Breast cancer in young women

Niels Kroman

Overlæge, dr. med.

Brystkirurgisk afdeling

Rigshospitalet, København

NK

Sir George Thomas Beatson

1848 - 1933

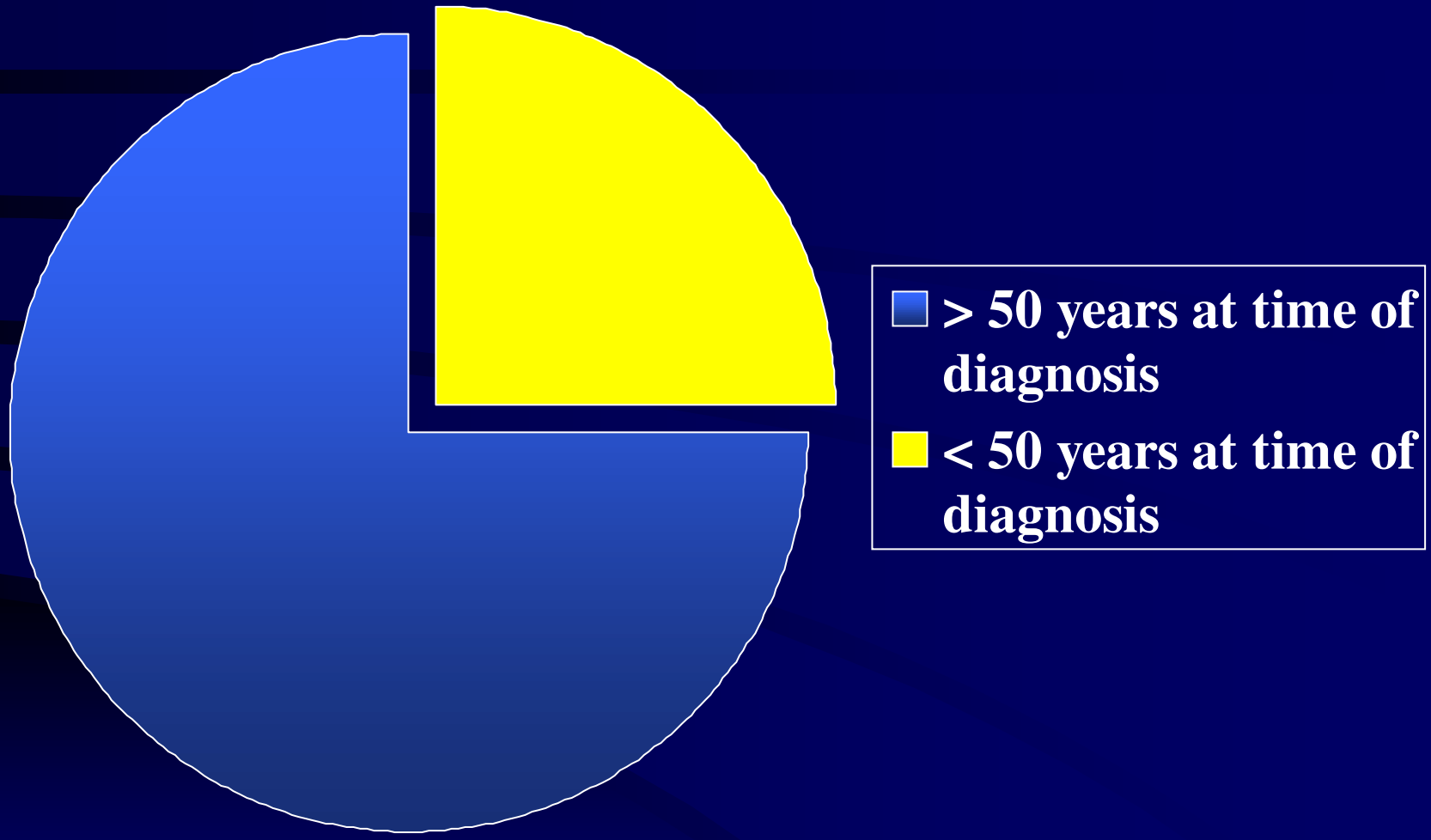
ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,

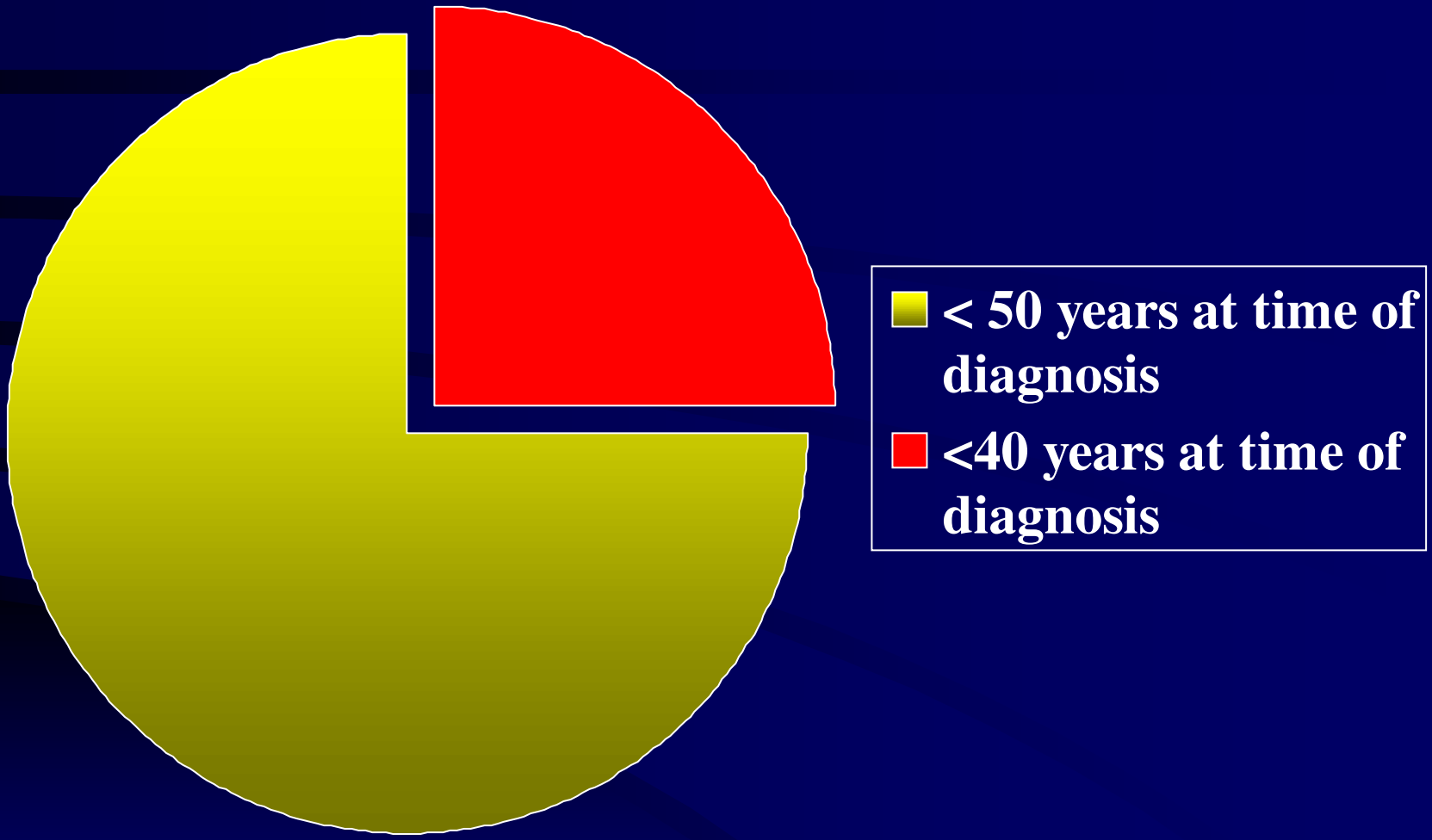
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

5. That clinically it is a matter of common observation that the younger the patient the more rapid the cell proliferation and the more quickly fatal the disease

