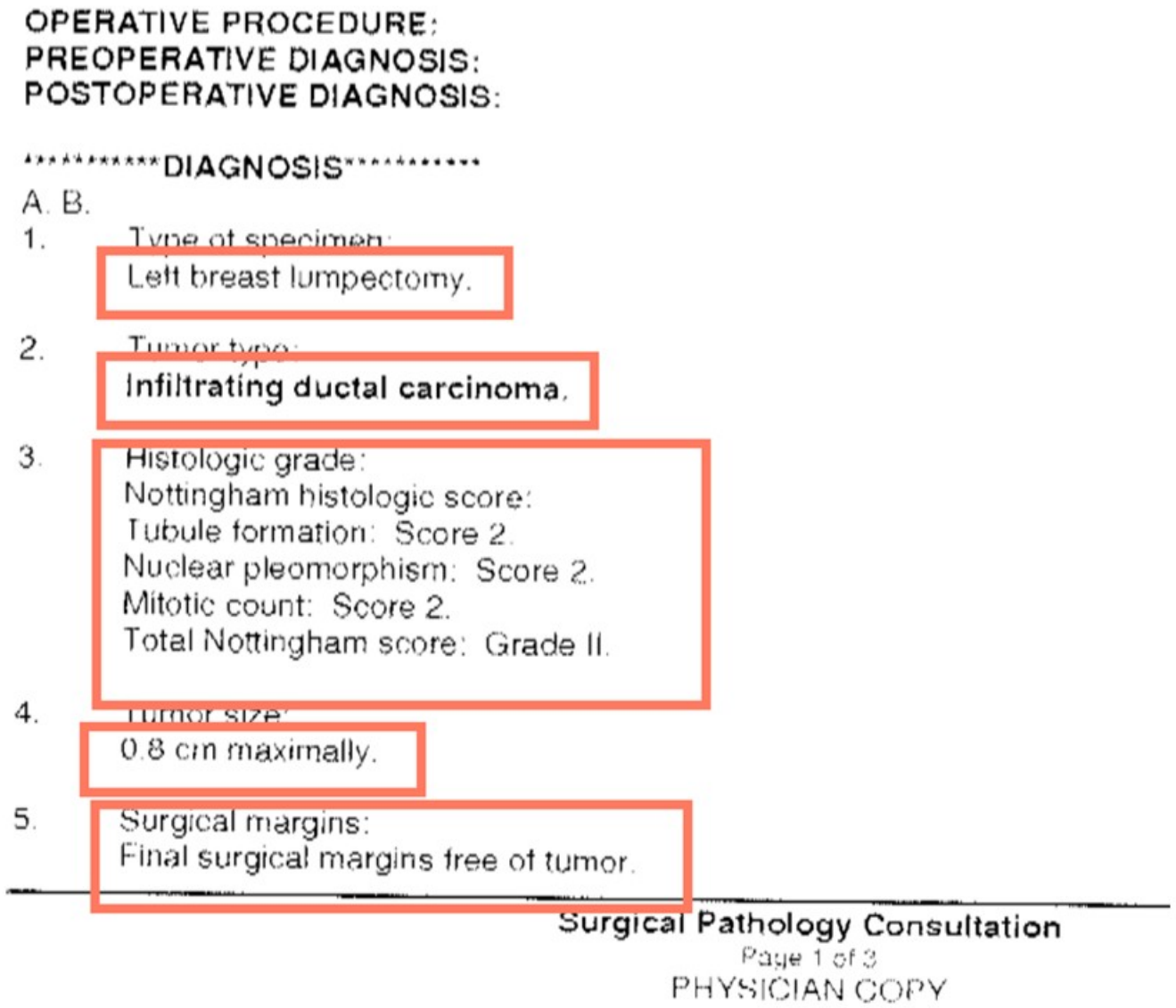
Bottom Line:

Breast Cancer Risk

What 'Risk' all comes down to....



