Nolvadex-D®
tamoxifen

New PBS listing effective 1st October 2016[1]

A new risk reduction treatment option for patients at moderate to high risk of breast cancer.[2†]

NEW INDICATION[2†]

Nolvadex is now indicated for the primary reduction of breast cancer risk in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).[2]

ATLAS Approval Number: 434103.022. Date prepared: November 2016.

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REFERENCE

1. http://www.pbs.gov.au/pbs/search?term=nolvadex (accessed 1st October 2016)
2. Nolvadex Approved Product Information. April 2016.

Nolvadex-D®
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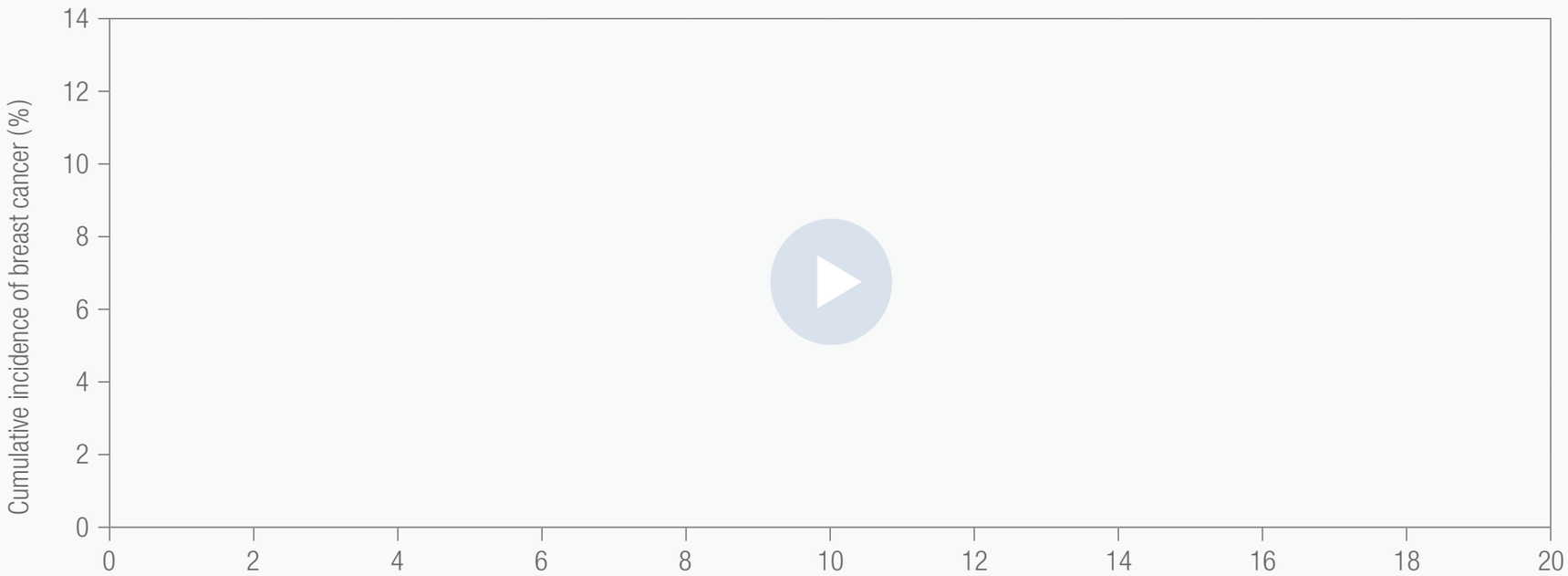
Nolvadex for 5 years, reduces the risk of breast cancer for up to 16 years.[1,2]*

*For women with a lifetime breast cancer risk of 1.5 to 3 times the population average compared to placebo.[1] Reductions in risk were recorded for invasive ER positive cancers and ductal carcinoma in situ, but not for invasive ER negative cancers. Median follow up 16 years.[1,2]

Cumulative incidence of breast cancers over time[1]



Number at Risk											
Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

Adapted from Cuzick J et al, 2015[1]

IBIS-1 STUDY DESIGN[1,2]
Randomised controlled trial, 7,154 women at increased risk of developing breast cancer received 5 years of tamoxifen 20 mg or placebo daily. Median follow-up 16 years. **Primary endpoint:** occurrence of any type of breast cancer. 601 breast cancers reported (251 [7·0%] in 3579 patients in the tamoxifen group vs 350 [9·8%] in 3575 women in the placebo group; hazard ratio [HR] 0·71 [95% CI 0·60–0·83], p<0·0001).