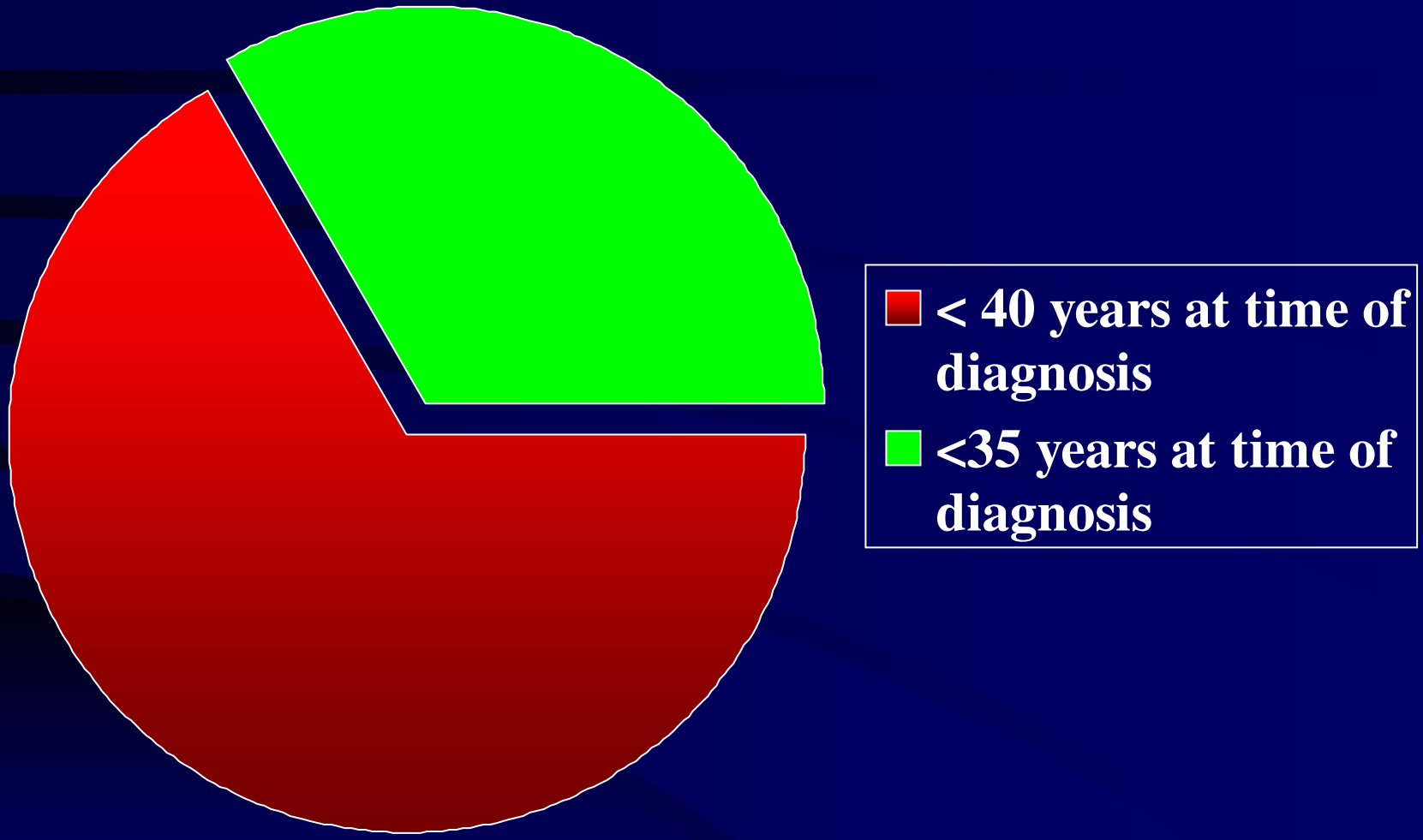
Breast cancer in young women



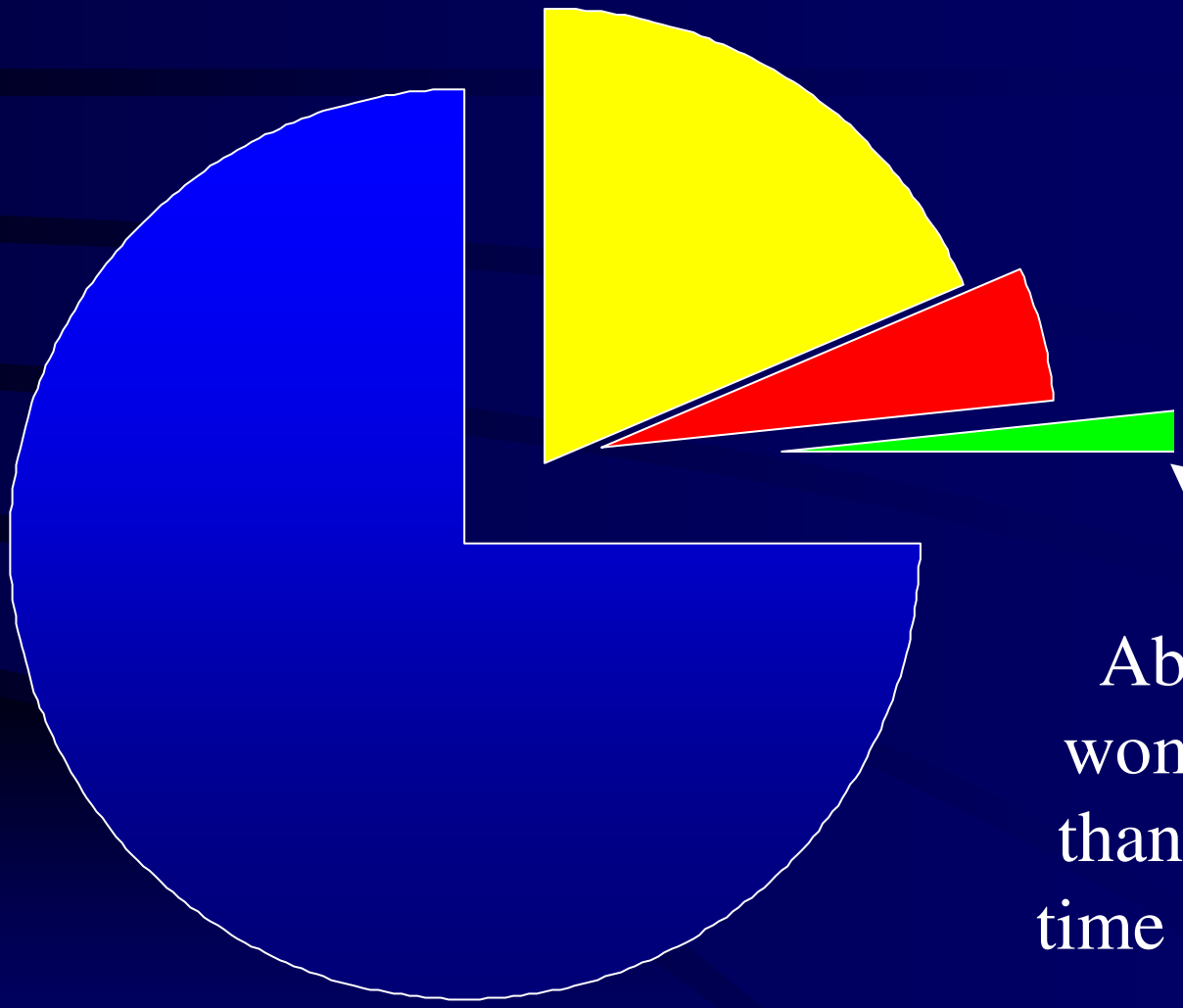
Breast cancer in young women



Breast cancer in young women



Breast cancer in young women



About 2% of women are less than 35 years at time of diagnosis

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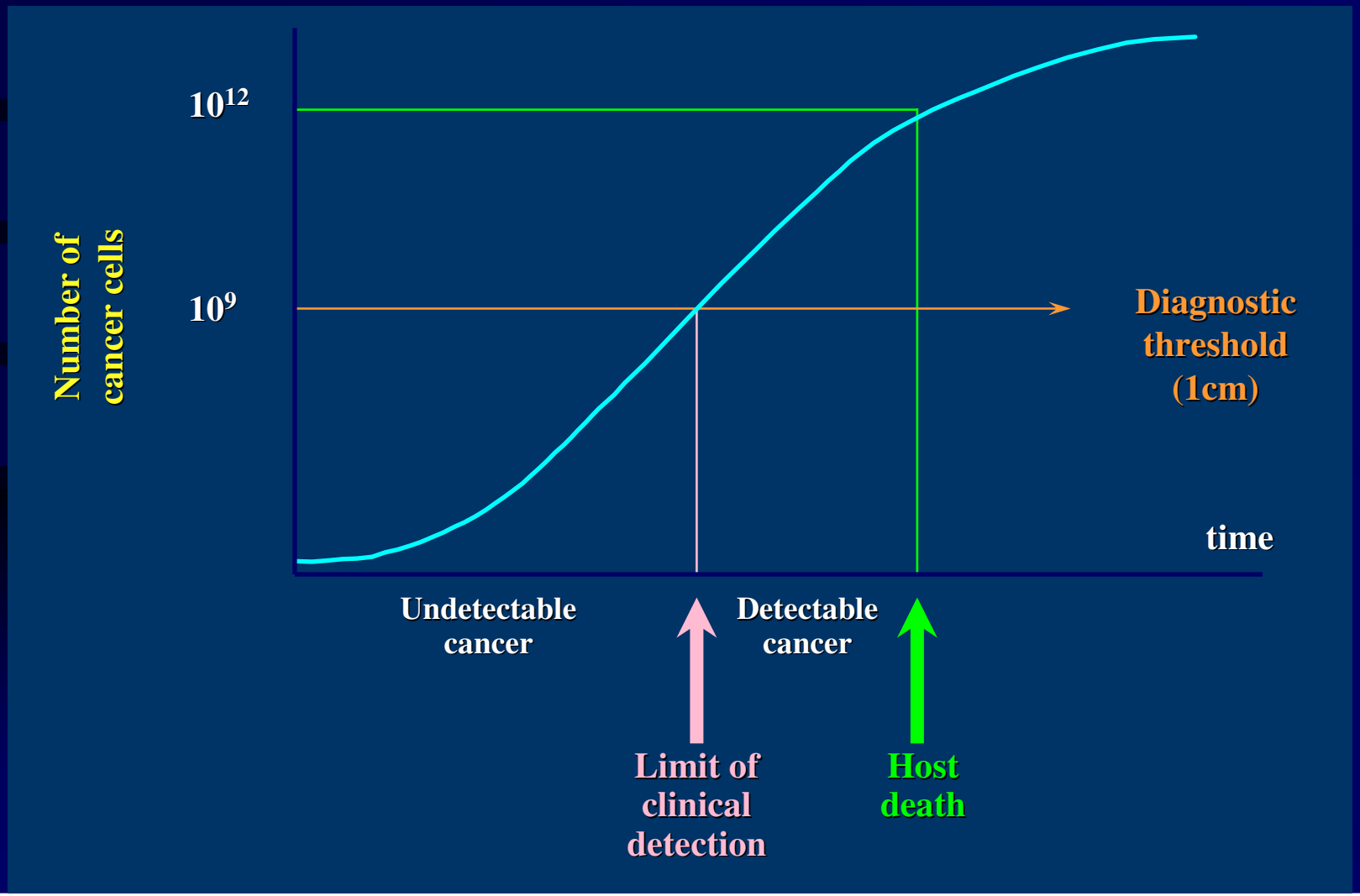
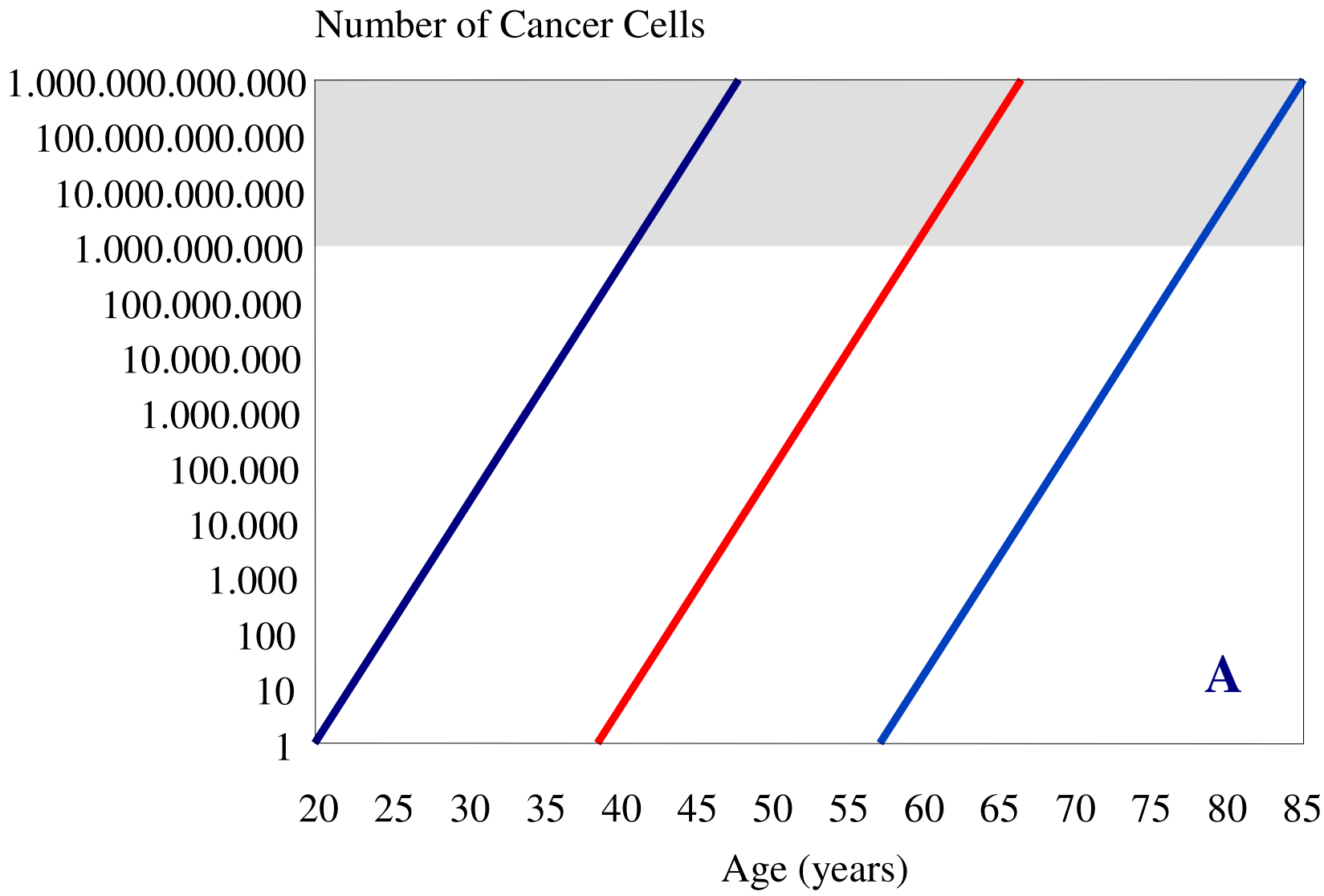
ONCOLOGY

Cancer biology

Tumor growth and detection

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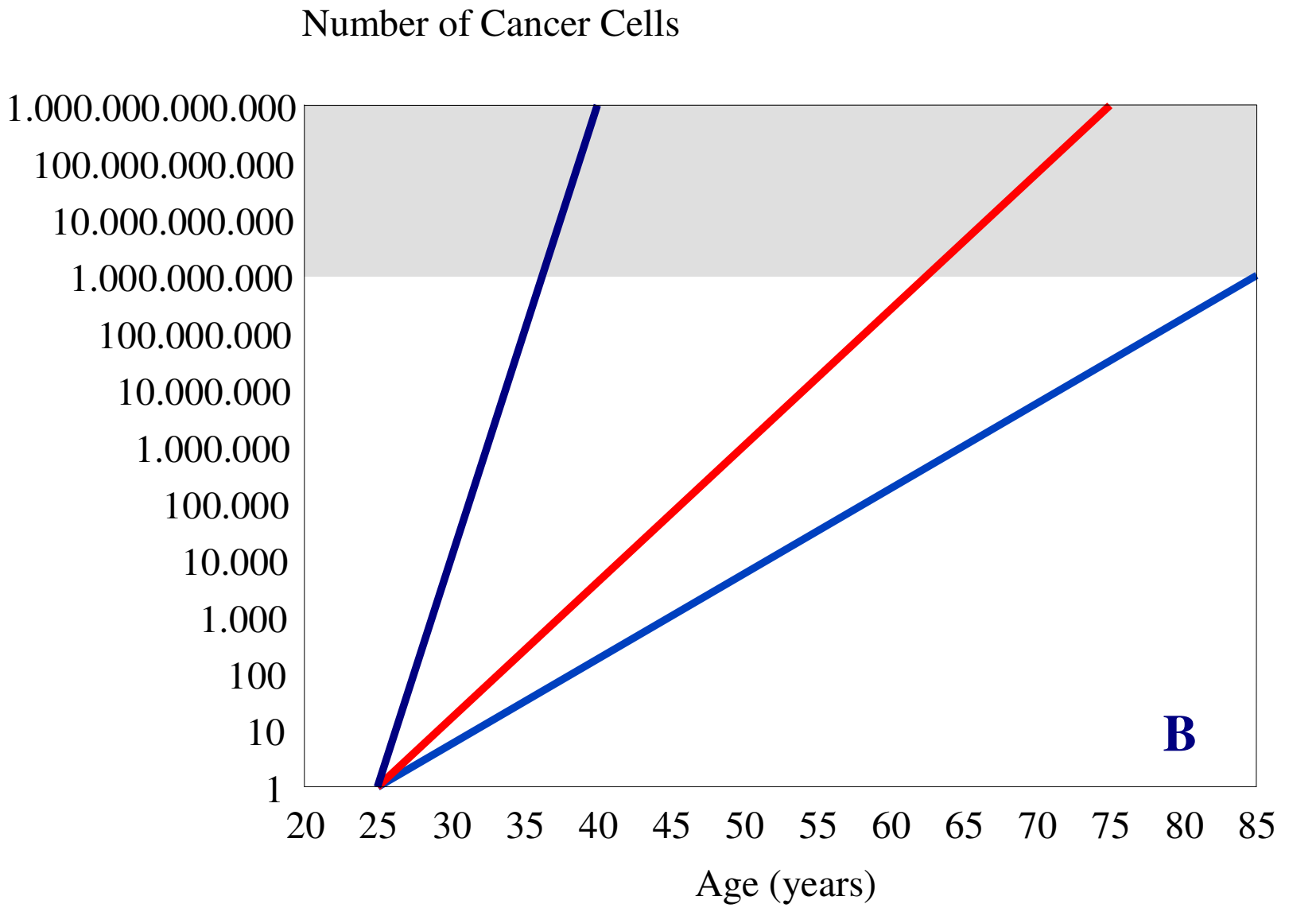
Age (years)
A


Number of Cancer Cells
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20 25 30 35 40 45 50 55 60 65 70 75 80 85
Age (years)
B

Breast cancer in young women

High risk of:

- Node +
- High grade
- ER -
- Diagnostic delay

Should all young women with breast cancer receive adjuvant cytotoxic therapy?

- 10,356 women with primary breast cancer
- Operated 1978-1996
- Less than 50 years at time of diagnosis
- 52,462 person-years of follow-up

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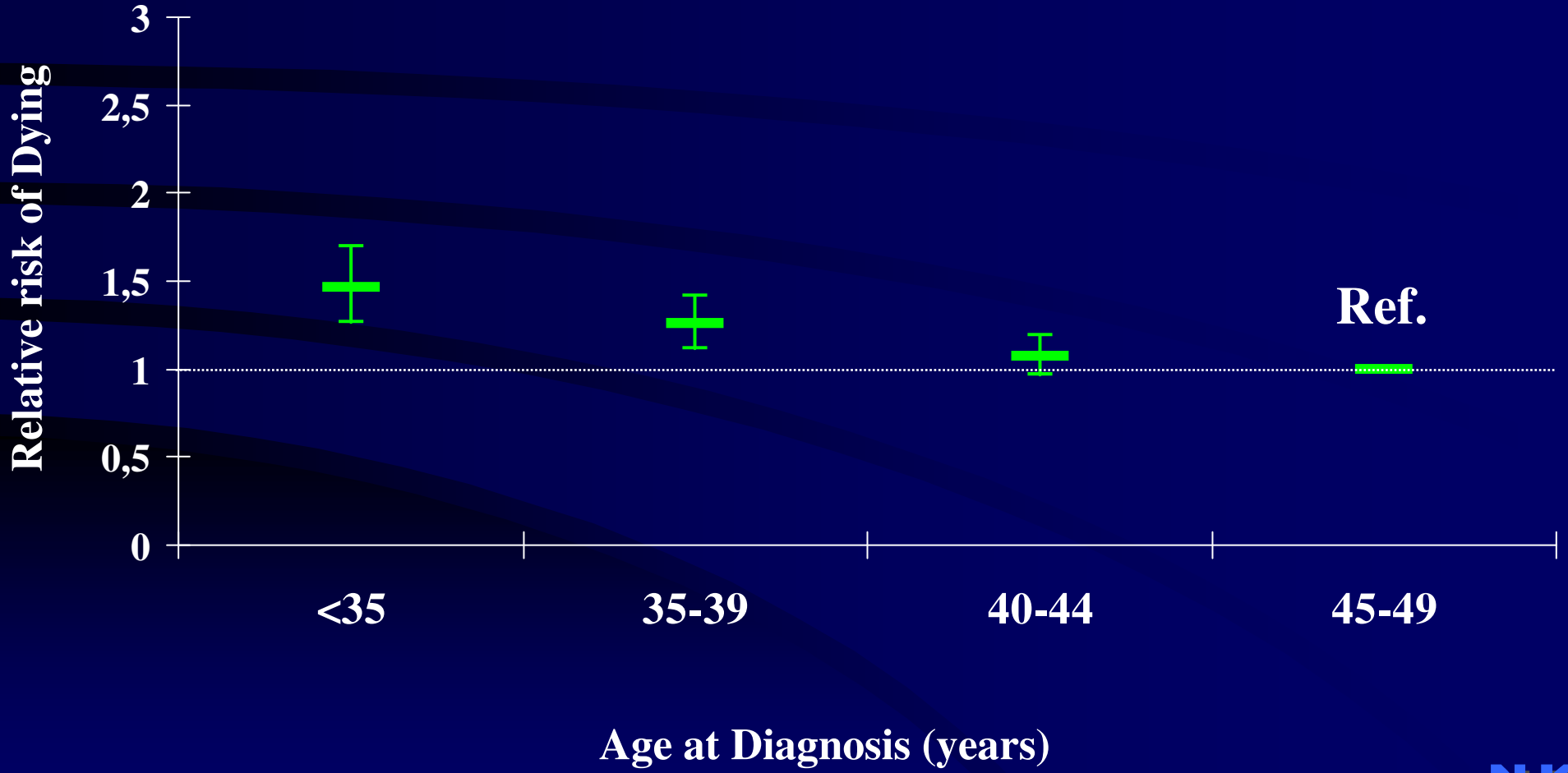
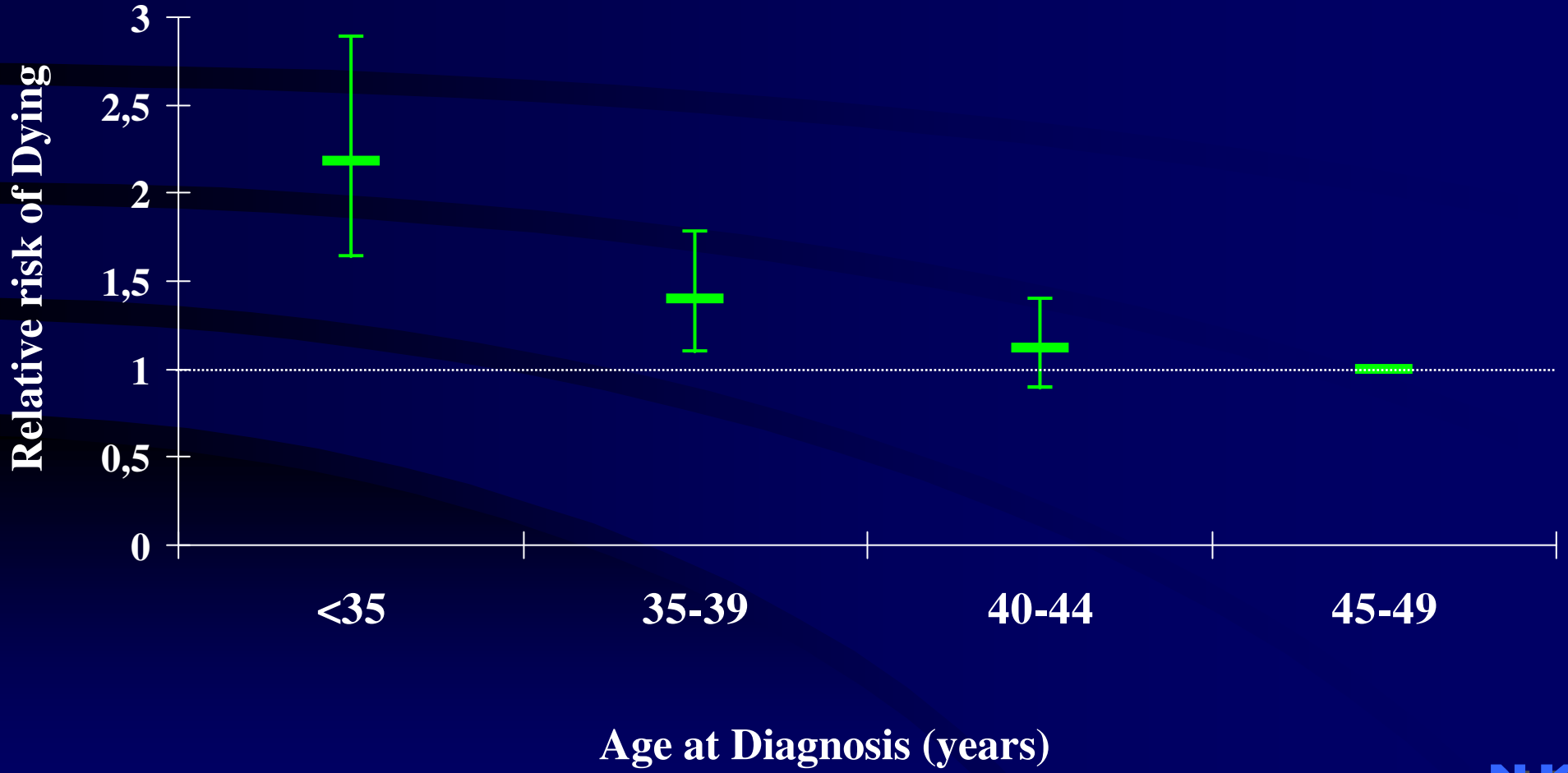
Adjusted relative risk of dying according to age at diagnosis