OPERATIVE PROCEDURE:
PREOPERATIVE DIAGNOSIS:
POSTOPERATIVE DIAGNOSIS:

**********DIAGNOSIS**********

A. B.

1. Type of specimen:
Left breast lumpectomy.

2. Tumor type:
Infiltrating ductal carcinoma.

3. Histologic grade:
Nottingham histologic score:
Tubule formation: Score 2.
Nuclear pleomorphism: Score 2.
Mitotic count: Score 2.
Total Nottingham score: Grade II.

4. Tumor size:
0.8 cm maximally.

5. Surgical margins:
Final surgical margins free of tumor.

Surgical Pathology Consultation
Page 1 of 3
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Breast cancer risk with postmenopausal hormonal treatment.

Abstract

This review was designed to determine from the best evidence whether there is an association between postmenopausal hormonal treatment and breast cancer risk. Also, if there is an association, does it vary according to duration and cessation of use, type of regimen, type of hormonal product or route of administration; whether there is a differential effect on risk of lobular and ductal cancer; and whether hormone treatment is associated with breast cancers that have better prognostic factors? Data sources for the review included Medline, the Cochrane Database of Systematic Reviews (Cochrane Library, 2005) and reference lists in the identified citations.... **The average risk of invasive breast cancer with estrogen use was 0.79** [95% confidence interval (95% CI) = 0.61–1.02] in four randomized trials involving 12 643 women. **The average breast cancer risk with estrogen–progestin use was 1.24** (95% CI = 1.03–1.50) in four randomized trials involving 19 756 women. The average risks reported in recent epidemiological studies were higher: 1.18 (95% CI = 1.01–1.38) with current use of estrogen alone and 1.70 (95% CI = 1.36–2.17) with current use of estrogen–progestin. The association of breast cancer with current use was stronger than the association with ever use, which includes past use. For past use, the increased breast cancer risk diminished soon after discontinuing hormones and normalized within 5 years. Reasonably adequate data do not show that breast cancer risk varies significantly with different types of estrogen or progestin preparations, lower dosages or different routes of administration, although there is a small difference between sequential and continuous progestin regimens. Epidemiological studies indicate that estrogen–progestin use increases risk of lobular more than ductal breast cancer, but the number of studies and cases of lobular cancer remains limited. Among important prognostic factors, the stage and grade in breast cancers associated with hormone use [corrected] do not differ significantly from those in non-users, but breast cancers in estrogen–progestin users are significantly more likely to be estrogen receptor (ER) positive. In conclusion, valid evidence from randomized controlled trials (RCTs) indicates that breast cancer risk is increased with estrogen–progestin use more than with estrogen alone. Epidemiological evidence involving more than 1.5 million women agrees broadly with the trial findings. Although new studies are unlikely to alter the key findings about overall breast cancer risk, research is needed, however, to determine the role of progestin, evaluate the risk of lobular cancer and delineate effects of hormone use on receptor presence, prognosis and mortality in breast cancer.

Collins JA, et al. Hum Reprod Update. 2005 Nov-Dec;11(6):541-3.Review article
Breast cancer risk with postmenopausal hormonal treatment.

Title or General Subject

Excerpt from article

Main point

Literature citation
Authors

Second slide

[2 'Arms' of the WHI study:

1] Premarin alone

2] Prempro]

- The average risk of invasive breast cancer with estrogen use was 0.79…[while]
- The average breast cancer risk with estrogen-progestin use was 1.24

Focus on
main point

Additional references
available: appendix

Appendix: 3h
Bio-identical references

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Hormonally Mediated Indicators of the Risk of Breast Cancer

TABLE 1. HORMONALLY MEDIATED INDICATORS OF THE RISK OF BREAST CANCER.