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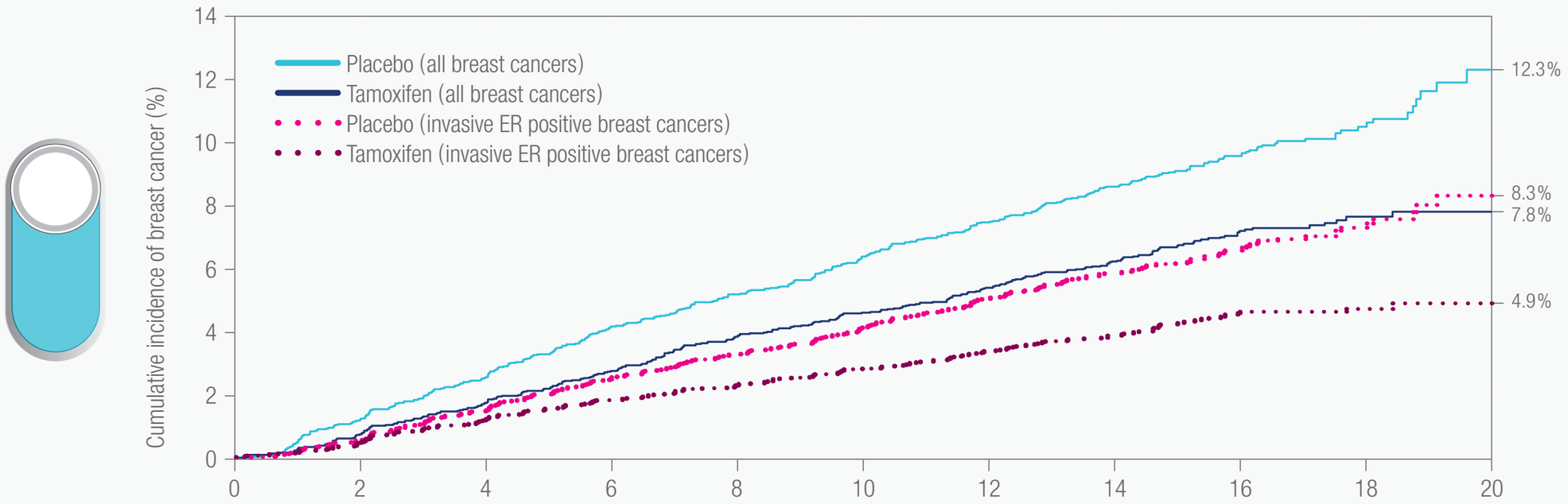