All patients



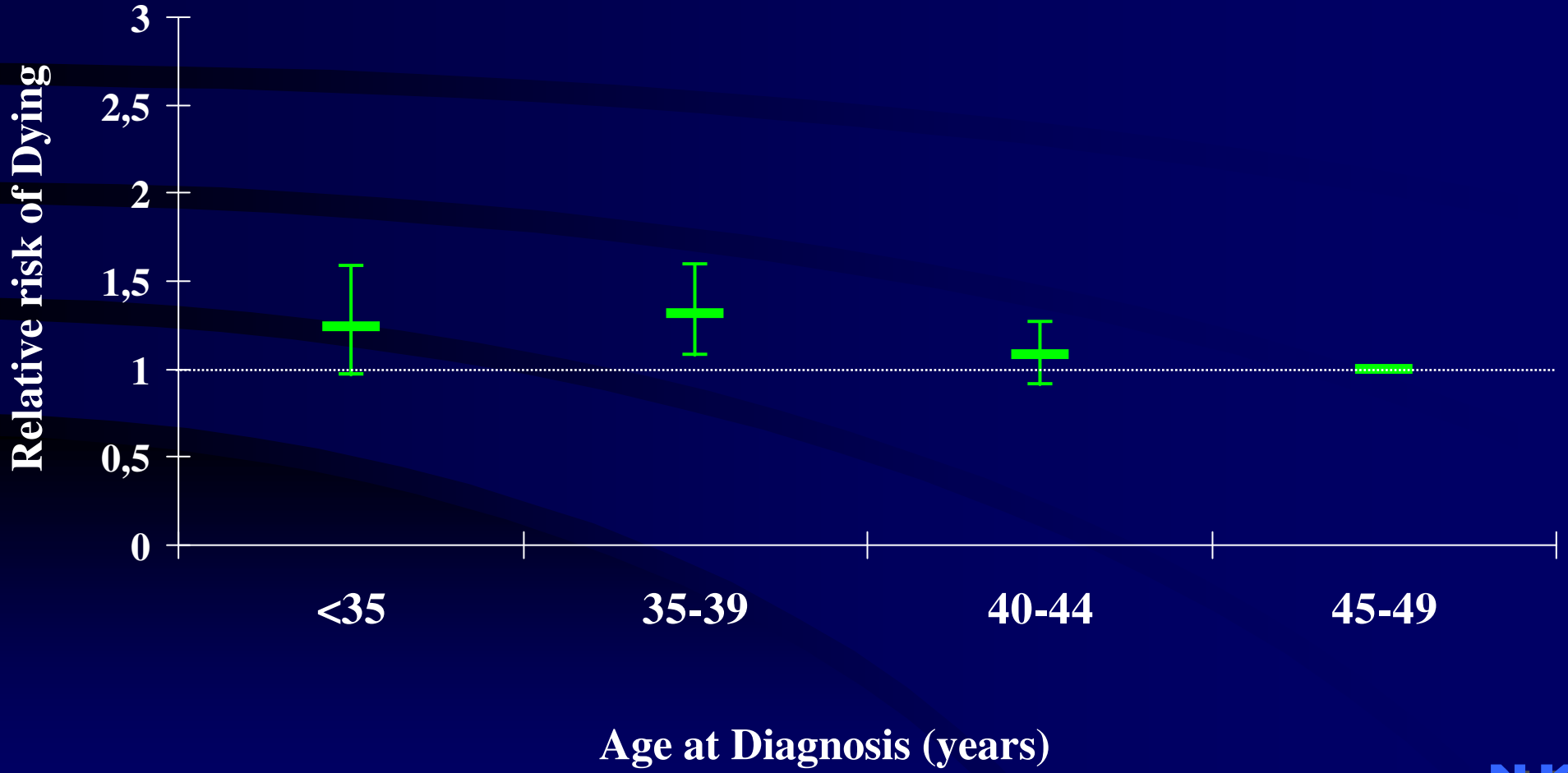
Adjusted relative risk of dying according to age at diagnosis

Patients receiving **no** adjuvant treatment



Adjusted relative risk of dying according to age at diagnosis

Patients receiving adjuvant cytotoxic treatment



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Should all young women with breast cancer receive adjuvant cytotoxic therapy?

Adjusted relative risk of dying for women <35 years at diagnosis receiving no adjuvant cytotoxic treatment:
2.18 (1.64-2.89)

(Women 45-49 years at diagnosis reference = 1)

Breast Concerving Treatment

- In generel less than 10% local relapses in the first ten years
- **More than 30% local relapses among women less than 35 years at diagnosis**

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Breast Concerving Treatment

- Is local relapse an independent risk factor?

Breast conserving treatment and age at diagnosis

- 9,825 premenopausal women with primary breast cancer
- Less than 50 years at time of diagnosis
- Operated 1982-1998
- 60,246 person-years of follow-up

Breast conserving treatment and age at diagnosis

- Mastectomy: 7,165 (77.2%)
- Breast conserving treatment: 2,120 (22.8%)

Breast conserving treatment and age at diagnosis

- Breast conserving treatment: 22.8%
- <35 years: 30.5%
- 45-49 years: 21.8%
- Significantly more patients <35 years received breast conserving treatment ($p<0.001$)

Breast conserving treatment and age at diagnosis

Age at diagnosis (years)	Mastectomy
< 35	1. ref
35-39	1. ref
40-44	1. ref
45-49	1. ref

Breast conserving treatment and age at diagnosis

Age at diagnosis (years)	Mastectomy	Lumpectomy All
< 35	1. ref	0.87 (0.64-1.19)
35-39	1. ref	1.02 (0.78-1.34)
40-44	1. ref	0.80 (0.62-1.04)
45-49	1. ref	0.66 (0.50-0.88)

Breast conserving treatment and age at diagnosis

Age at diagnosis (years)	**Mastectomy**	**Lumpectomy** All	**Lumpectomy** No adjuvant Treatment
< 35	1. ref	0.87 (0.64-1.19)	1.31 (0.77-2.22)
35-39	1. ref	1.02 (0.78-1.34)	1.18 (0.74-1.90)
40-44	1. ref	0.80 (0.62-1.04)	0.94 (0.59-1.48)
45-49	1. ref	0.66 (0.50-0.88)	0.63 (0.41-1.01)

Breast conserving treatment and age at diagnosis

Age at diagnosis (years)	**Mastectomy**	**Lumpectomy** All	**Lumpectomy** No adjuvant Treatment	**Lumpectomy** Cytotoxic Treatment
< 35	1. ref	0.87 (0.64-1.19)	1.31 (0.77-2.22)	0.73 (0.44-1.22)
35-39	1. ref	1.02 (0.78-1.34)	1.18 (0.74-1.90)	0.69 (0.43-1.12)
40-44	1. ref	0.80 (0.62-1.04)	0.94 (0.59-1.48)	0.81 (0.54-1.21)
45-49	1. ref	0.66 (0.50-0.88)	0.63 (0.41-1.01)	0.64 (0.41-1.01)

Breast conserving treatment and age at diagnosis

- Results were unchanged when analysis were restricted to women with tumours <2 cm

Breast conserving treatment and age at diagnosis

- No general risk associated with breast conserving treatment among young patients

Breast conserving treatment and age at diagnosis

- No general risk associated with breast conserving treatment among young patients
- Adjuvant cytotoxic treatment seems to be outmost important in young women receiving breast conserving treatment

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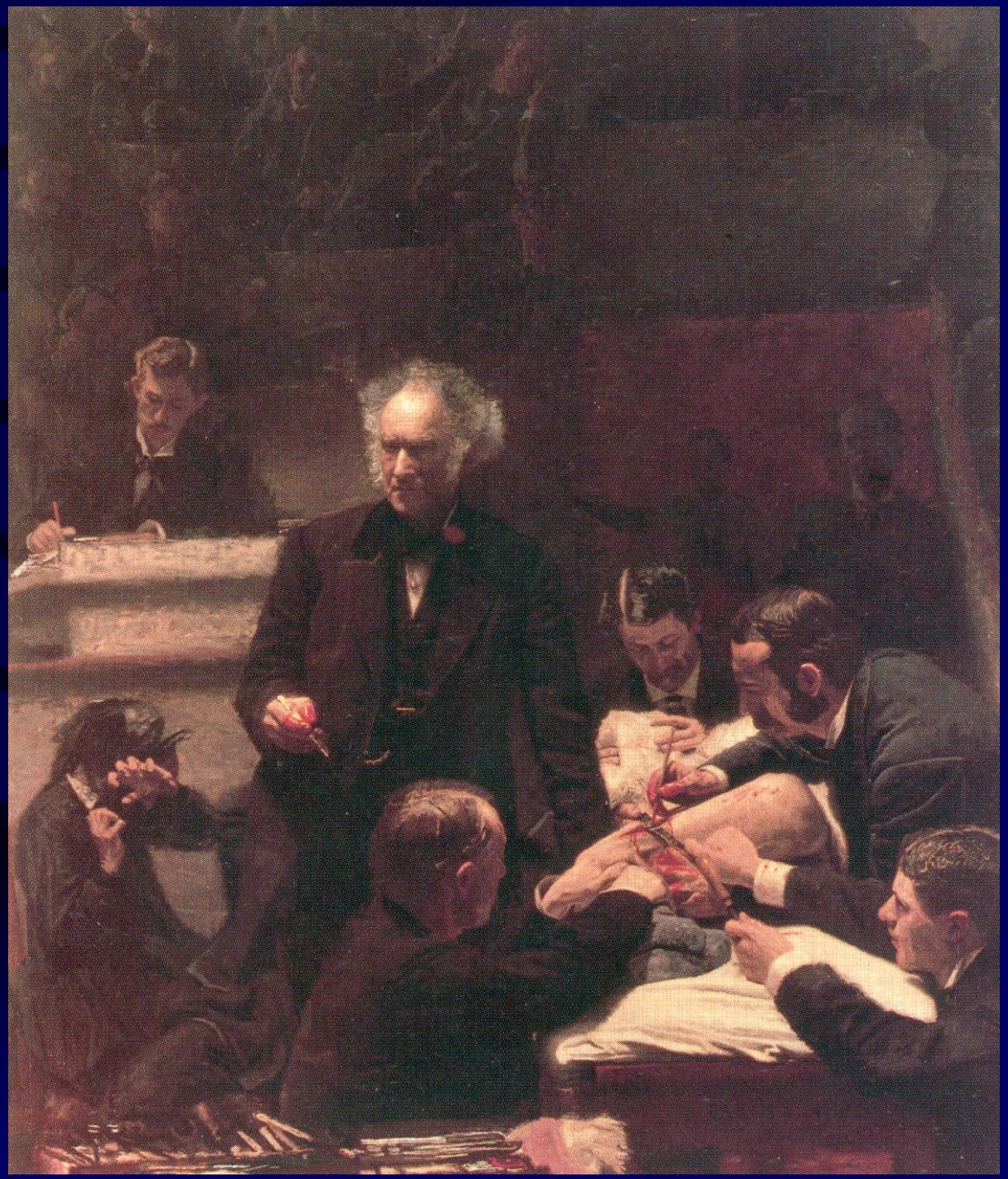
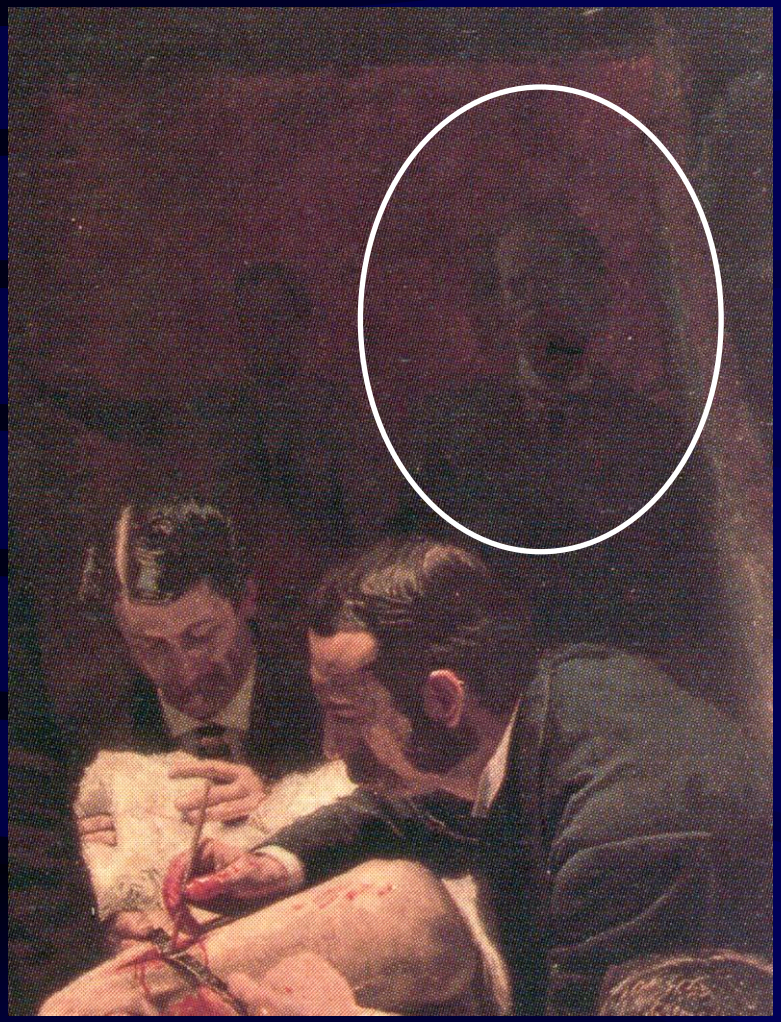


Samuel David Gross

1805 - 1884

Painting by Thomas Eakins

1875



Samuel Weissel Gross

1837 - 1889

Painting by Thomas Eakins, 1875

A

PRACTICAL TREATISE

ON

TUMORS OF THE MAMMARY GLAND:

EMBRACING THEIR

HISTOLOGY, PATHOLOGY, DIAGNOSIS, AND TREATMENT.

BY

SAMUEL W. GROSS, A. M., M. D.,

SURGEON TO, AND LECTURER ON CLINICAL SURGERY IN, THE JEFFERSON MEDICAL COLLEGE HOSPITAL AND THE PHILADELPHIA HOSPITAL; PRESIDENT OF THE PATHOLOGICAL SOCIETY OF PHILADELPHIA; FELLOW OF, AND FORMERLY MÜTTER LECTURER ON SURGICAL PATHOLOGY IN, THE COLLEGE OF PHYSICIANS OF PHILADELPHIA; FELLOW OF THE ACADEMY OF SURGERY OF PHILADELPHIA, ETC.

ILLUSTRATED BY TWENTY-NINE ENGRAVINGS.

