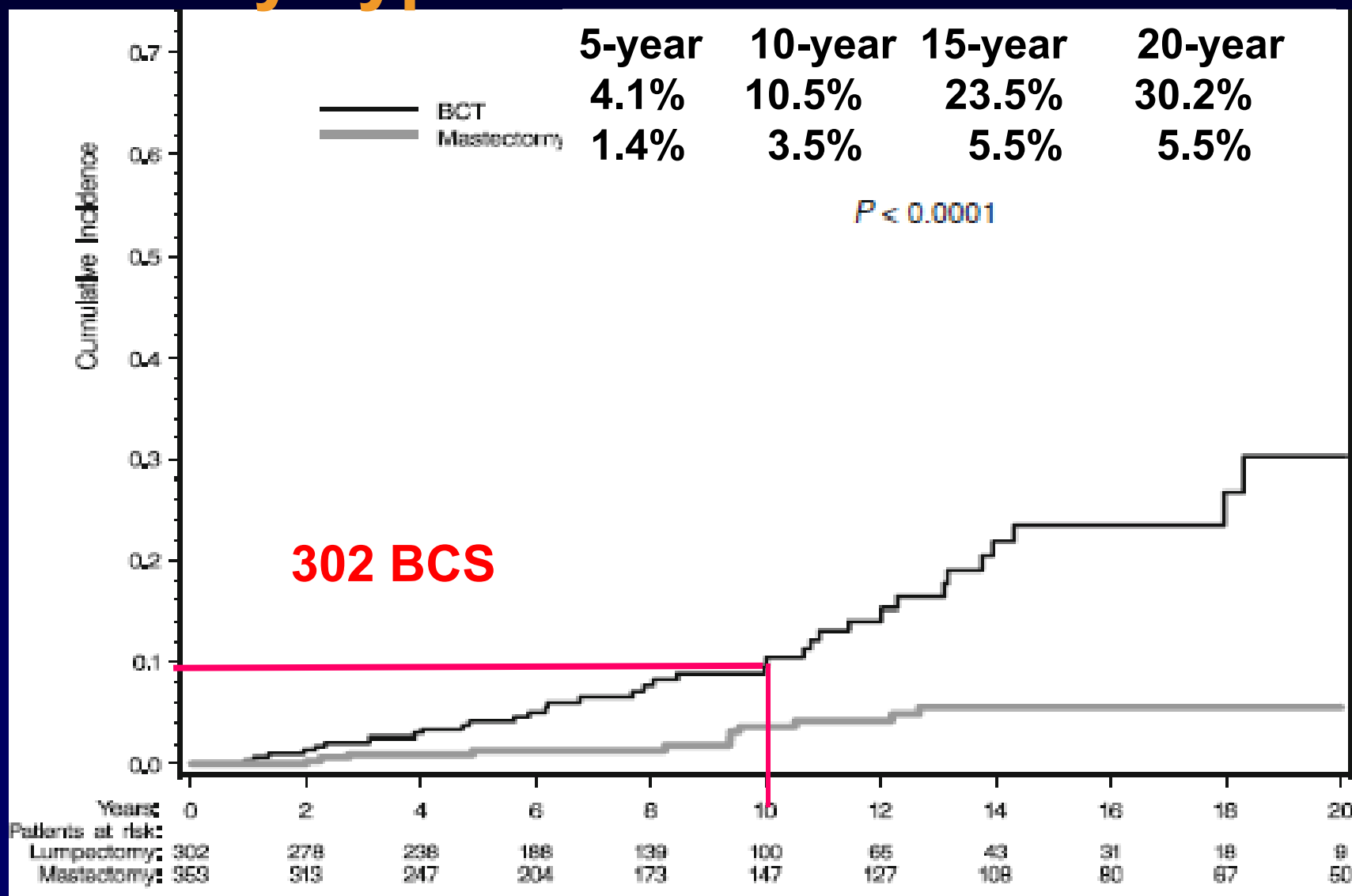
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Local Failure as First Failure By Type of Local Treatment