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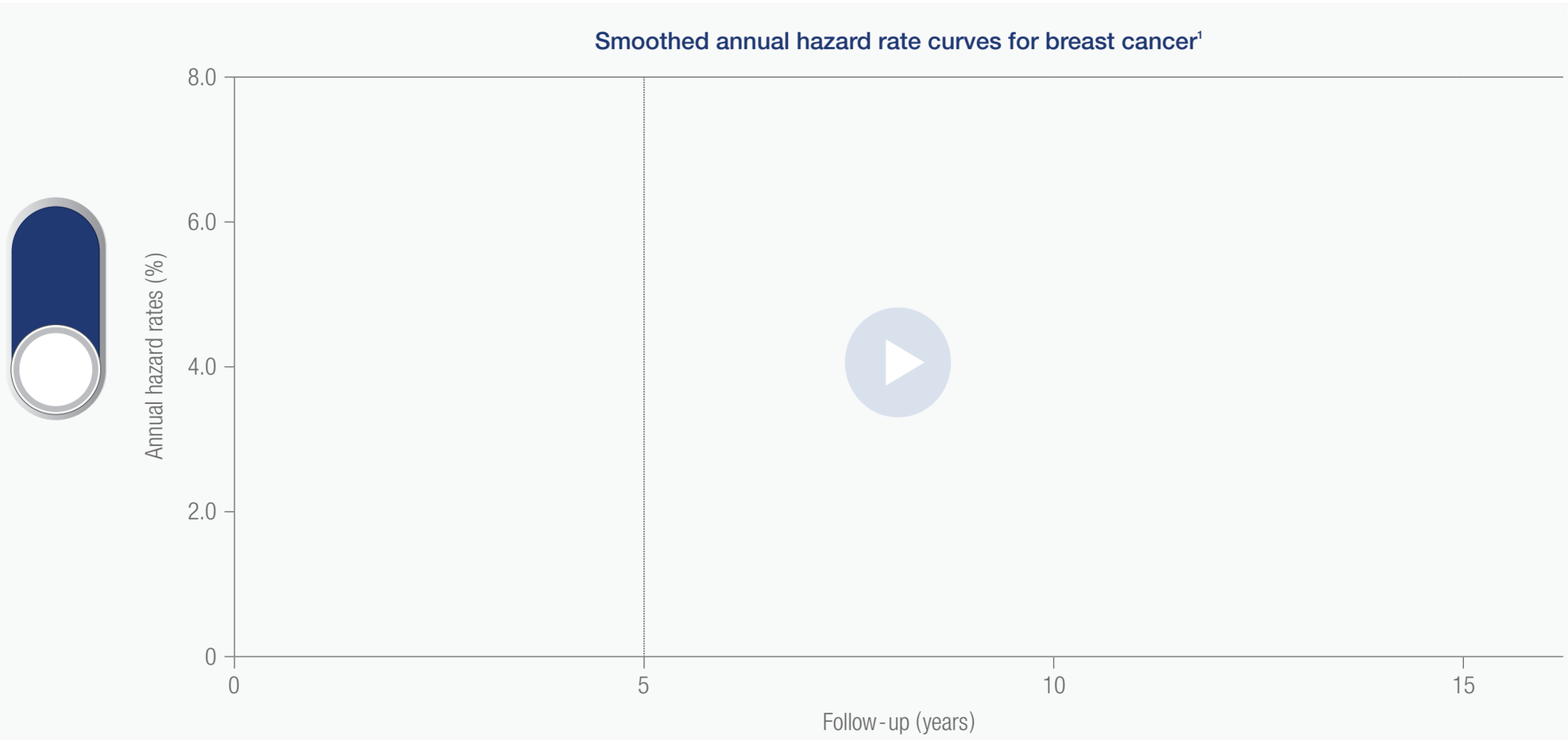