INDICATOR	RISK GROUP		RELATIVE RISK*	REFERENCE
	LOW	HIGH		
Sex	Male	Female	150.0	Hulka[7]
Age (yr)	30–34	70–74	17.0	Madigan et al.[8]
Age at menarche (yr)	>14	<12	1.5	Hulka[7]
Use of oral contraceptives	Never	Previous or current	1.07–1.2	Hulka,[7] Ursin et al.,[9] Collaborative Group[10]
Age at birth of first child (yr)	<20	≥30	1.9–3.5	Hulka,[7] Leon et al.,[11] Madigan et al.,[8] Ramon et al.,[12] Lambe et al.[13]
Breast-feeding (mo)	≥16	0	1.37	Enger et al.[14]
Parity	≥5	0	1.4	Hulka,[7] Madigan et al.,[8] Ramon et al.,[12] Lambe et al.[13]
Age at oophorectomy (yr)	<35	—†	3.0	Hulka[7]
Age at natural menopause (yr)	<45	≥55	2.0	Hulka[7]
Estrogen therapy	Never	Current	1.2–1.4	Hulka,[7] Grodstein et al.[15]
Estrogen–progestin therapy	Never	Current	1.4	Grodstein et al.[15]
Postmenopausal body-mass index	<22.9	>30.7	1.6	Hulka[7]
Family history of breast cancer	No	Yes	2.6	Madigan et al.[8]
Serum estradiol concentration	Lowest quartile	Highest quartile	1.8–5.0	Toniolo et al.,[16] Thomas et al.[17,18]
Breast density on mammography (%)	0	≥75	6.0	Boyd et al.[19]
Bone density	Lowest quartile	Highest quartile	2.7–3.5	Cauley et al.,[20] Zhang et al.[21]

*The relative risk was calculated with the low-risk group as the reference group.

†There is no association between the risk of breast cancer and oophorectomy performed at 35 years of age or older.

Clemons M, Goss P. N Engl J Med. 2001 Jan 25;344(4):276-85.Estrogen and the risk of breast cancer.

	Risk	
	Low	High
Age	30 - 34	70 - 74
Age of menarche	>14	<12
Use of BCP	never	Previous or current
Age at P1 (yr)	<20	>30
Breast feeding (mo)	>16	0
Parity	>5	0
Age at oopherectomy	<35	-
Age @ menopause	<20	>30
Estrogen Rx	0.79*	
Estrogen-Progestin	1.29*	
Postmenopausal BMI	<22.9	>30.7
Family Hx of BCa	10%*	
Breast density	Yes*	

*= I replaced Colin's data as their study came out in 2001

Also:

	Risk	
	Low	High
Bone density	Lowest Quartile	Highest Quartile
Ionizing Radiation		
Alcohol (4 drinks/d)		

Mammographic density. Potential mechanisms of breast cancer risk

There is now **extensive evidence that mammographic density is an independent risk factor for breast cancer that is associated with large relative and attributable risks for the disease.** The epidemiology of mammographic density, including the influences of age, parity and menopause, is consistent with it being a marker of susceptibility to breast cancer, in a manner similar to the concept of 'breast tissue age' described by the Pike model. Mammographic density reflects variations in the tissue composition of the breast. It is associated positively with collagen and epithelial and nonepithelial cells, and negatively with fat. **Mammographic density is influenced by some hormones and growth factors as well as by several hormonal interventions.** It is also associated with urinary levels of a mutagen. Twin studies have shown that most of the variation in mammographic density is accounted for by genetic factors. The hypothesis that we have developed from these observations postulates that the combined effects of cell proliferation (mitogenesis) and genetic damage to proliferating cells by mutagens (mutagenesis) may underlie the increased risk for breast cancer associated with extensive mammographic density. There is clearly a need for improved understanding of the specific factors that are involved in these processes and of the role played by the several breast tissue components that contribute to density. In particular, identification of the genes that are responsible for most of the variance in percentage density (and of their biological functions) is likely to provide insights into the biology of the breast, and may identify potential targets for preventative strategies in breast cancer.