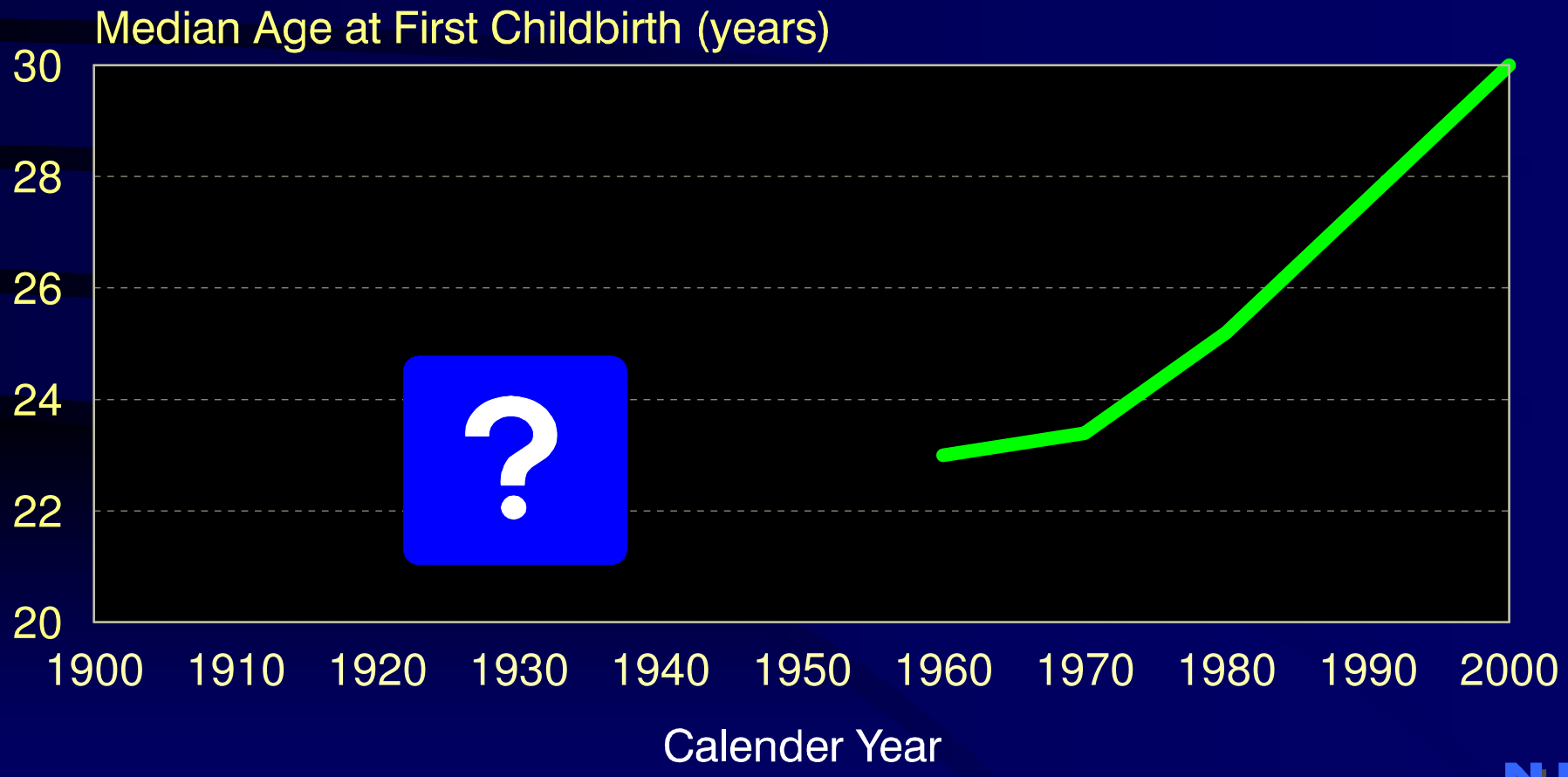
LONDON:
H. K. LEWIS, 136 GOWER STREET.
1880.

The rate of growth is not, contrary to the generally received opinion, influenced by the early age of the patient, since I have failed to discover that the increase is more rapid before the age of forty than when the tumor develops later in life. When, however, carcinoma appears during pregnancy or during lactation, its growth is wonderfully rapid, and its course is excessively malignant, of which fact several striking instances are recorded by Klotz [1] and Paget.[2] In a case reported by Billroth,[3] the disease developed in both breasts five weeks before the woman's eighth confinement; and on death, one week after an easy and natural delivery, or six weeks after the first observation of the disease, the mammæ were larger than a child's head, and secondary deposits were found in the thyroid gland, pericardium, liver, omentum, and kidneys.

When, however, carcinoma appears during pregnancy or during lactation, its growth is wonderfully rapid, and its course is excessively malignant,

Breast Cancer Etiology

Age at First Childbirth According to Calender Year



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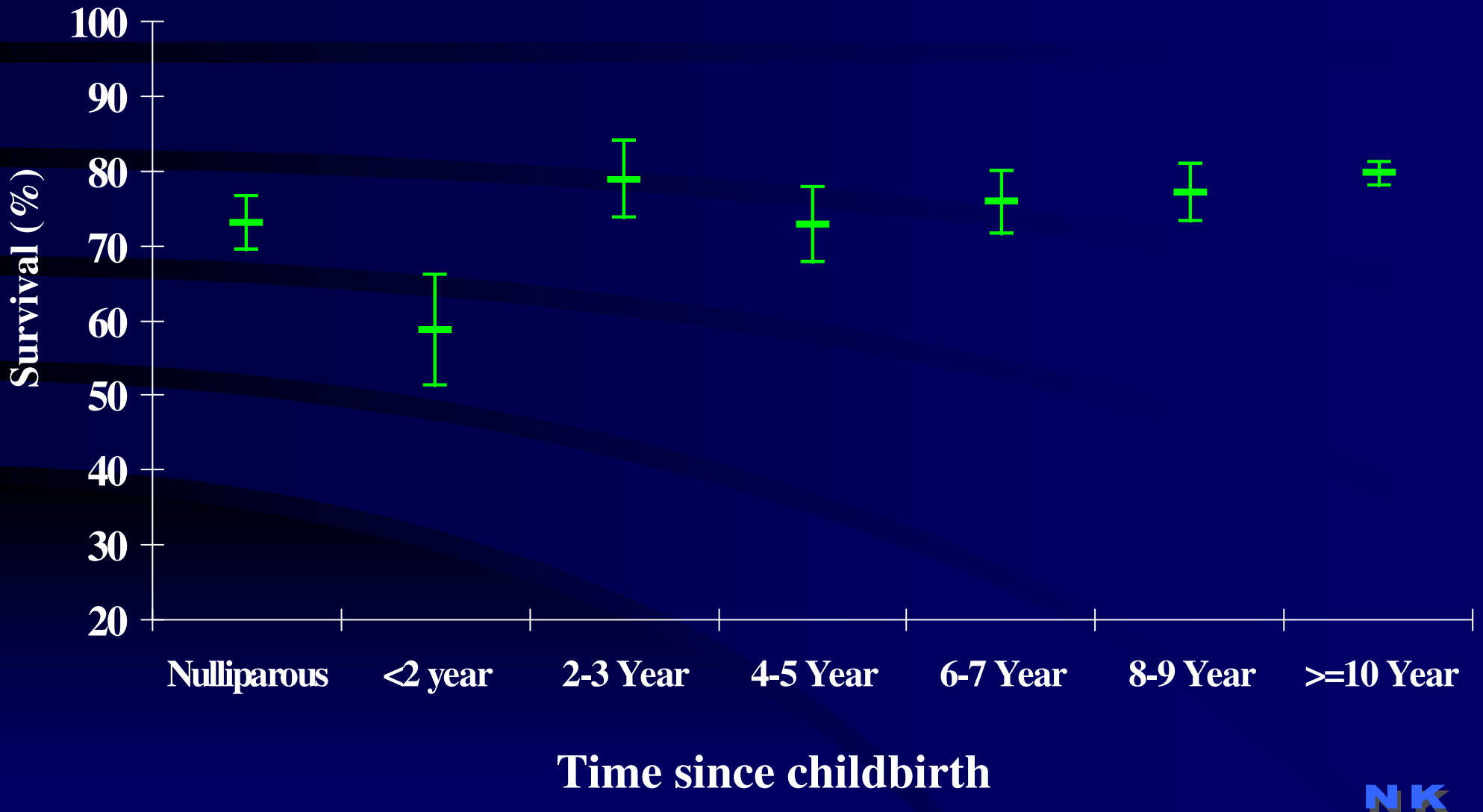
Time Since Childbirth
5 Years Crude Survival



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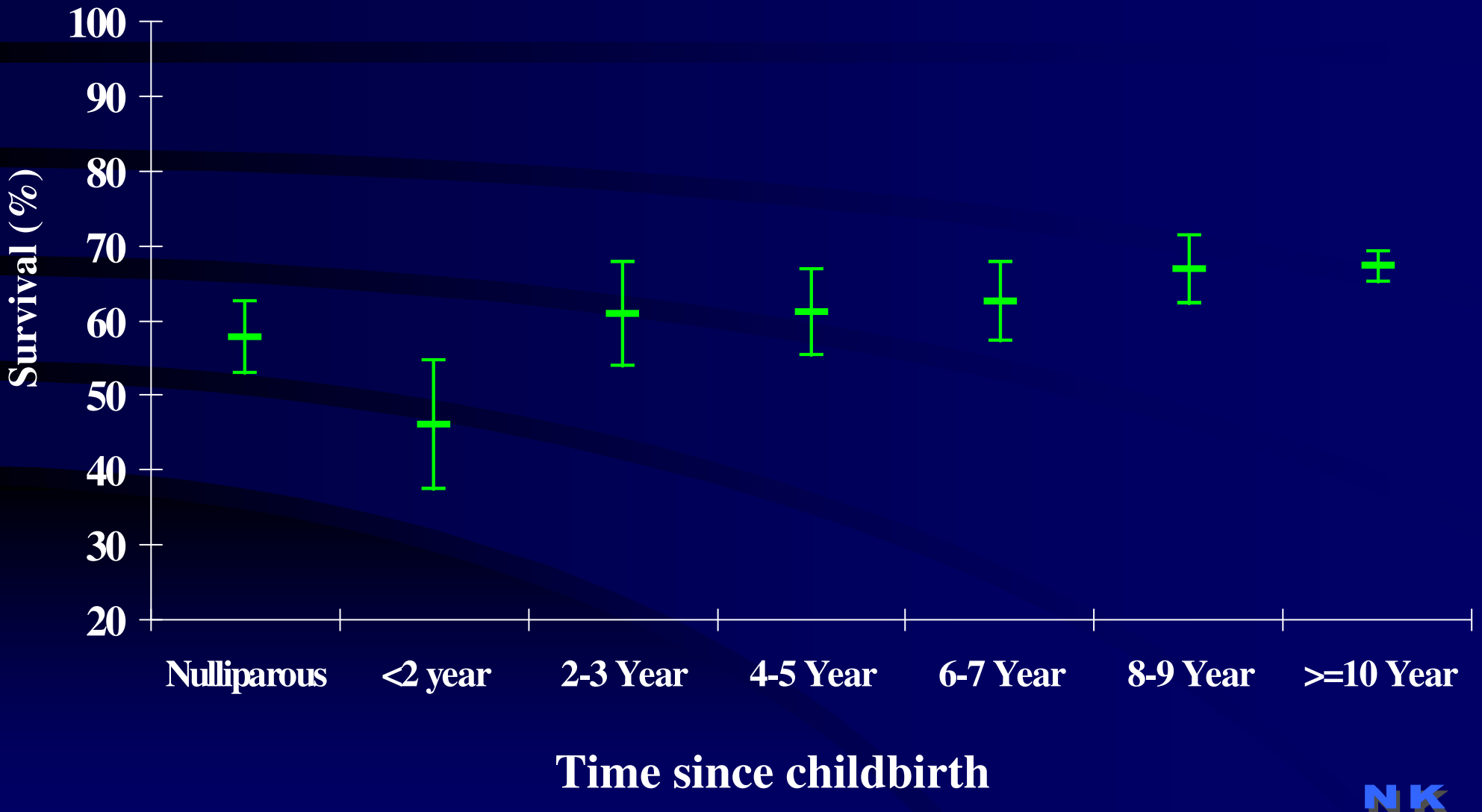
Time Since Childbirth
10 Years Crude Survival



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Time Since Childbirth

Adjusted relative risk of dying 1.58 (1.24-2.02) for women given birth less than two years before diagnosis of breast cancer

Fertility after treatment of breast cancer

Proportions reporting regular bleedings at start of CMF and two years later (*Grønvold et al.*)

		Regular bleedings		Amenorrhea
Age group				
Years	N	At start	At 2 years	At 2 years
30-34	10	90%	80%	0%
35-39	20	75%	55%	25%
40-44	49	74%	8%	59%
45-49	88	65%	0%	93%
50-54	22	71%	0%	100%
Total	**189**	**69%**	**14%**	**73%**

Only women reporting bleeedings within 12 months before chemotherapy were included. Amenorrhea was defined as no bleedings within the last 12 months. Patients from two trials combined

NK

THE LANCET

Updating

Should women be advised against pregnancy after breast-cancer treatment?

Niels Kroman Maj-Britt Jensen Mads Melbye
Jan Wohlfahrt Henning T Mouridsen

NK

Pregnancy after treatment of breast cancer

- 10.236 women treated for primary breast cancer
- 1978-2005
- <= 45 year at time of diagnosis
- 95.616 person-years follow-up

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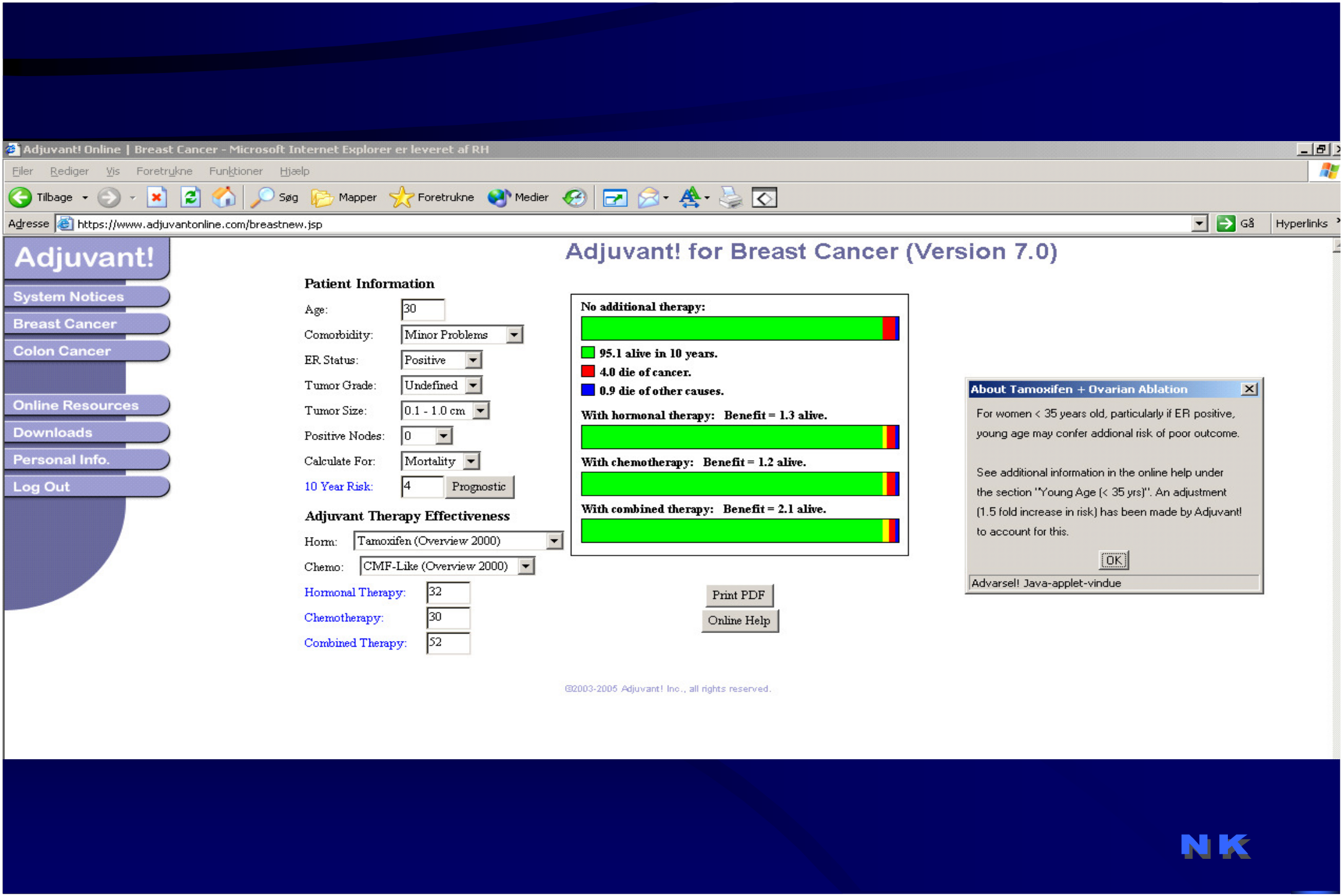
Pregnancy after treatment of breast cancer

- 371 women pregnant after time of diagnosis
- 465 pregnancies
  - 236 full-term births
  - 36 spontaneous abortions
  - 193 induced abortions

Pregnancy after treatment of breast cancer

- Birth: RR of death: 0,73 (0,54-0,99)


Adjuvant! Online | Breast Cancer - Microsoft Internet Explorer er leveret af RH
Filer Rediger Vis Foretrukne Funktioner Hjælp
Tilbage Søg Mapper Foretrukne Medier
Adresse https://www.adjuvantonline.com/breastnew.jsp
Gå Hyperlinks
Adjuvant!
System Notices
Breast Cancer
Colon Cancer
Online Resources
Downloads
Personal Info.
Log Out
Adjuvant! for Breast Cancer (Version 7.0)
Patient Information
Age: 30
Comorbidity: Minor Problems
ER Status: Positive
Tumor Grade: Undefined
Tumor Size: 0.1 - 1.0 cm
Positive Nodes: 0
Calculate For: Mortality
10 Year Risk: 4 Prognostic
Adjuvant Therapy Effectiveness
Horm: Tamoxifen (Overview 2000)
Chemo: CMF-Like (Overview 2000)
Hormonal Therapy: 32
Chemotherapy: 30
Combined Therapy: 52
No additional therapy:
95.1 alive in 10 years.
4.0 die of cancer.
0.9 die of other causes.
With hormonal therapy: Benefit = 1.3 alive.
With chemotherapy: Benefit = 1.2 alive.
With combined therapy: Benefit = 2.1 alive.
Print PDF
Online Help
About Tamoxifen + Ovarian Ablation
For women < 35 years old, particularly if ER positive, young age may confer addional risk of poor outcome.
See additional information in the online help under the section "Young Age (< 35 yrs)". An adjustment (1.5 fold increase in risk) has been made by Adjuvant! to account for this.
OK
Advarsel! Java-applet-vindue
©2003-2005 Adjuvant! Inc., all rights reserved.

