Breast Cancer

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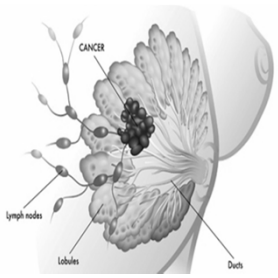
Agenda

» **Types of Breast Cancer and Staging**
» **How do we treat breast cancer**
  – **Surgery**
  – **Chemotherapy**
  – **Radiation Therapy**
  – **Hormonal Therapy**
» **Risk of breast cancer**
  – **Genetics**
» **Screening**

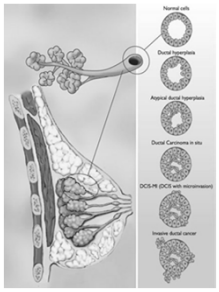
Definitions

- Lobules: Milk making machinery of the breast
- Ducts: Carry milk from lobules to the nipple; terminate in nipple
  - Breast cancer more commonly arises from ductal tissue



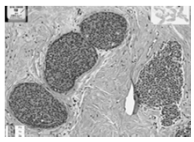
Definitions

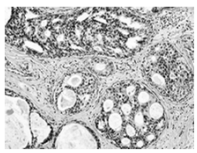
- Carcinoma in situ
  - Cancer cells have not become invasive, by definition cancer cannot spread to other parts of the body
- Invasive carcinoma
  - Cancer cells have invaded surrounding cells; can spread to other parts of the body



Types of carcinoma in situ

» **Lobular carcinoma in situ**
  – **Usually found incidentally**
  – **Treated with resection**
  – **Increased risk of breast cancer in EITHER breast**
» **Ductal carcinoma in situ**
  – **Stage 0 breast cancer**
  – **Treated more similarly to other stages of breast cancer**





Invasive Breast Cancer

» **Breast Cancer Staging**
  – **T: Tumor size**
    - **T1: 0-2 cm**
    - **T2: 2-5 cm**
    - **T3: >5 cm**
    - **T4: inflammatory breast cancer, breast cancer involving skin or muscle**
  – **N: Lymph node status**
  – **M: Metastasis**

Invasive Breast Cancer

- Staging previously based on T, N, M only
  - Now includes other factors
    - Estrogen/Progesterone receptor
      - Naturally occurring hormones that may fuel cancer growth
    - Her-2 Neu status
      - Tumor growth factor, indication of more aggressive cancer
    - Tumor grade
      - 1: low 2: intermediate 3: high

Staging

- Stages I&II
  - Early stage breast cancer
  - Treated with combination of surgery, radiation therapy, chemotherapy and endocrine therapy
  - Can sometimes omit one or more treatments
    - Depends on patient age, how aggressive tumor is, other health problems

Staging

- Stage III
  - IN GENERAL, Locally advanced breast cancer or "unfavorable biology"
    - High grade, "triple negative"
    - Large tumors with lymph node involvement
    - Any size tumor with significant lymph node involvement
  - Often treated with chemotherapy first followed by surgery, radiation therapy and endocrine therapy

Staging

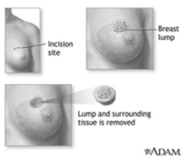
- Stage IV
  - Metastatic breast cancer
  - Usually treated WITHOUT surgery
    - Except in cases of patients with long disease free interval
  - Not all metastasis is the same

How do we treat breast cancer

- Surgery
- Chemotherapy
- Radiation therapy
- Endocrine therapy

Surgery: lumpectomy

- Removes the tumor itself as well as a small margin of benign tissue
- Most often is performed in association with radiation therapy
  - Radiation sometimes omitted in women >age 75
- Also known as "breast conserving surgery"
- No difference in survival compared to mastectomy



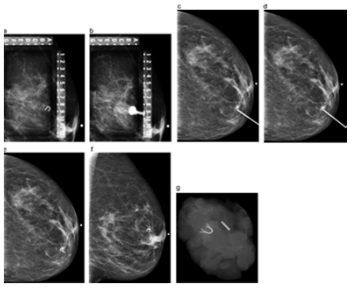
Contraindications to lumpectomy

Absolute

- **Pregnancy before 18wks**
- **Prior Radiation**
- **Diffuse areas of suspicious calcifications**
- **Inflammatory Breast Cancer**
- **Persistent + margins**

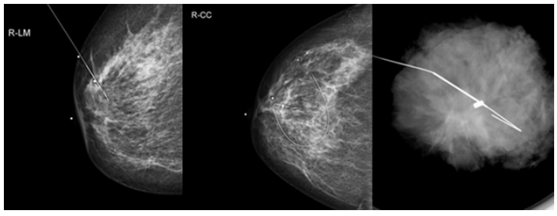
Surgery: lumpectomy

» **Seed localized lumpectomy**
  » **Radioactive seed placed in the breast at the site of the mass**