Martin LJ, Boyd NF Breast Cancer Res. 2008;10(1):201. Epub 2008 Jan 9.

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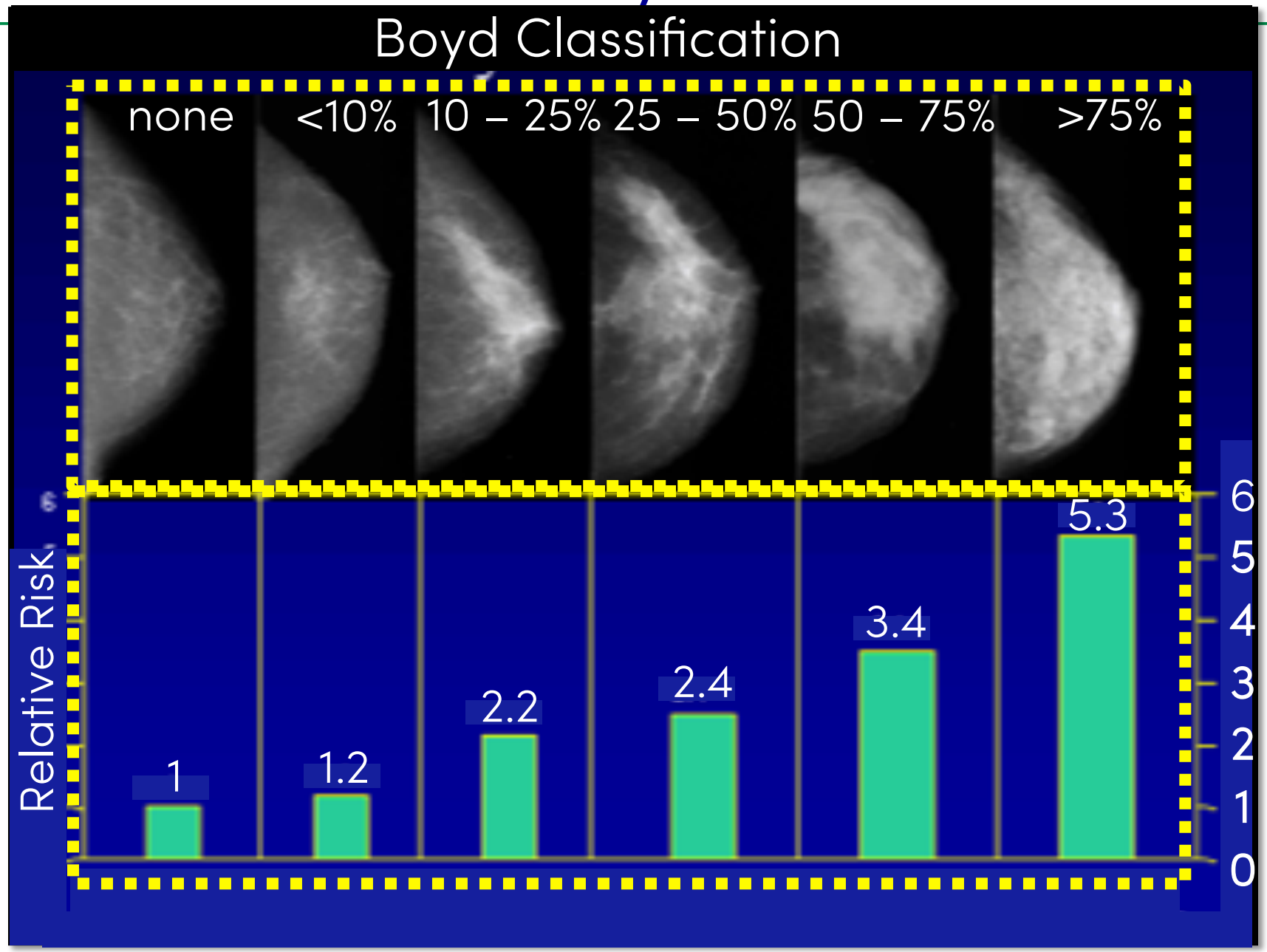
Breast Density & BCa Risk



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Collins JA, et al. Hum Reprod Update. 2005 Nov-Dec;11(6):541-3 Review article

Breast cancer risk with postmenopausal hormonal treatment.