About Tamoxifen + Ovarian Ablation

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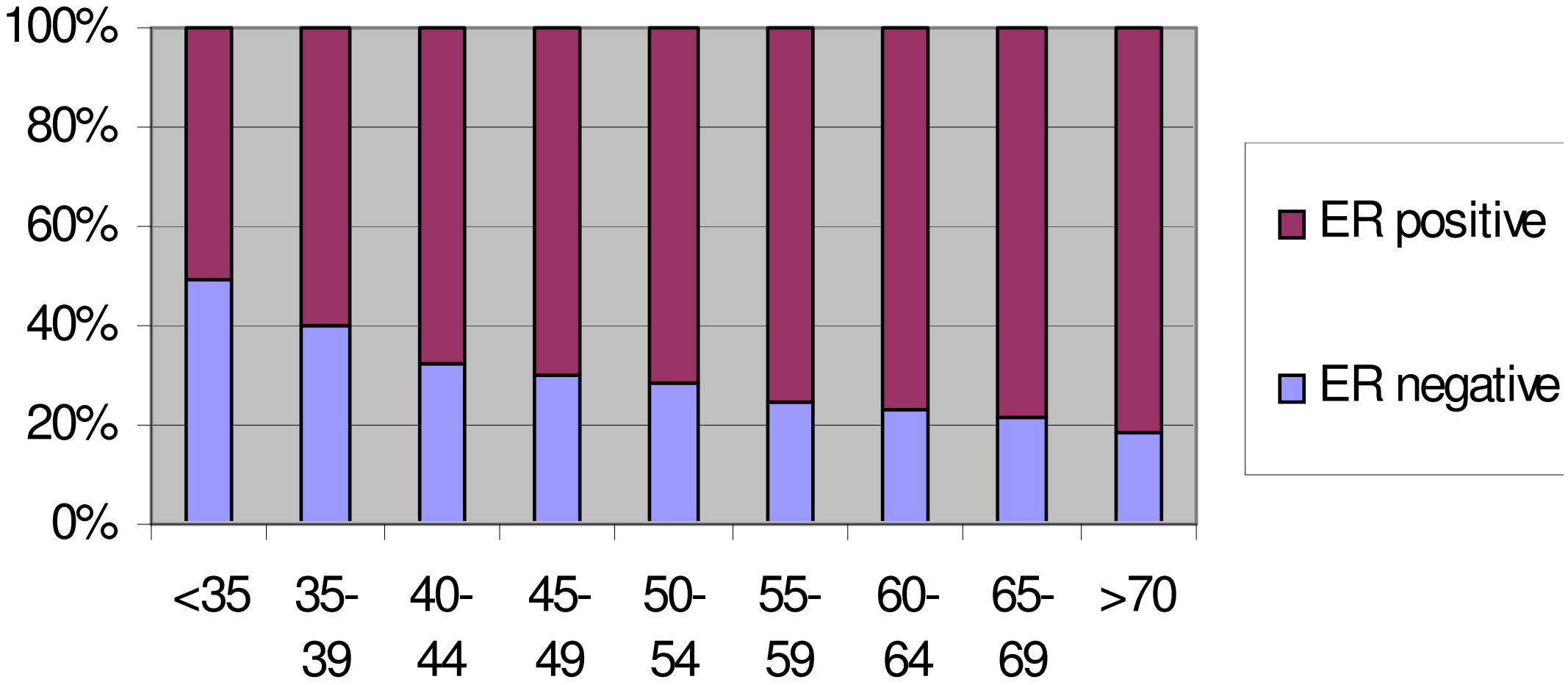
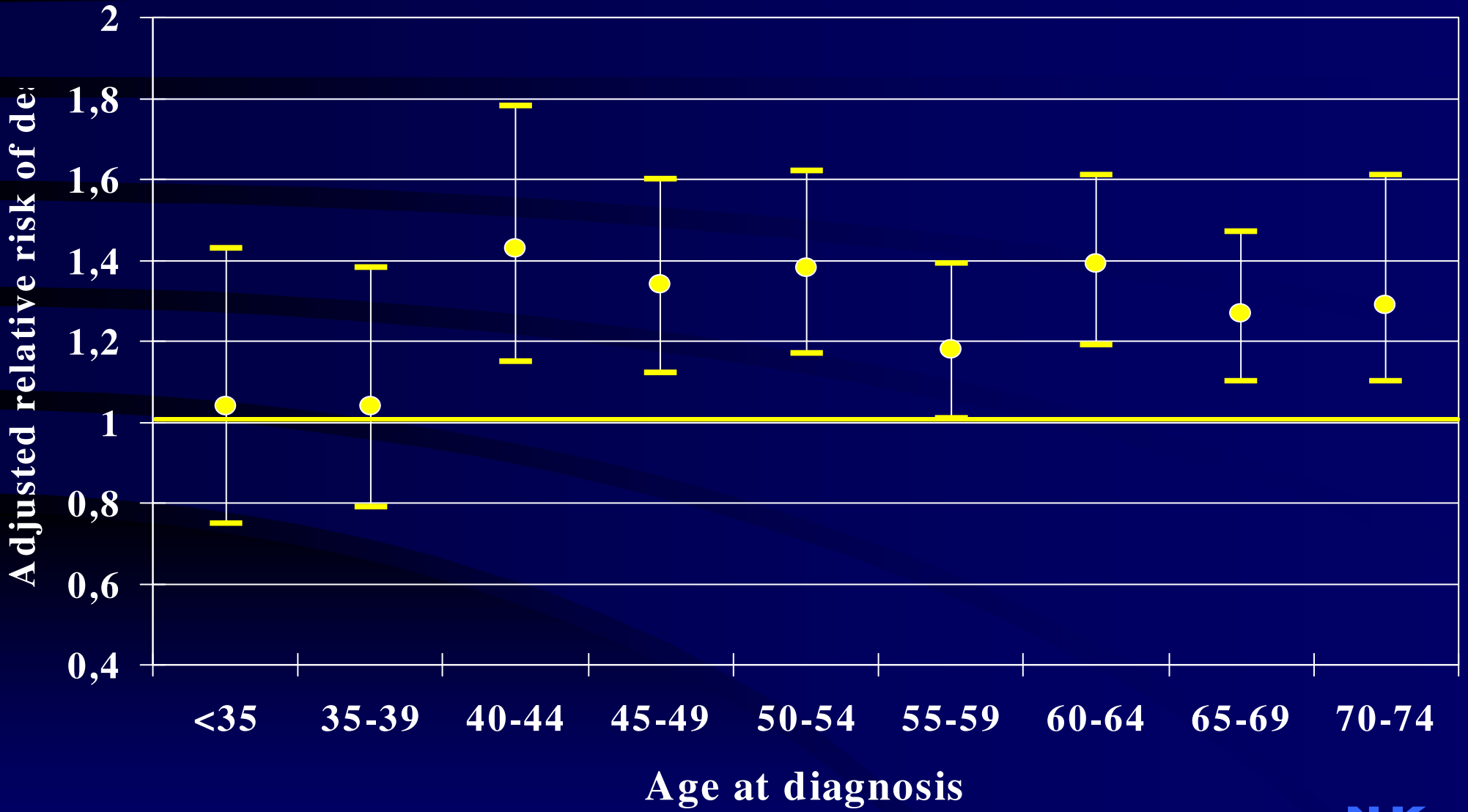
See additional information in the online help under the section "Young Age (< 35 yrs)". An adjustment (1.5 fold increase in risk) has been made by Adjuvant! to account for this.

OK

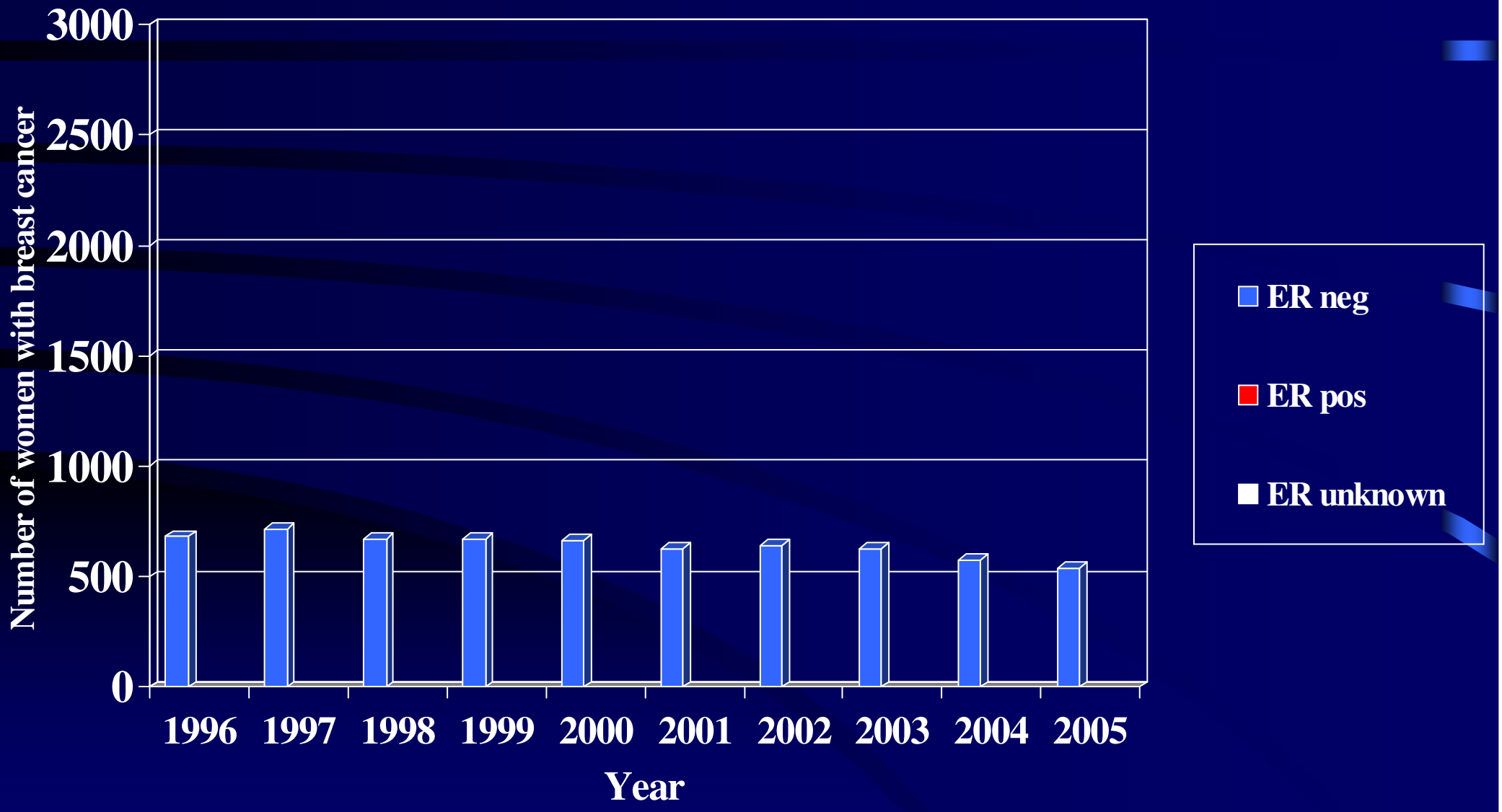


Distribution of ER status related to age in 26,944 danish women < 75 yrs. operated 1989 - 2004

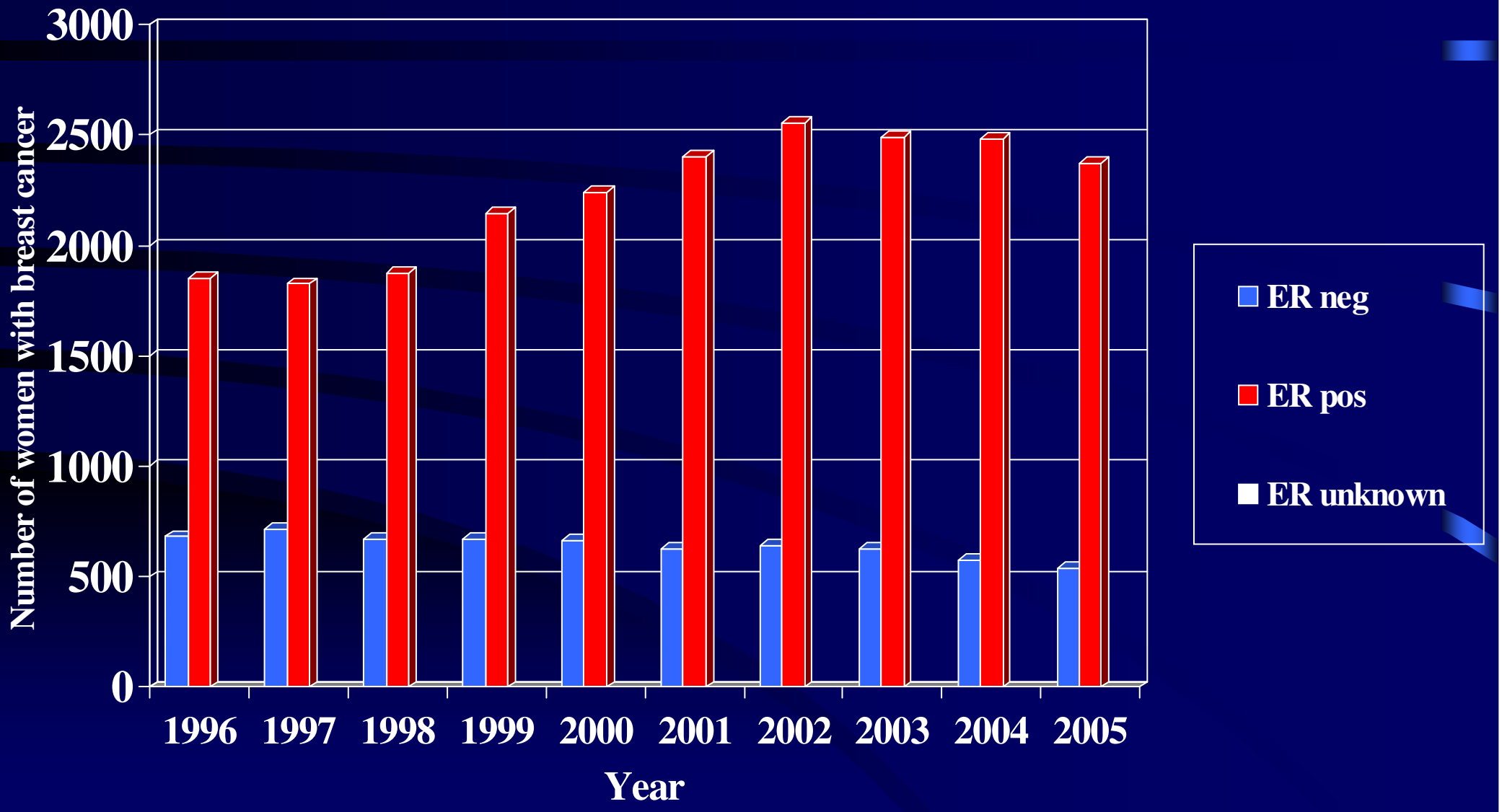
Prognosis according to age and ER status (Ref.: ER+)