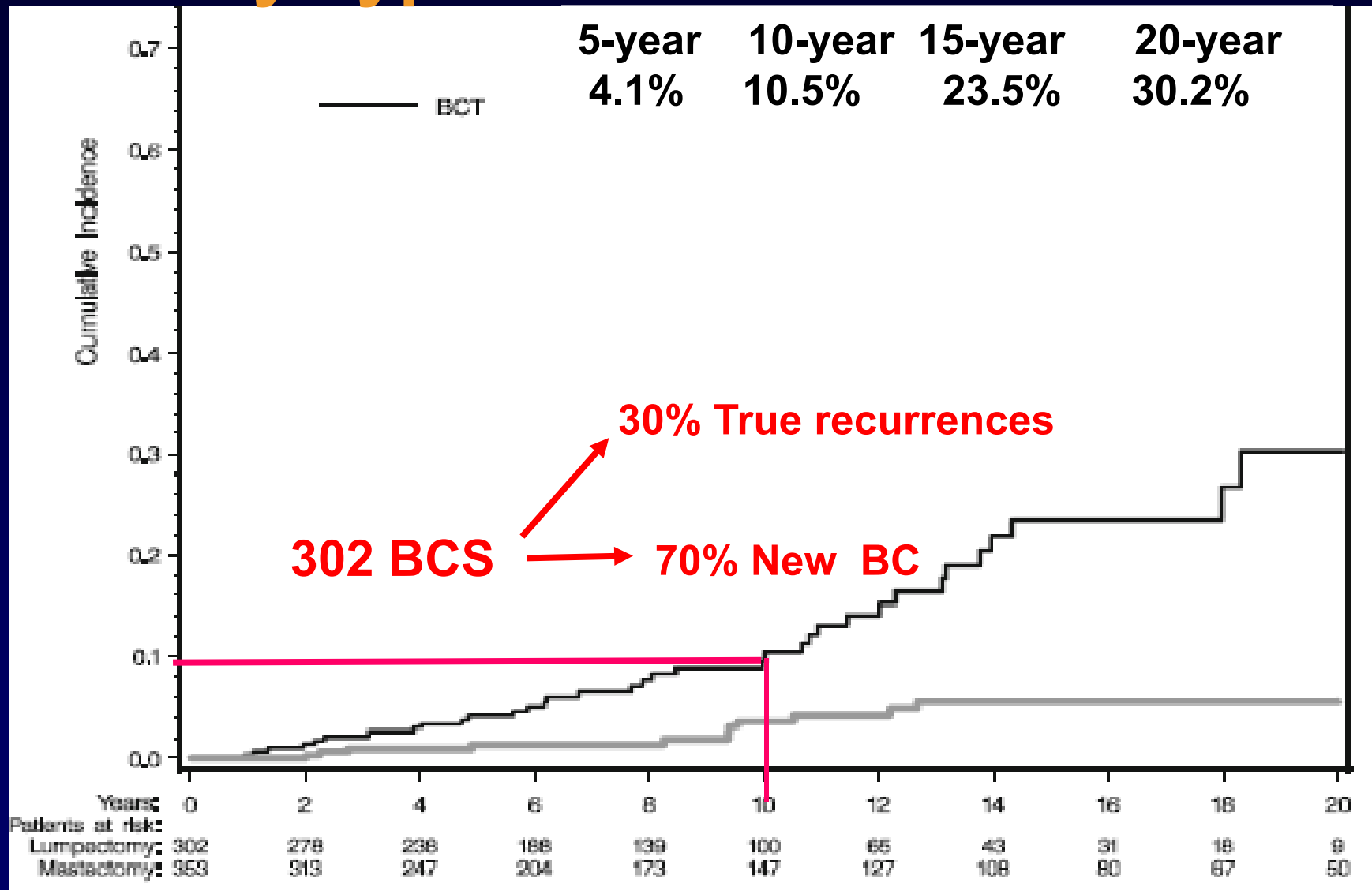
Pierce LJ, et al. *Breast Cancer Res Treat.* 2010;121(2):389-398.

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Factors Influencing LR in BRCA Carriers

Sample/Characteristic	Hazard Ratio (95% CI)	P Value
Total sample (N = 655)		
Treatment decision		
BCT	4.5 (2.3 – 8.9)	<0.0001
Mastectomy	1.0	
BCT sample (N = 302)		
Gene mutation		
<i>BRCA1</i>	1.00	
<i>BRCA2</i>	2.9 (1.2 – 7.1)	0.019
Adjuvant chemotherapy		
Yes	1.0	
No	5.4 (2.3 – 13.3)	0.0001

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Factors Influencing LR in BRCA Carriers

- Studies have shown that both prophylactic bilateral oophorectomy and tamoxifen use can reduce the risk of breast cancer in carriers, with risk reductions of approximately 40% to 50%
- These interventions could also reduce the risk of IBTR in known carriers with breast cancer who opt to be treated with breast conservation
- These facts may complicate analysis of outcome in carriers and should be taken into account when comparing results across series

Metcalfe K, et al. *J Clin Oncol*. 2004;22(12):2328-2335. Narod SA, et al. *Lancet*. 2000;356(9245):1876-1881. Gronwald J, et al. *Int J Cancer*. 2006;118(9):2281-2284. Rebbeck TR, et al. *N Engl J Med*. 2002;346(21):1616-1622. Pierce LJ, et al. *J Clin Oncol*. 2006;24(16):2437-2443.