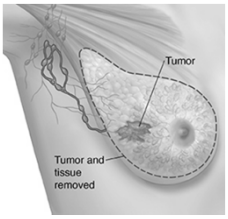
Surgery: Lumpectomy

» **Wire localized lumpectomy**
  » **Wire placed through the outside of the breast toward the site of the mass**

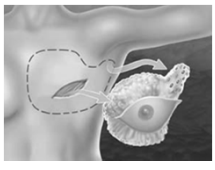


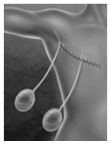
Surgery: mastectomy

» **Removes entire breast**
  – **Performed as nipple-removing or nipple-sparing**
» **Often performed with immediate reconstruction**
  – **Implant (85%) or tissue-based (15%) reconstruction**



Mastectomy





- **Removal of entire breast**

Mastectomy

Nipple Sparing

Skin Sparing

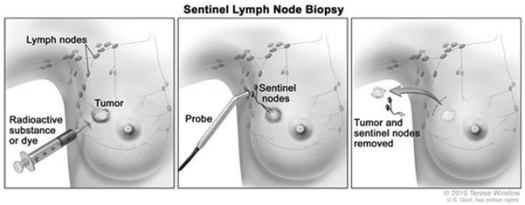
Lumpectomy vs Mastectomy

Institution	Years	#of pts	Overall Survival
Milan	73-80	348 (M)	41%
		352 (Q+RT	41% 20 yrs
NSABP B-06	76-84	590 (M)	47%
		629(L+RT)	46% 20yrs
NCI	80-86	116(M)	75%
		88 (L+RT)	77% 10 yrs
Insitut Gustave-Roussy	72-79	91(M)	65%
		88(L+RT)	73% 15 yrs

Surgery: Lymph node evaluation

- Breast cancer spreads first to lymph nodes
  - Considered regional spread of disease
- Lymph nodes evaluated clinically
  - If not enlarged, evaluated at time of surgery with sentinel lymph node biopsy

Sentinel lymph node biopsy



Nodes with the first and most direct connection to the place where the tracer was injected. If the sentinel node is removed and shows no signs of cancer, then the other lymph nodes rarely have any cancer.

Completion lymph node dissection

- Z0011 trial
  - T1-T2 tumors with clinically negative axilla on presentation, treated with breast conserving therapy
  - Majority of patients had systemic therapy and all received whole breast radiotherapy (RT)
  - No significant difference in overall or disease free survival in patients with 1-2 positive lymph nodes with or without axillary lymph node dissection

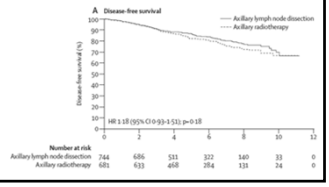
Completion lymph node dissection

- AMAROS trial
  - Women with T1 or T2 primary tumors
  - Treated with mastectomy or lumpectomy
  - 1 or 2 positive sentinel lymph nodes
  - Randomized to axillary radiotherapy vs axillary lymph node dissection
  - No significant difference in disease free survival or overall survival
  - Axillary radiation led to lower lymphedema

AMAROS TRIAL

	ALND	RadTx
Axillary Recurrence	.5%	1 %
Lymphedema	23%	11%

Median F/U 6.1 yrs



Standard of Care for Lumpectomy

- Clinically Stage I or II
  - Small tumors <5cm and clinically negative nodes

SLN Bx

Biopsy Negative
Or <2 positive
No further surgery

3 + nodes
AxDx

Standard of Care for Mastectomy

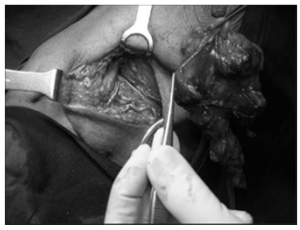
- Clinically Stage I or II
  - Small tumors <5cm and clinically negative nodes

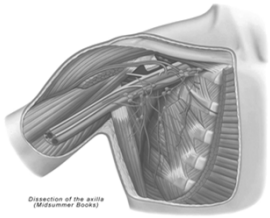
SLN Bx

Biopsy Negative
or ITC/micromet
No further surgery

+macromets
AxDx or RadTx

Completion lymph node dissection





Reasons for AxDx
1) Bulky Positive disease after chemotherapy
2) + nodes in mastectomy patients wanting to avoid Radtx
3) Multiple + nodes in patients undergoing lumpectomy

Complications of lymph node surgery

	SLN	Ax Dx
2yr Complications		
Seroma	4.5%	13.9%
Infection	2.7%	8.7%
10yr Complications		
Paresthesia	10%	33%
Lymphedema	5.4%	18%

Wernicke et al, Am J Clin Oncol 2011

Complications

Webbing

Seroma

Lymphedema

Nerve injury
(Winging)

Myth of the lymph node surgery

- Patients with history of lymph node surgery, limited evidence to support AVOIDING
  - Venipuncture
  - Limb constriction (blood pressure)
  - Elevation
  - Heat/cold
  - Air travel
- J Am Coll Surg 2011 Oct; 231 (4)