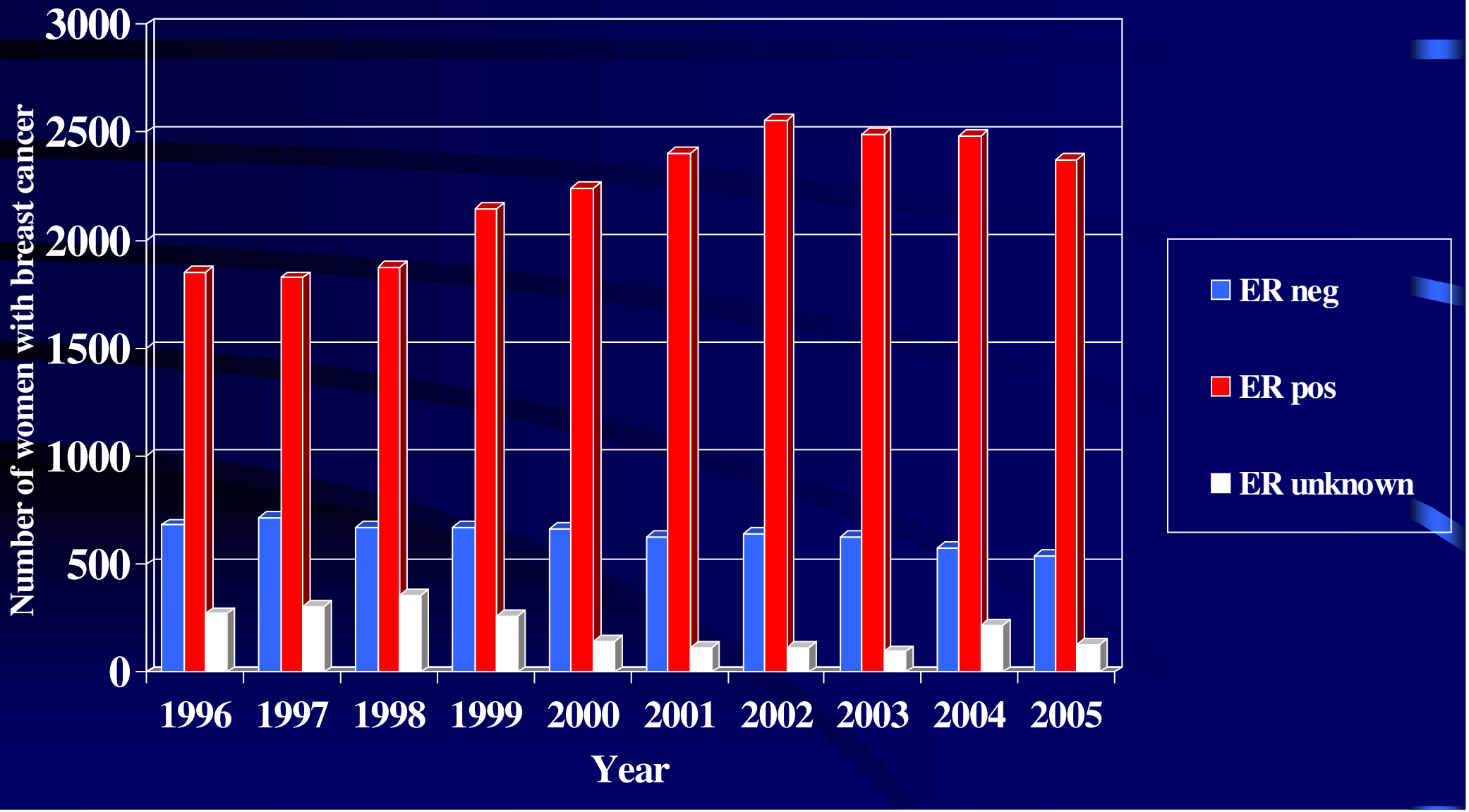
Breast cancer incidence and ER status



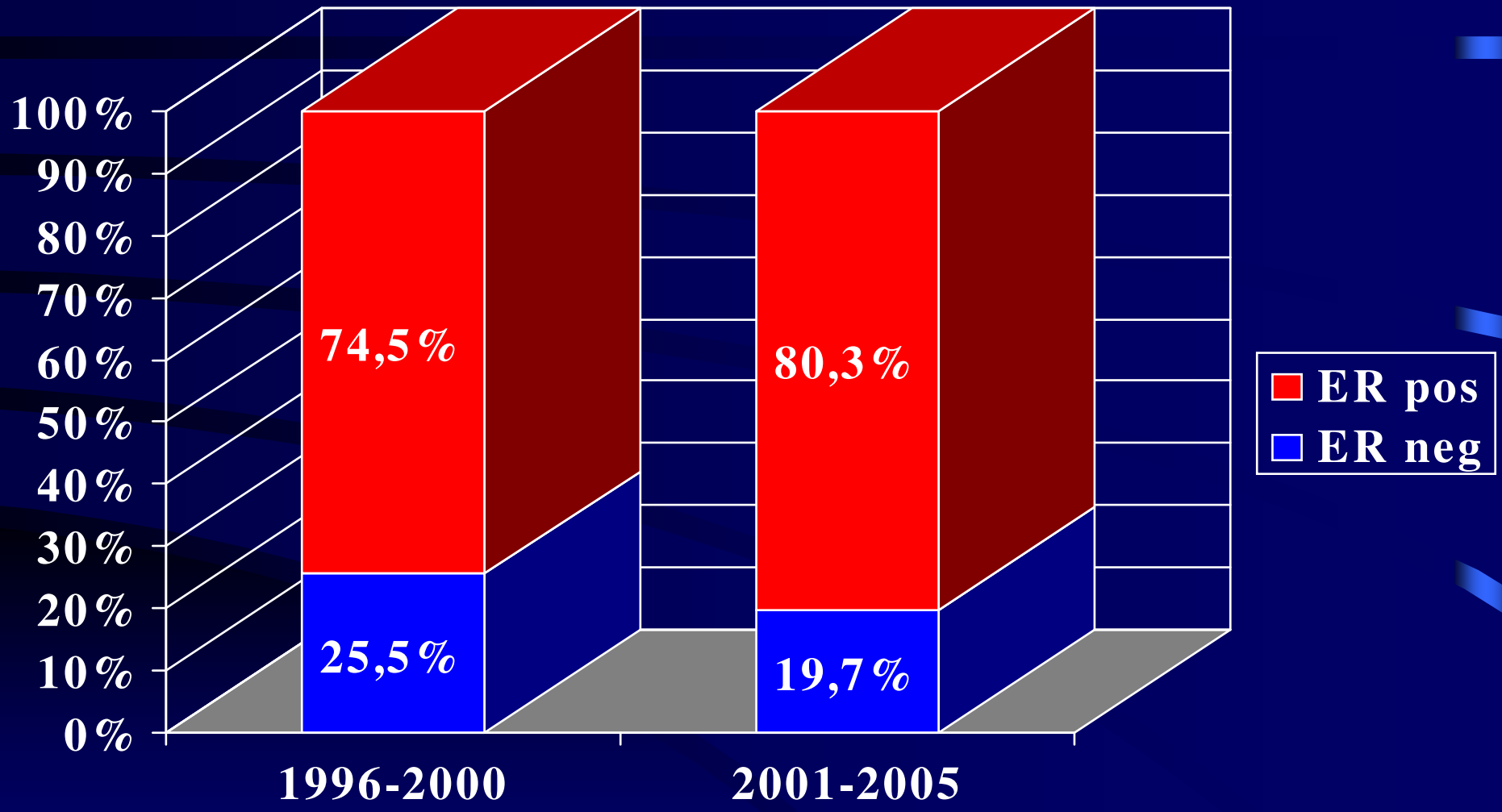
Breast cancer incidence and ER status



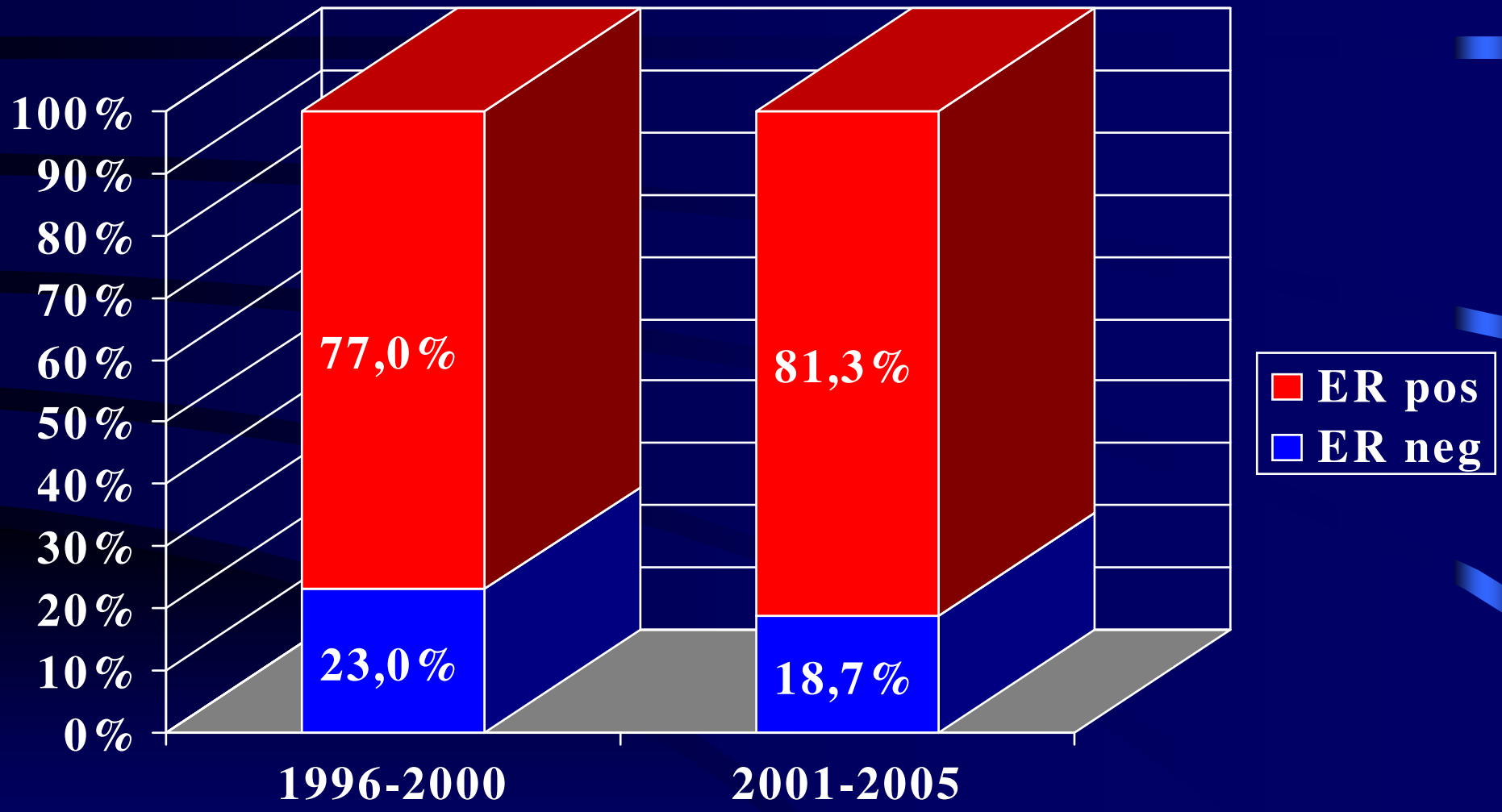
Breast cancer incidence and ER status



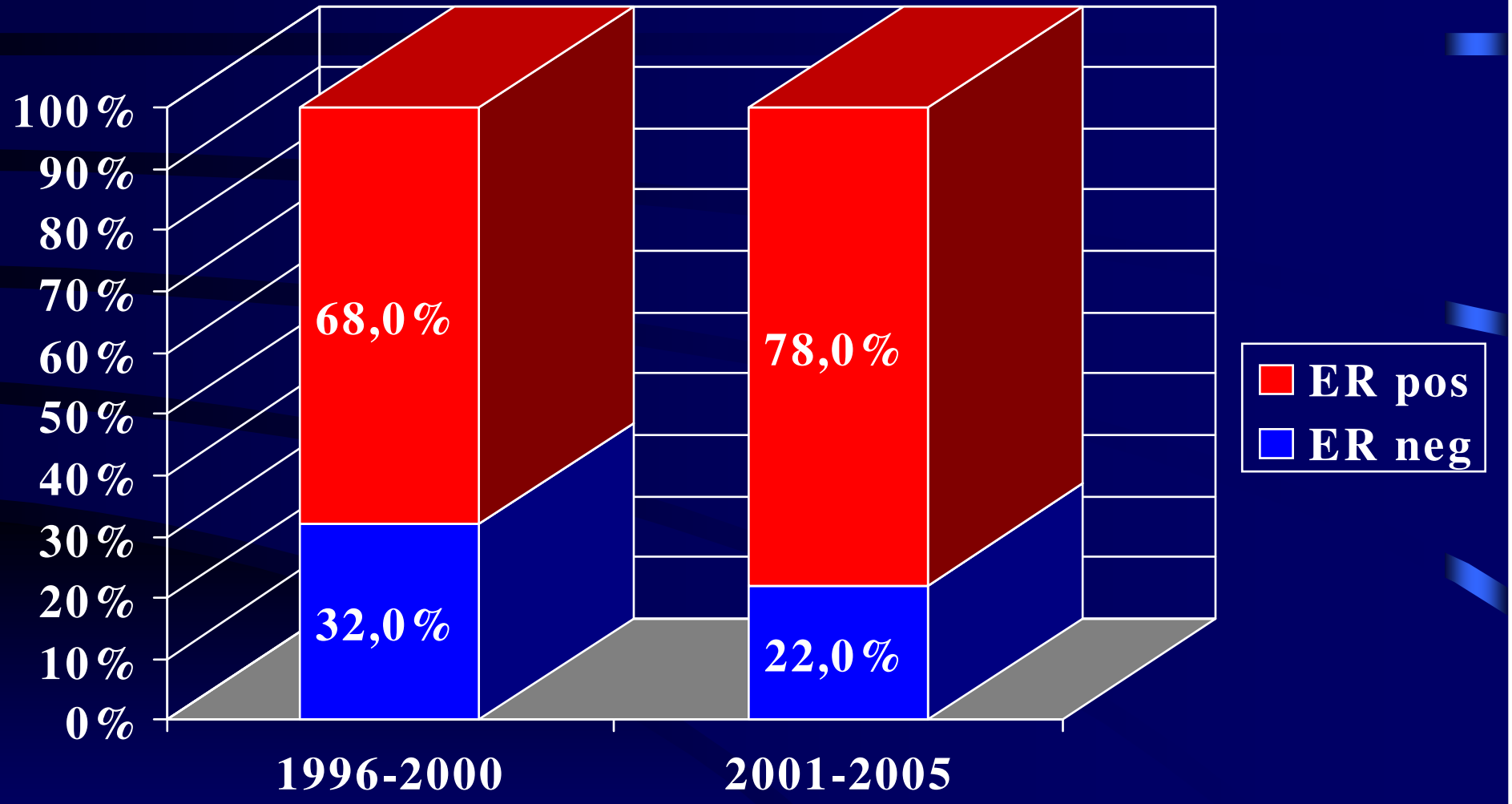
Breast cancer incidence and ER status
n= 28,652 aged under 80



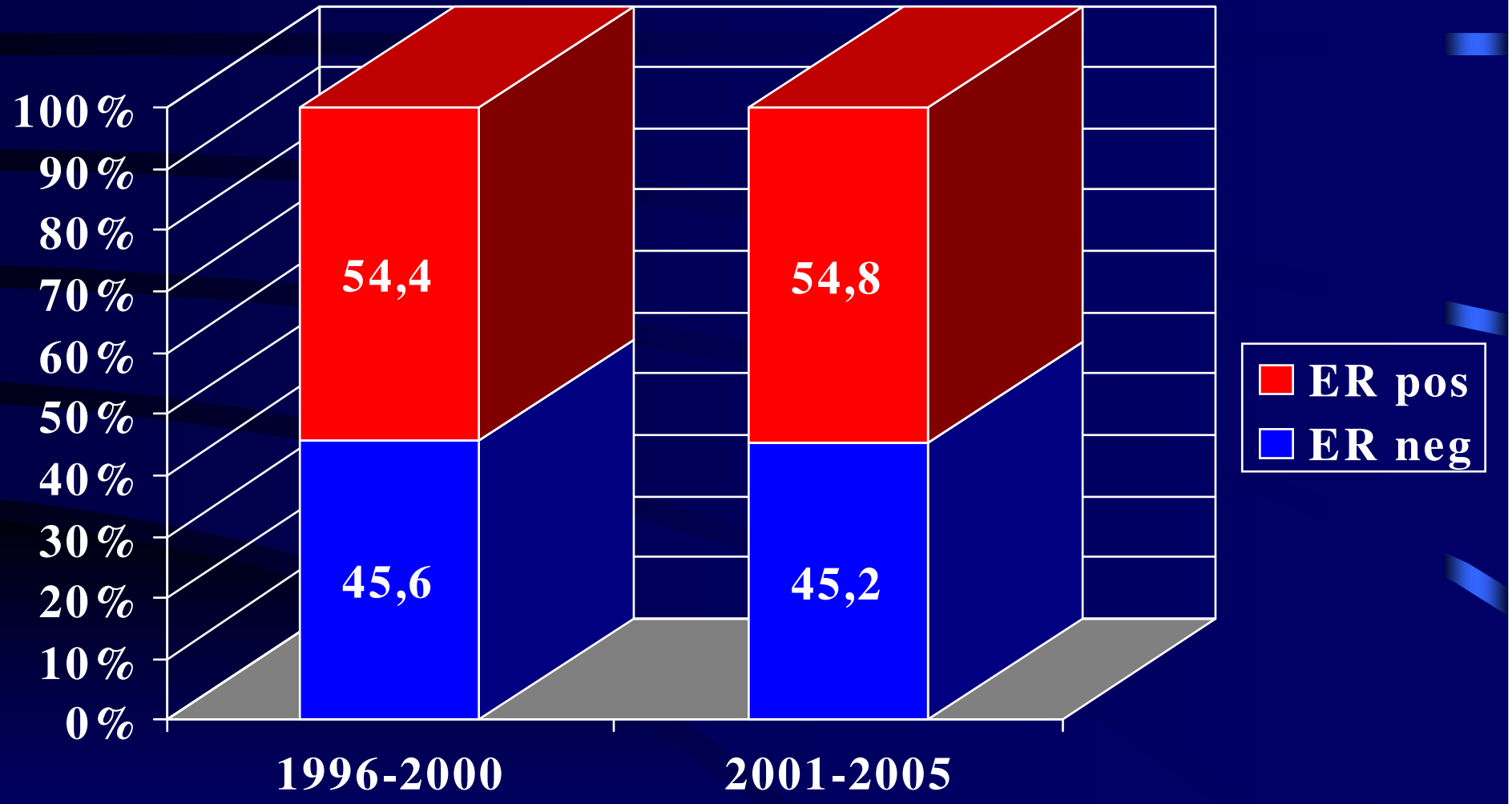
Breast cancer incidence and ER status
n= 20,573 postmenopausal women aged under 80