Local Control in BRCA Carriers After BCS and XRT

- Comparable to sporadic cases
- May be further influenced by (yet) unknown factors
- Chemotherapy use
- *BRCA* gene
- Suggested to be influenced by same factors as in sporadic cases
 - Stage
 - Age
 - Margins

Radiation Sensitivity in *BRCA* Carriers

Radiation Sensitivity in *BRCA* Carriers

- *BRCA1/2* genes are involved in repairing DNA damage
- Having only one normal allele—would there be greater risk of acute and chronic radiation-associated toxicities??
- ?? Would there be an incomplete repair of radiation-induced damage compared to patients with two normal copies of the genes ??

Radiation Sensitivity in *BRCA* Carriers

- Only 3 series in the literature evaluated acute or chronic toxicity in *BRCA* carriers

- Gaffney et al reported toxicity in 21 carriers—retrospective cohort, no control group

Higher acute side effects than generally reported following standard radiation in patients with sporadic disease (non standard radiation protocols)

No late sequelae of RT with a mean follow-up of approximately 8.5 years

Radiation Sensitivity in *BRCA* Carriers

- Pierce et al reported no difference in acute skin toxicity, pulmonary symptoms or breast pain between carriers and sporadic breast cancer patients (matched controls) receiving radiation
- The incidence of chronic RT-associated adverse events, specifically chronic sequelae in the skin, subcutaneous tissues, lung, and bone was the same for both groups

Radiation Sensitivity in *BRCA* Carriers

- A report by Shanley et al also compared rates of acute and late toxicities in *BRCA1/2* carriers and matched controls
- More carriers noted some degree of breast pain with RT, no significant differences in degree of breast erythema, moist desquamation, or fatigue
- Chronic toxicity, as rib fractures, lung fibrosis, soft tissue/bone necrosis, did not differ by group
- Cosmesis was the same in *BRCA1/2* carriers and controls

Radiation Sensitivity in *BRCA* Carriers

- Therefore, in the reports of acute toxicity in which carriers and noncarriers were matched, rates of acute toxicity were comparable between *BRCA1/2* carriers and controls
- All three series demonstrated similar rates of chronic radiation events with up to 7 years of follow-up
- As the latency period for radiation-induced malignancies has been shown to be 10 years and longer, additional follow-up will be needed to insure there is no increase in the incidence of second cancers beyond baseline levels observed in carriers