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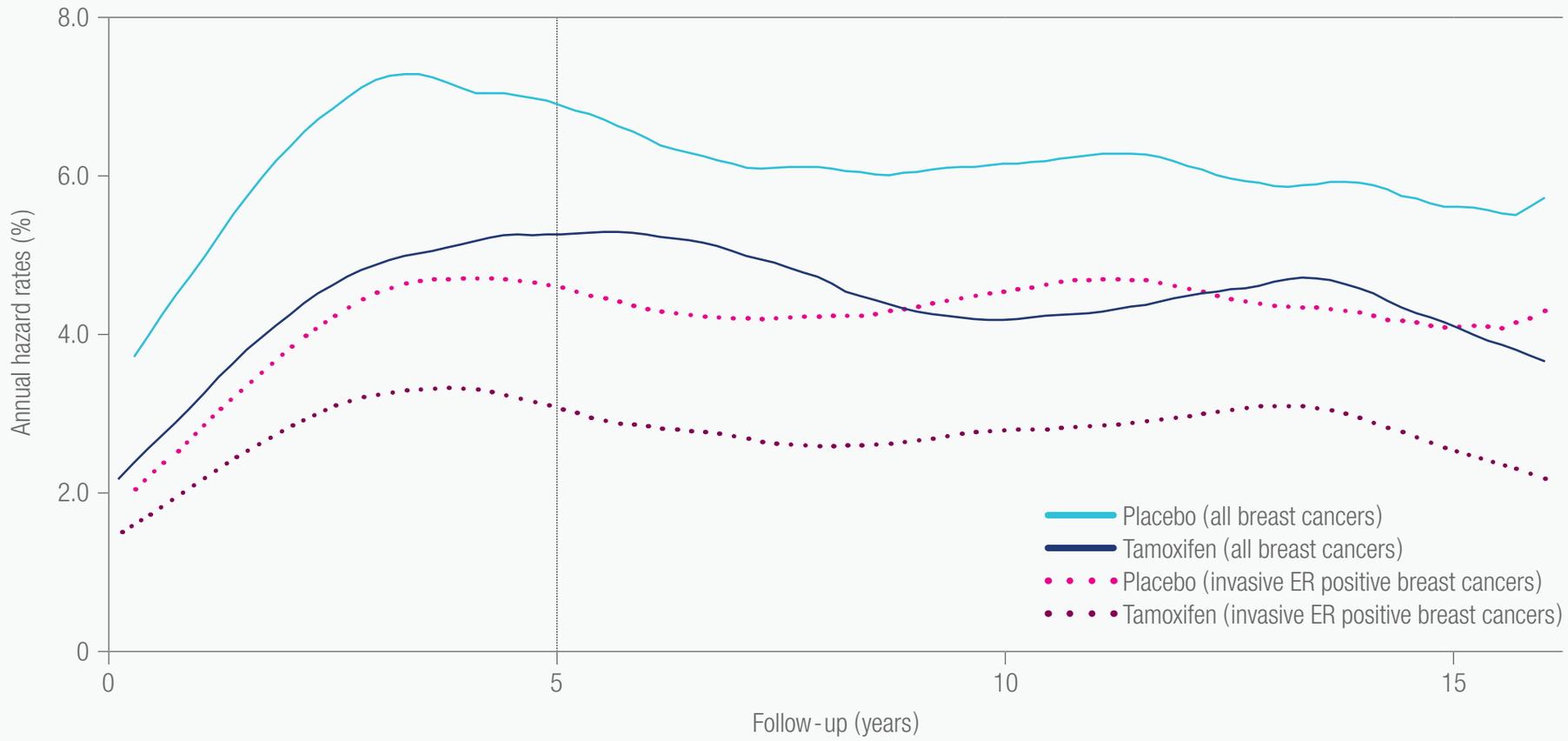
Smoothed annual hazard rate curves for breast cancer[1]



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Randomised controlled trial, 7,154 pre and post menopausal women 35–70 years of age from 37 centres in eight countries at increased risk of developing breast cancer received oral tamoxifen 20 mg daily or matching placebo for 5 years. Patients were deemed to be at an increased risk of developing breast cancer based on a family history of breast cancer or abnormal benign breast disease.

The primary endpoint was the occurrence of any type of breast cancer (including ductal carcinoma *in situ*). Secondary endpoints included the occurrence of invasive oestrogen receptor-positive breast cancer, all-cause mortality, and adverse events.