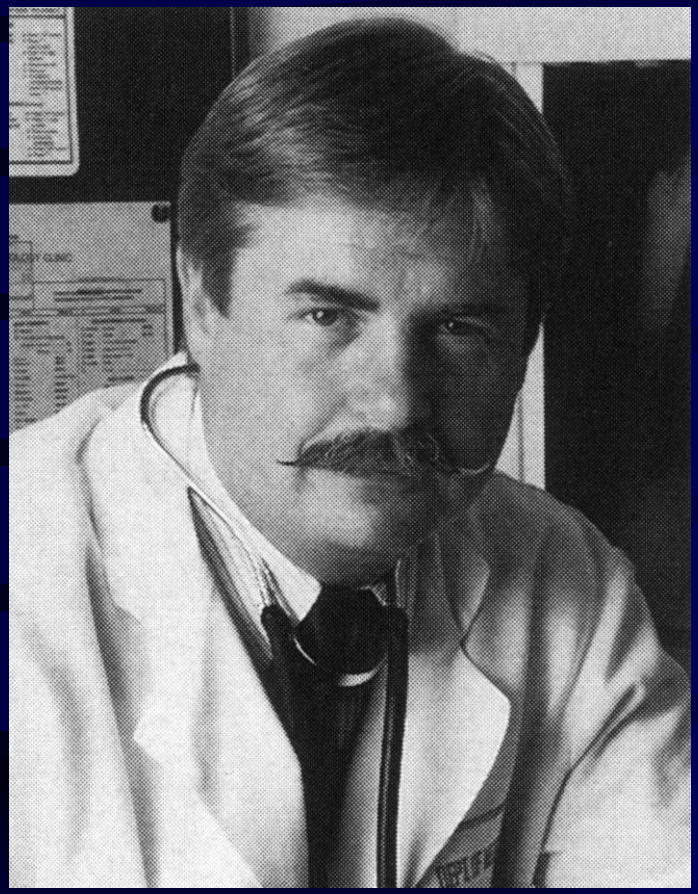


Breast cancer incidence and ER status
n= 8,079 premenupausal women



Breast cancer incidence and ER status
n= 489 women < 35 years





William J. M. Hrushesky

THE LANCET, OCTOBER 21, 1989

Preliminary Communication

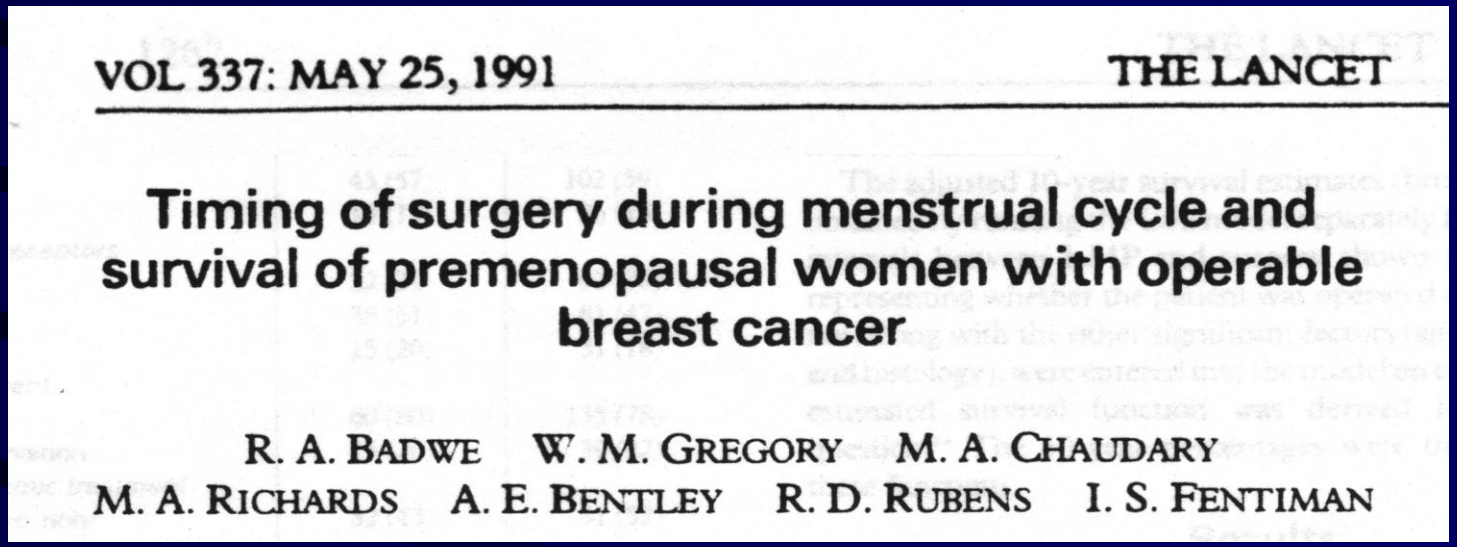
MENSTRUAL INFLUENCE ON SURGICAL CURE OF BREAST CANCER

WILLIAM J. M. HRUSHESKY[1] AVRUM Z. BLUMING[2]
SCOTT A. GRUBER[3] ROBERT B. SOTHERN[1]

Departments of Medicine and Microbiology/Immunobiology, Albany Medical College of Union University and Albany V.A. Medical Center, Albany, New York, USA;[1] Hematology-Oncology Medical Group of the San Fernando Valley, Encino, California;[2] and Department of Surgery, University of Minnesota Hospitals, Minneapolis, Minnesota[3]

Summary In a retrospective study of 44 premenopausal women who underwent resection of a primary breast cancer and were followed for 5 to 12 years, disease recurrence and metastasis were more frequent and more rapid in women who had been operated upon during the perimenstrual period (days 0–6 and 21–36 of the menstrual cycle). By multivariate analysis, the time of resection in relation to the menstrual cycle is an independent predictor of the likelihood of future metastatic disease. Patients who underwent resection during the perimenstrual period had a more than quadrupled risk of recurrence and death compared with women operated upon during days 7 to 20 of the menstrual cycle.

Timing of breast cancer surgery



VOL 337: MAY 25, 1991 THE LANCET

Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer

R. A. BADWE W. M. GREGORY M. A. CHAUDARY
M. A. RICHARDS A. E. BENTLEY R. D. RUBENS I. S. FENTIMAN

- 249 patients included
- Day 3-12 associated with high risk

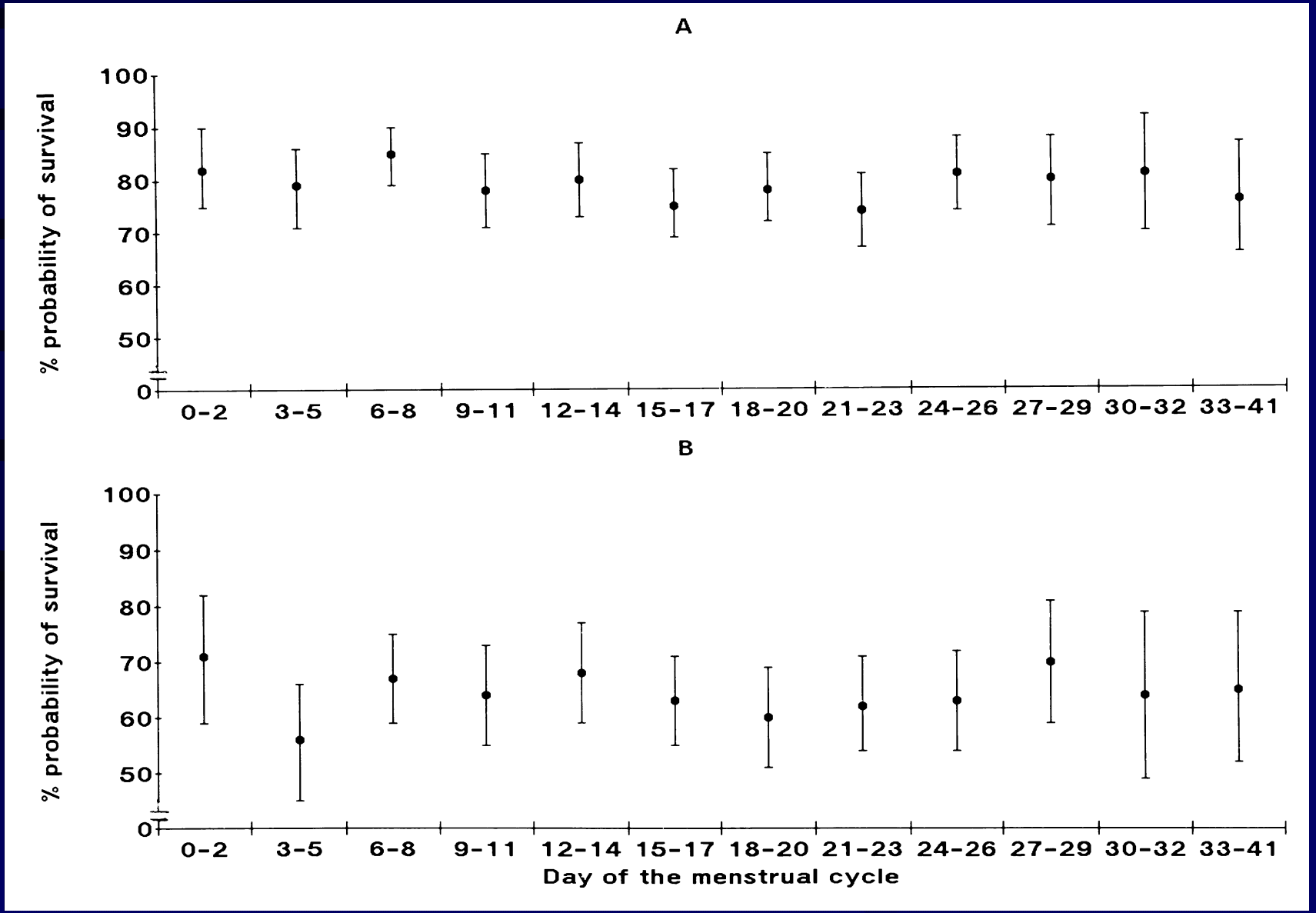
NK

Timing of breast cancer surgery

DBCG study

- 1,635 patients included
- No prognostic influence of menstrual timing of surgery

Timing of breast cancer surgery



Breast Cancer Research and Treatment

Manuscript # BREA 92-040

Authors: KROMAN/HOJGAARD/ANDERSEN/GRAVERSEN/et. al

Reviewer: Dr. Hrushesky, #2

Comments to the Authors:

This study is neither positive nor negative, it is not conclusive nor inconclusive; it is not good science.

REVIEW

Menstrual Timing of Breast Cancer Surgery

Andreas A. Hagen, MD, *Berlin, Germany,* William J. M. Hrushesky, MD, *Albany, New York*

Hagen & Hrushesky

Am J. Surgery

1998

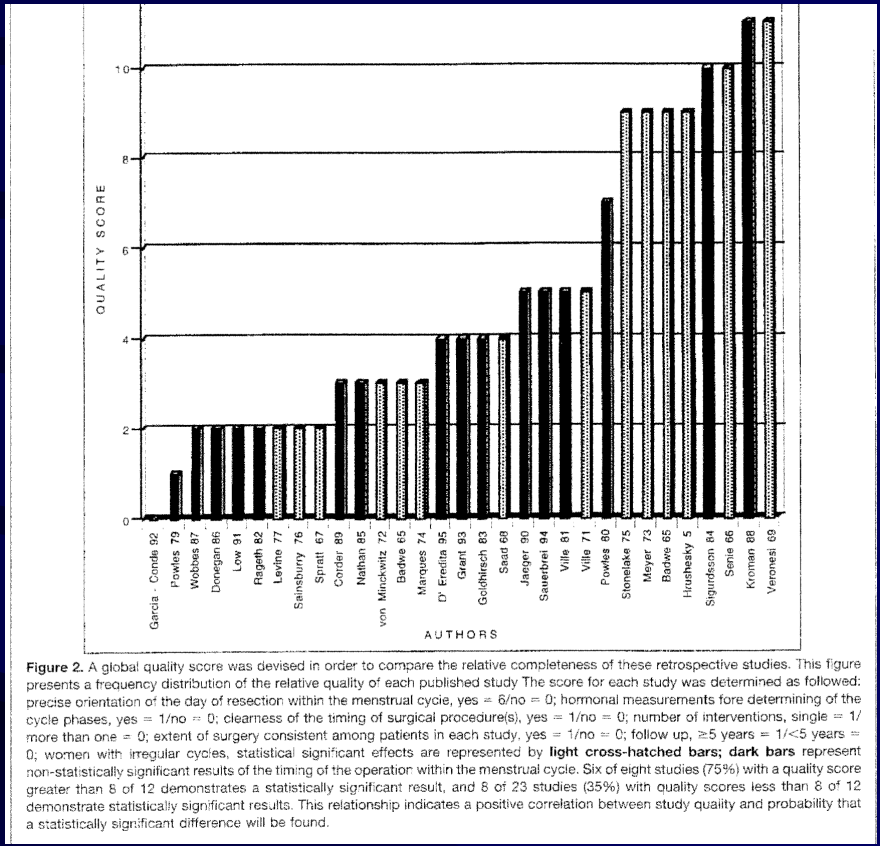
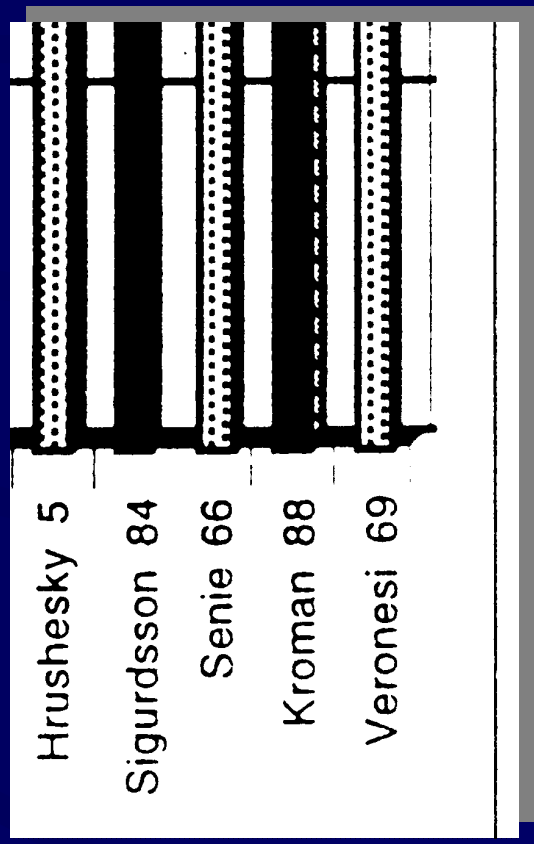


Figure 2. A global quality score was devised in order to compare the relative completeness of these retrospective studies. This figure presents a frequency distribution of the relative quality of each published study The score for each study was determined as followed: precise orientation of the day of resection within the menstrual cycle, yes = 6/no = 0; hormonal measurements fore determining of the cycle phases, yes = 1/no = 0; clearness of the timing of surgical procedure(s), yes = 1/no = 0; number of interventions, single = 1/ more than one = 0; extent of surgery consistent among patients in each study, yes = 1/no = 0; follow up, ≥5 years = 1/<5 years = 0; women with irregular cycles, statistical significant effects are represented by **light cross-hatched bars; dark bars** represent non-statistically significant results of the timing of the operation within the menstrual cycle. Six of eight studies (75%) with a quality score greater than 8 of 12 demonstrates a statistically significant result, and 8 of 23 studies (35%) with quality scores less than 8 of 12 demonstrate statistically significant results. This relationship indicates a positive correlation between study quality and probability that a statistically significant difference will be found.