- "Data sources for the review included Medline, the Cochrane Database of Systematic Reviews (Cochrane Library, 2005) and reference lists in the identified citations"
- Two 'arms' of the Women's Health Initiative (WHI) study:
  - Premarin alone (Conjugated Equine Estrogen CEE)
  - Prempro (CEE + a "progestin" medroxyprogesterone)
- The average risk of invasive breast cancer with estrogen use was 0.79…[while]
- The average breast cancer risk with estrogen-progestin use was 1.24

Premarin: 0.79	PremPro 1.24

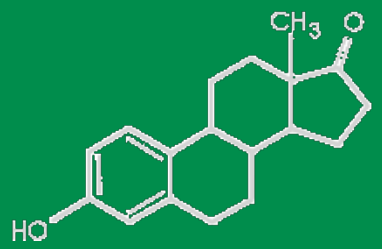
Breast Cancer Risk: Mainstream View

- One in 8 women will be diagnosed with breast cancer and risk increases with age.
- *Estrogen, a trophic growth hormone, may promote the growth of preexisting breast cancer.*
- *It is still unknown whether it may also induce the growth of new cancers.*
- Use of Estrogen alone for at least five years, may be associated with a slightly increased risk of breast cancer according to the Nurses' Health Study.

Reprinted from www.endotext.org

Michelle Warren, M.D. and Aimee Shu M.D.

Updated September 2010



Estrogen, a trophic growth hormone, may promote the growth of preexisting breast cancer. It is still unknown whether it may also induce the growth of new cancers.

Many studies have not shown an increased risk of breast cancer with estrogen use.

Holtorf's Review:
Are Bio-identical Hormones Safer or More Efficacious?

- This literature review presents the substantial evidence for the safety and efficacy of bio-identical hormone therapy, including estradiol, estriol, and progesterone, which shows that it presents lower risks for breast cancer and cardiovascular disease than synthetic or animal-derived hormones. Studies show that progestins have a number of negative effects on the cardiovascular system and an association with breast cancer risk that can be avoided by using bioidentical progesterone.

The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy?

Holtorf K Postgrad Med 2009;121(1):1-13..

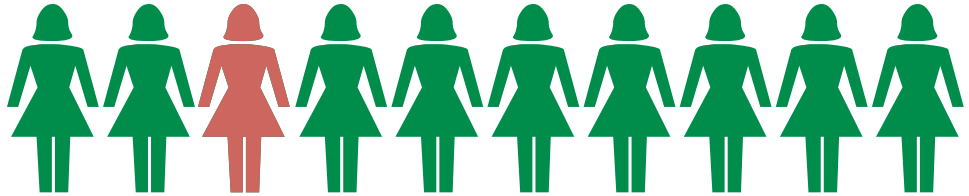
- This literature review presents the substantial evidence for the safety and efficacy of bio-identical hormone therapy, including estradiol, estriol, and progesterone, which shows that it presents lower risks for breast cancer and cardiovascular disease than synthetic or animal-derived hormones.