The Contralateral Breast and Radiation

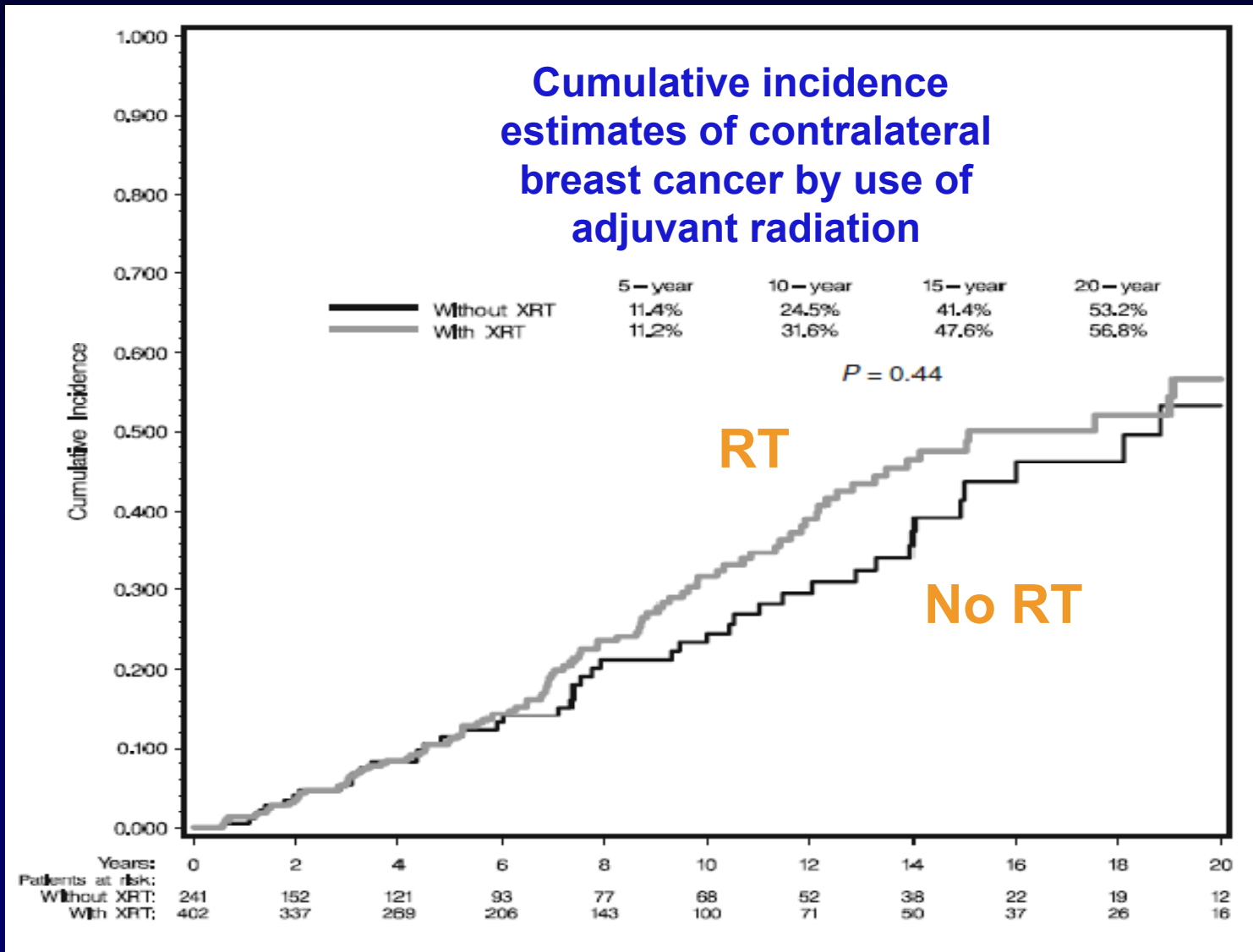
The Contralateral Breast and Radiation

- **The baseline risk of contralateral breast cancer reported to be as high as 40% in carriers at 10 years after treatment of the index breast cancer**
- **Whether this elevated baseline risk could be further increased as a result of scattered radiation following definitive treatment of the initial breast cancer has been questioned**

The Contralateral Breast and Radiation

- Eccles and colleagues reported similar rates of contralateral breast cancer in patients with a positive family history of breast cancer (approximately half were *BRCA1* positive) who received adjuvant RT compared to patients who did not received radiation, 33.3% and 39.3%, respectively, $P = 0.9520$.
- In a series by Metcalfe et al, the 5-year and 10-year actuarial estimates of contralateral breast cancer were 16.9% and 29.5%, respectively. RT was not associated with an elevated risk of contralateral breast cancer (HR 0.86; $P = 0.51$).

The Contralateral Breast and Radiation



Pierce LJ, et al. *Breast Cancer Res Treat.* 2010;121(2):389-398.

The Contralateral Breast and Radiation

- Thus, at present, there are no data to suggest that the risk of contralateral breast cancer is further increased beyond baseline rates in carriers who have received breast irradiation

Conclusions

- ***BRCA1/2* carriers with breast cancer who underwent BCS and radiation have comparable in-breast local recurrence rate to sporadic cases**
- **No excess acute or long term toxicity following radiation therapy in *BRCA* carriers**
- **There is no added risk from scatter radiation to the contralateral breast**

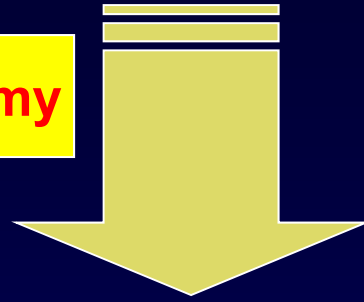
Prophylactic Contralateral Breast Irradiation in *BRCA* Carriers

Prophylactic Contralateral Breast Irradiation in *BRCA* Carriers

- IRB approved
- Multicenter study in Israel
- Non-randomized
- Breast cancer, never irradiated
- Need RT post mastectomy or post BCS
- Normal MRI of the healthy breast
- Sign informed consent

BRCA1/2 Breast Cancer

Refuse Mastectomy



**Radiation therapy to
affected breast**

**Contralateral breast
irradiation, 50 Gy**

Control

Prophylactic Contralateral Breast Irradiation in *BRCA* Carriers

- **Primary endpoint:**

To evaluate the effectiveness of contralateral breast radiation in preventing breast cancer in carriers

- **Secondary endpoints:**

Acute and long term toxicity evaluation

Psychological factors associated with decision making in this population

Prophylactic Contralateral Breast Irradiation in *BRCA* Carriers

- 2 years on study
- 35 patients
- 16 control and 19 patients who opted for contralateral healthy breast prophylactic radiation
- Acute and late toxicity evaluation
- Detailed questionnaire before and after radiation– decision making...

Prophylactic Contralateral Breast Irradiation in *BRCA* Carriers

- Median age 48.3 years
- No contralateral breast cancer events
- Very long term follow-up is needed

Thank you