A global quality score was devised in order to compare the relative completeness

The British Journal of Surgery

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Dr N Kroman
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18 October 1993

Dear Dr Kroman

Contribution number: 93/ 1137

The Editor of the British Journal of Surgery acknowledges receipt of your article entitled:

Timing of surgery in relation to menstrual cycle does not predict the prognosis in primary breast cancer

Your article will be considered by the Editorial Committee and a decision given as soon as possible.

Please quote the contribution number at the beginning of this letter in all future correspondence regarding your manuscript.

Thank you for submitting your work to the Journal.

Yours sincerely

Emma Lawrence
Editorial Secretary

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Dr N Kroman
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7 January 1994

Dear Dr Kroman

Contribution no: 93/ 1137

Title: Timing of surgery in relation to menstrual cycle does not predict the prognosis in primary breast cancer

The Editorial Team has now considered your paper in the light of reports from our referees. I am sorry to say that we are unable to accept the article for publication. Some of the reasons for this decision are outlined in the enclosed comments from our referees. Although the paper was considered to be of interest, it failed to gain sufficient support at a time when the Journal has many papers awaiting publication.

I would like to thank you for sending your work to the Journal and look forward to receiving future submissions.

Yours sincerely

pp RCN Williamson
Senior Editor

18 October 1993

7 January 1994

I am sorry to say that we are unable to accept the article for publication.

NK

British Journal of Surgery 1994, 81, 217–220

British Journal of Surgery 1994, **81**, 217–220

Timing of surgery in relation to the menstrual cycle in premenopausal women with operable breast cancer

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Recent studies have suggested that the timing of surgery in relation to the menstrual cycle might influence survival of premenopausal women with operable breast cancer. The data of 96 premenopausal patients who underwent primary surgery for operable breast carcinoma between 1975 and 88 were analysed. At 10 years, disease-free and overall survival rates of patients whose initial surgery was 1–12 days after the starting date of the last menstrual period (follicular phase) were significantly poorer compared with surv… days after the last menstruation (luteal phase) (disease-free survival rate 40 *versus* 72 per cent, $P=0{\cdot}002$; overall survival rate 40 *versus* 79 per cent, $P=0{\cdot}001$). These differences in survival remained significant in a second analysis based on the menstrual phase at the time of both initial and definitive operation. Menstrual phase had the greatest impact on the survival of patients with positive axillary nodes ($P=0{\cdot}009$). Prospective studies are required to elucidate the relationship between the timing of all …vival.

data of 96 premenopausal patients

survival rates of patients whose initial surgery was 1–12 days after the starting date of the last menstrual period (follicular phase) were significantly poorer compared with survival of those who underwent operation more than 12

Available studies on timing of surgery in relation to the menstrual cycle

Author, Year (Reference)	Number of patients	Days of menstrual cycle associated with poor outcome
Hrushesky, 1989	41	0-6, 21-36
Powles, 1989	81	No relationship
Gelber, 1989	245	No relationship
Ville, 1990	279	No relationship
Badwe, 1991	249	3-12
Low, 1991	125	No relationship
Rageth, 1991	224	No relationship
Senie, 1991	283	7-14
Sigurdsson, 1992	382	No relationship
Gnant, 1992	385	No relationship
Sainsbury, 1993	143	0-2, 13-32
Donegan, 1993	97	No relationship
Marques, 1993	63	3-12*
Spratt, 1993	40	7-20*
Nathan, 1993	132	No relationship
Corder, 1994	157	No relationship
Kroman, 1994	1,635	No relationship
Wobbes, 1994	89	No relationship
Saad, 1994	96	1-12
Veronesi, 1994	1,175	0-14
Jager, 1995	562	No relationship
Von-Minckwitz, 1995	226	3-12 †
D´eredita, 1995	133	No relationship
Kurebayashi, 1995	100	3-12 ‡
Holli, 1995	267	1-14*
Stonelake, 1995	221	0-2, 13-28
Tsuchiya, 1995	159	No relationship
Toscano, 1996	254	No relationship
Goldhirsch, 1997	1,033	3-12 §
Mondini, 1997	165	No relationship
Vanek, 1997	150	No relationship

Studies supporting the unopposed oestrogen theory

Badwe, 1991	249	3-12
Senie, 1991	283	7-14
Marques, 1993	63	3-12*
Saad, 1994	96	1-12
Veronesi, 1994	1,175	0-14
Von-Minckwitz, 1995	226	3-12 †
Kurebayashi, 1995	100	3-12 ‡
Holli, 1995	267	1-14*
Goldhirsch, 1997	1,033	3-12 §
Chang, 1997	262	8-15*

* Result not significant

†Result only significantly positive among 119 patients operated in a two-step procedure

‡ Result only significantly positive in univariate analysis

§ Result only significantly positive among 300 oestrogen receptor negative patients

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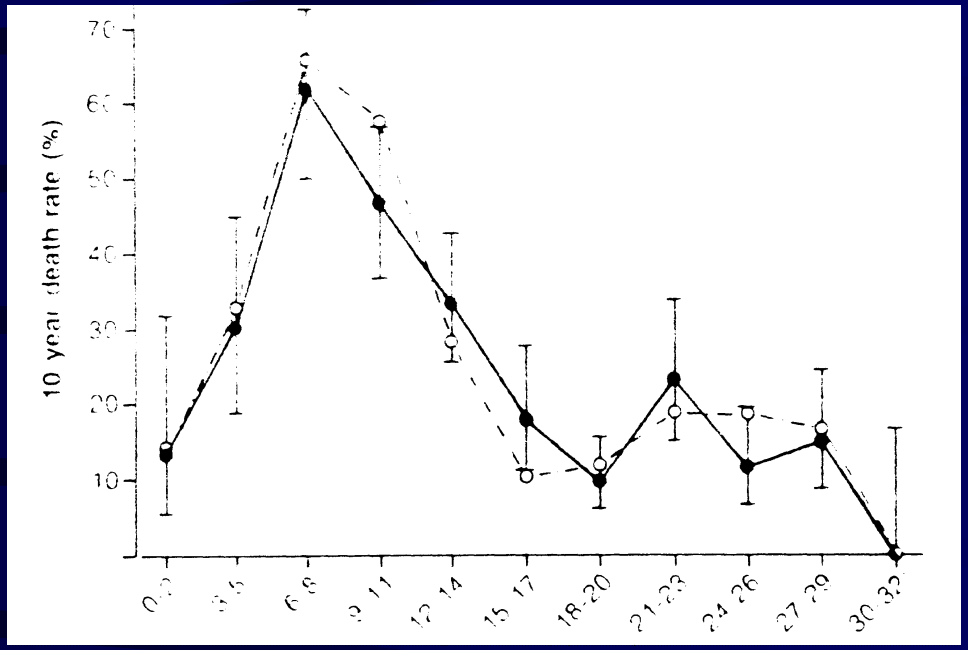

Badwe et al

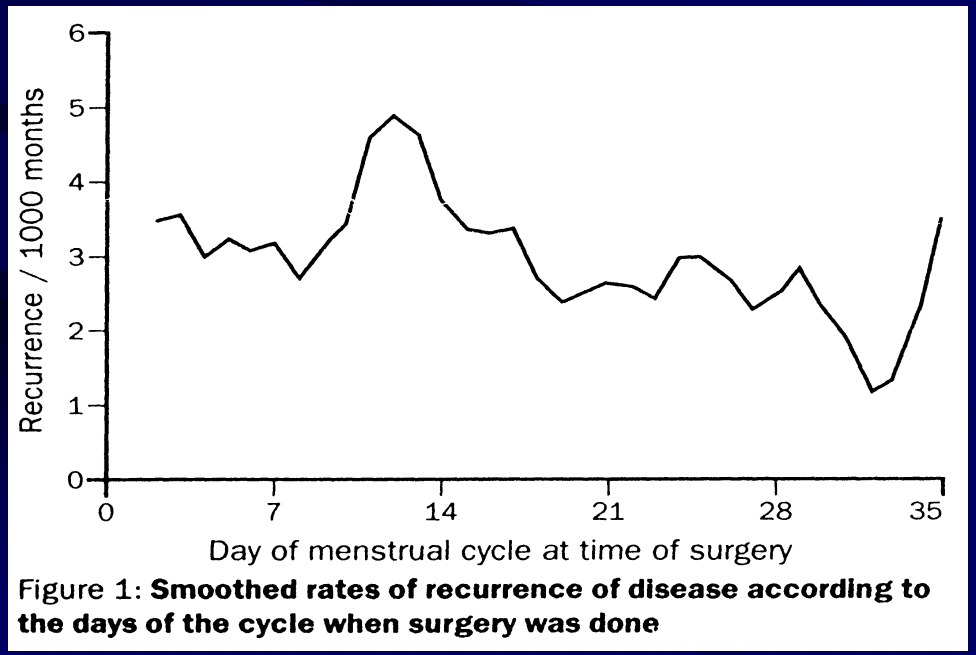

Figure 1: **Smoothed rates of recurrence of disease according to the days of the cycle when surgery was done**

Veronesi et al.

Timing of breast cancer surgery

- 675 breast cancer patients from San Antonio Tumor Bank
- Randomly assigned day of the menstrual cycle 100 times
- Identification of a 14 day window with a significantly impaired survival.

McGuire et al. JNCI 84: 346-48, 1992

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Timing of breast cancer surgery

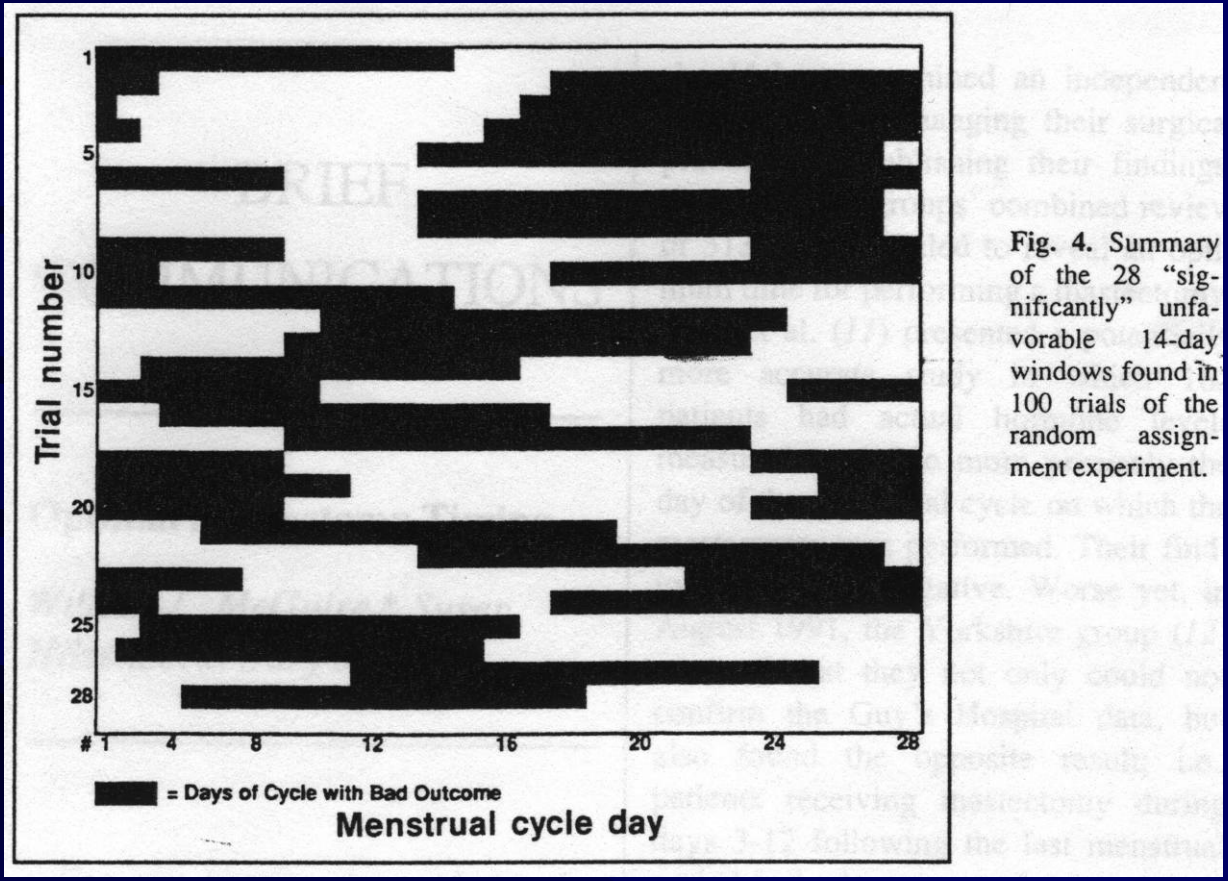


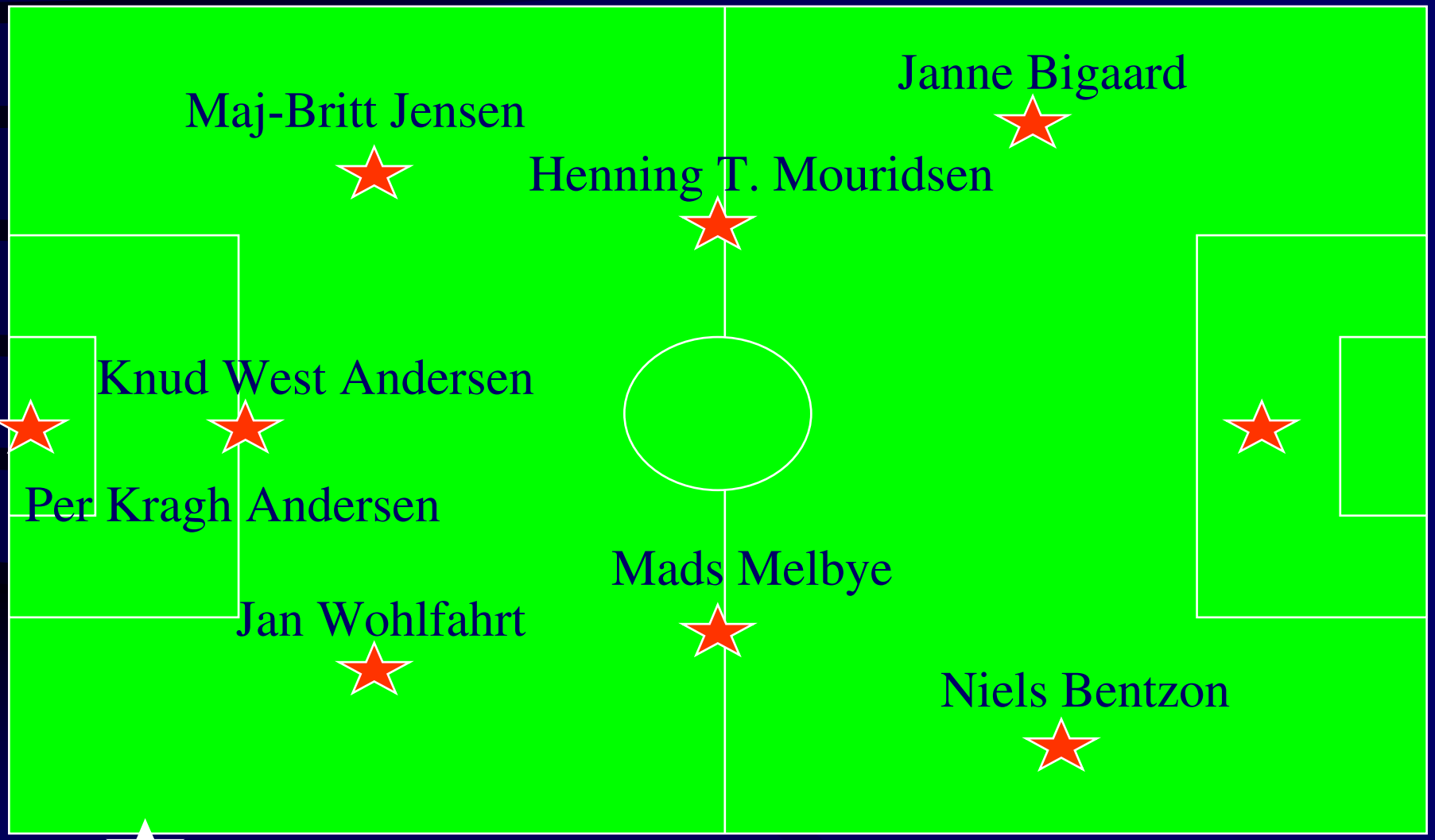
Fig. 4. Summary of the 28 "significantly" unfavorable 14-day windows found in 100 trials of the random assignment experiment.

McGuire et al. JNCI 84: 346-48, 1992

Average impact factor of journals publishing results of menstrual timing of breast cancer surgery

- Studies with positive results: 6.5
- Studies with negative results: 1.5

The Dream Team



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