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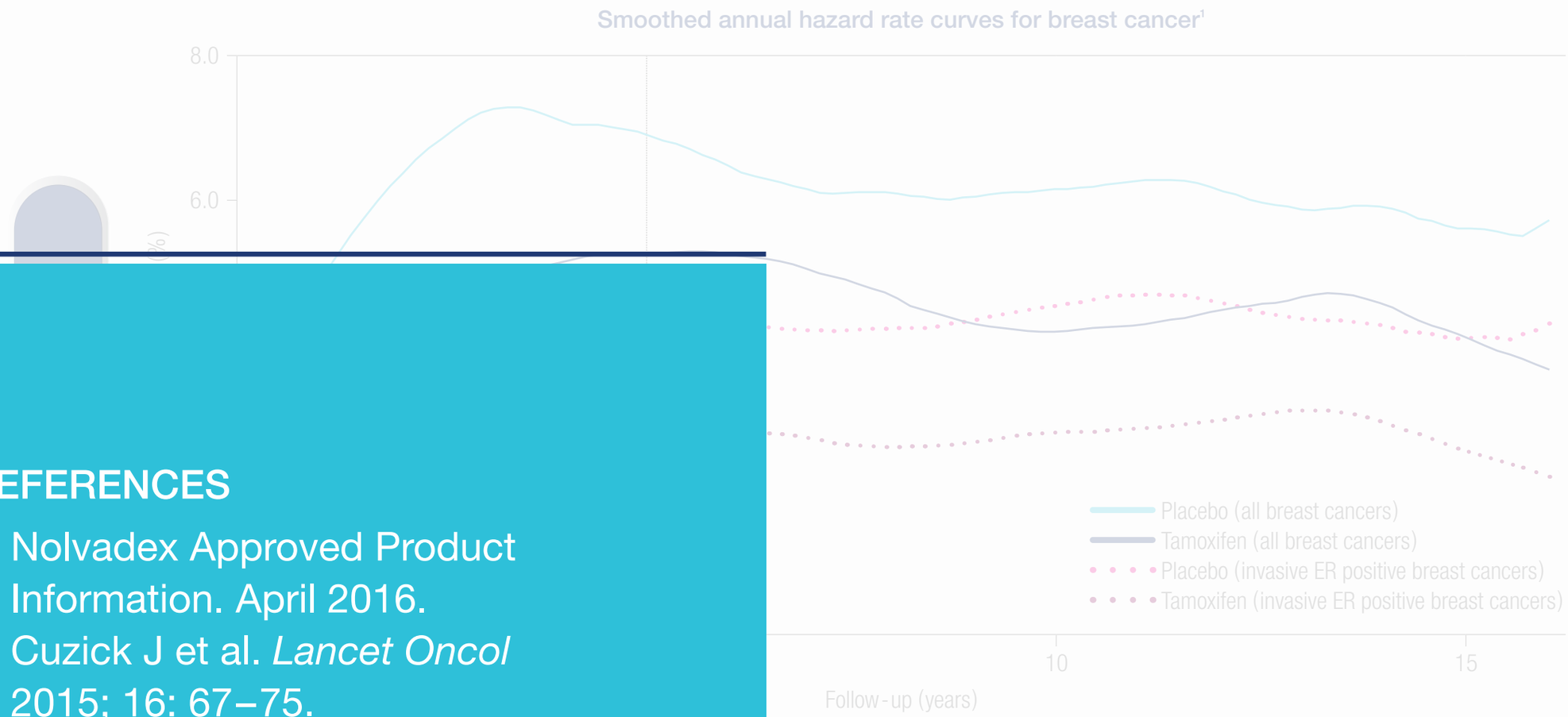

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Breast cancers according to treatment allocation and follow-up period

TOTAL NUMBER OF BREAST CANCERS					
	Placebo (n=3575)	**Tamoxifen (n=3579)**	**HR (95% CI)**	**p value**	
Overall	350	251	0.71 (0.60–0.83)	p<0.0001	
0–10 year follow-up period	226	163	0.72 (0.59–0.88)	p=0.0011	Ratio≥10 years: 0-10 years (95% CI) 0.98 (0.74-1.30) p=0.91
≥10 year follow-up period	124	88	0.69 (0.53–0.91)	p=0.0075	

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Nolvadex Safety & Tolerability[1]

Summary of adverse events from the primary risk reduction trials[1]

Frequency	System Order Class	Event
Common >10%	Vascular	Hot flushes
	Gastrointestinal	Nausea and vomiting
Less Common <5%	Reproductive system and breast	Vaginal bleeding, vaginal discharge, menstrual irregularities
	General	Tumour flare, tumour pain
	Musculoskeletal and bone	Increased bone pain
	Skin and subcutaneous tissue	Alopecia
Other <1%	Metabolism and nutrition	Hypercalcaemia
	Cardiovascular	Peripheral oedema
	Reproductive system and breast	Pruritis vulvae
	Nervous system	Dizziness and light-headedness

Before prescribing, please review full Product Information available on request from AstraZeneca on 1800 805 342 or https://www.astrazeneca.com.au/medicines/product-information.html

PRECAUTIONS[1]

Use for primary reduction of breast cancer risk: **Uncommon serious side effects -** pulmonary embolus and uterine cancer (women <50 years did not have an increased risk of endometrial cancer or pulmonary embolism); increased risk of serious and sometimes fatal adverse events (endometrial cancer and thromboembolic events); less serious side effects such as hot flushes, vaginal discharge, menstrual irregularities and gynaecological conditions; risk benefit assessment depends on the woman's age, history, and level of breast cancer risk. Benign gynaecological conditions, gynaecological procedures and cataracts were more frequent with tamoxifen use. Investigation required if abnormal gynaecological symptoms develop, especially non-menstrual vaginal bleeding.