Appendix:
3h

Bio-identical references

Genetic Polymorphisms

All Breast Cancer Risks

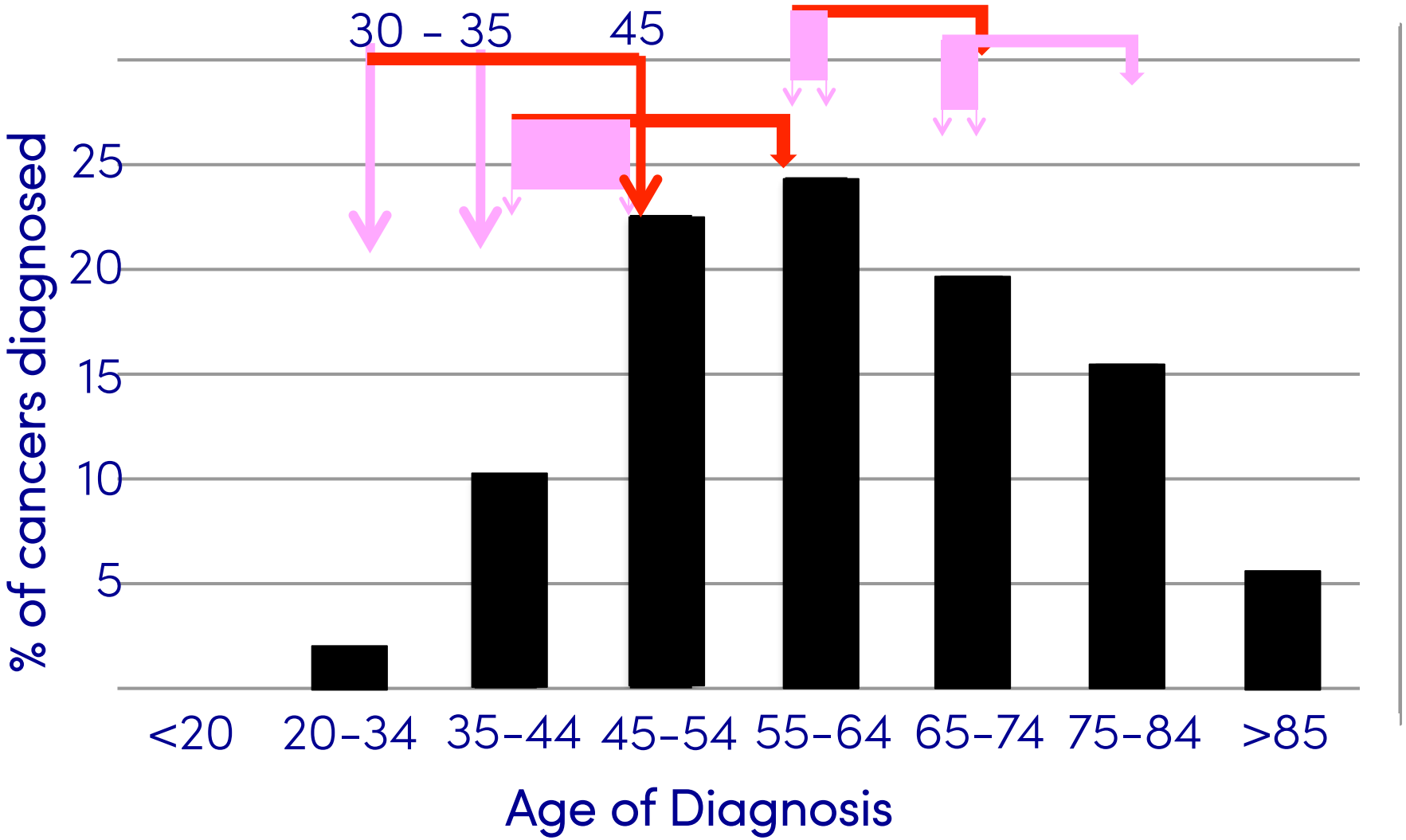


Unknown Factor(s) Known Inherited Factor

Appendix:
3g

Benefits &
Risks
continued

BCa: Age of Onset Related to Age of Diagnosis: 10 – 15 year gap



http://seer.cancer.gov/statfacts/html/breast.html

A Special Vulnerability as it relates to Menopause Practice and BCa