Women <30 years old excluded from primary risk reduction trials - efficacy and safety of tamoxifen treatment in these younger women is unknown. NOLVADEX is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus. Concomitant oral contraceptive or hormone replacement therapy is not recommended in women taking tamoxifen. Tamoxifen should be stopped ~3 weeks before undergoing elective surgery to reduce the risk of thromboembolic events. Consider discontinuing tamoxifen during periods of immobility. Associated with reduced bone density in premenopausal women. Maintenance of bone health advised.

Nolvadex Safety & Tolerability[1]

Summary of serious adverse events from the primary risk reduction trials[1]

Risk factor	Cuzick meta-analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,192	Placebo n=14,214	Tamox n=3,579	Placebo n=3,575	Tamox n=6,597	Placebo n=6,610	Tamox n=1,238	Placebo n=1,233
All-cause mortality	214 (1.5%)	218 (1.5%)	182 (5.1%)	166 (4.6%)	126 (1.9%)	114 (1.7%)	54 (4.4%)	54 (4.4%)
Endometrial cancer	67 (0.6%)	31 (0.3%)	29 (0.81%)	20 (0.56%)	53 (0.8%)	17 (0.3%)	13 (1.1%)	5 (0.41%)
Other cancers	372 (2.6%)	367 (2.6%)	351 (9.8%)	315 (8.8%)	178 (2.7%)	155 (2.3%)	64 (5.2%)	70 (5.7%)
Deep vein thrombosis	131 (1.0%)	82 (0.6%)	50 (1.4%)	29 (0.81%)	49 (0.74%)	34 (0.51)	13 (1.1%)	9 (0.73%)
Pulmonary embolism			30 (0.84%)	22 (0.62%)	28 (0.42%)	13 (0.20%)		
Stroke	NR	NR	30 (0.84%)	28 (0.78%)	71 (1.1%)	50 (0.76%)	10 (0.81%)	16 (1.3%)
Transient ischaemic attack	NR	NR	NR	NR	31 (0.47%)	34 (0.51%)	NR	NR
Ischaemic heart disease/ cardiovascular events	144 (1.1%)	130 (1.0%)	141 (3.9%)	153 (4.3%)	113 (1.7%)	109 (1.6%)	21 (1.7%)	26 (2.1%)
Myocardial infarction	NR	NR	13 (0.36%)	17 (0.48%)	43 (0.65%)	44 (0.67%)	NR	NR
Cataracts	654 (6.4%)	583 (5.7%)	67 (1.9%)[e]	54 (1.5%)[e]	574 (9.4%)[f]	507 (8.3%)[f]	12 (0.97)	3 (0.24%)
Fractures	731 (7.2%)	791 (7.8%)	240 (6.7%)[e]	235 (6.6%)[e]	80 (1.2%)	116 (1.8%)	28 (2.3%)	33 (2.7%)

Abbreviations: NR = not reported, tamox = tamoxifen.

a Cuzick 2013[2] was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Royal Marsden primary risk reduction trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.

b Women aged 35-70 at increased risk of breast cancer were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.

c Women aged 35+ with a breast cancer risk ≥ 1.66% over next 5 years were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years

d Women aged 30-70 with a family history of breast cancer were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years

e Results from earlier analysis; median follow up was 8 years

f Results from earlier analysis; n=6,101 tamoxifen and 6,131 placebo; the median follow up was 4 years.

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Tamoxifen offers a long period of protection after treatment cessation and thus substantially improves the benefit-to-harm ratio of the drug for breast cancer prevention [in high risk women][2]*

*When compared to placebo

1. **Nolvadex is now PBS listed for the primary reduction of breast cancer risk in women at a lifetime breast cancer risk of 1.5 to 3 times the population average[1-3]**

2. **Dosage for the primary reduction of breast cancer risk: 20mg daily for 5 years[1]**

3. **AstraZeneca continues to invest in treatments like Nolvadex to ensure women at high risk of breast cancer have treatment options.**
   - 'Tick the box for no brand substitution' to support branded Nolvadex

4. **Nolvadex safety and tolerability:[2]**
   - No new late toxicities have been identified
   - Early excess of endometrial cancers have translated into an increased number of deaths (tamoxifen vs placebo, not significant) and should be considered in risk/benefit analysis for each patient

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