Myth of the lymph node surgery

- Patients with history of lymph node surgery, GOOD evidence to support
  - Maintaining normal body weight/avoiding weight gain
  - Participating in supervised exercise regimen

- J Am Coll Surg 2011 Oct; 231 (4)

Radiation Therapy

- Reduces the risk of breast cancer recurrence regionally
- Helps to omit the need for axillary lymph node dissection

Radiation Therapy

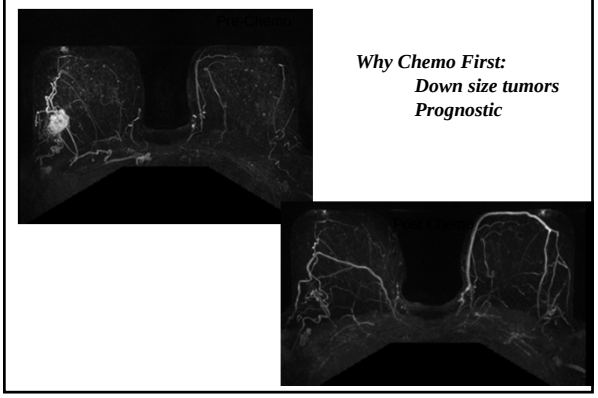
- ALWAYS offered following lumpectomy
  - Sometimes omitted in women >70 with low stage favorable tumors
- ONLY offered following mastectomy
  - Large tumors
  - Chest wall involvement, inflammatory
  - Positive lymph nodes

Chemotherapy

- Neoadjuvant chemotherapy
  - Aggressive, high grade tumors
  - Triple negative tumors
    - Estrogen receptor negative, progesterone receptor negative, Her-2-neu negative
  - Her2neu positive tumors

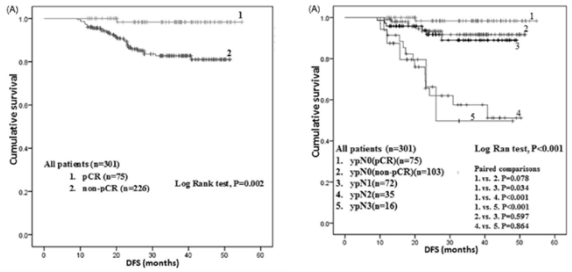
Chemotherapy

- Neoadjuvant chemotherapy
  - Does not improve survival compared to adjuvant chemotherapy
  - Does help to downstage tumor especially if breast conserving surgery desired
  - Can help to convert "positive" lymph nodes to "negative" lymph nodes
  - Can be important prognostically
    - Able to observe tumor in vivo



Why Chemo First:
Down size tumors
Prognostic

Response to chemotherapy is predictive of survival



Curr Oncol, Vol. 20, pp. e180-192;

Chemotherapy

- **Adjuvant chemotherapy**
  - **Her2neu tumors >0.5 cm**
  - **Triple negative tumors >0.5 cm**
  - **Hormone receptor positive tumors with multiple positive lymph nodes**
  - **High grade tumors**

Chemotherapy

- **Adjuvant therapy**
  - **Hormone receptor positive tumors without multiple positive lymph nodes**
    - **Molecular testing**
      - **Oncotype**
      - **Mammaprint**
      - **Prosigna**

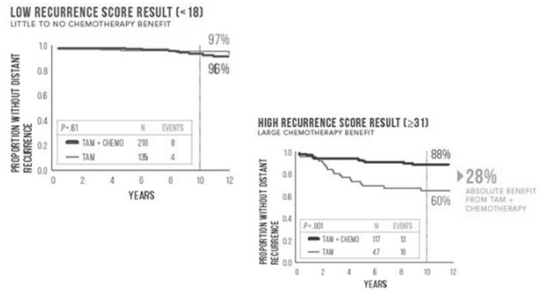
Estrogen + Tumors

Oncotype DX™ 21-Gene Recurrence Score (RS) Assay

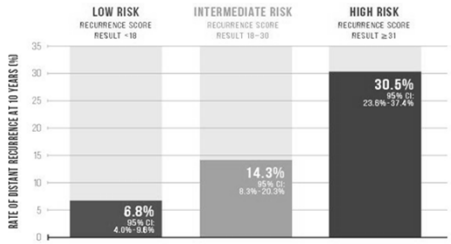
PROLIFERATION	ESTROGEN		
Ki-67	ER		
STK15	PR		
Survivin	Bcl2		
Cyclin B1	SCUBE2		
MYBL2			
	GSTM1	BAG1	
INVASION	CD68		
Stromelysin 3			
Cathepsin L2			
HER2	REFERENCE		
GRB7	Beta-actin		
HER2	GAPDH		
	RPLPO		
	GUS		
	TFRC		

Category	RS (0-100)
Low risk	RS <18
Int risk	RS ≥18 and <31
High risk	RS ≥31

Predicts Chemotherapy Effect For ER+ Tumors



RS predicts risk of systemic recurrences.



Tailor-X trial

- Hormone receptor positive, Her-2-neu negative
- Intermediate score (11-25) oncotype randomized to hormonal therapy only vs hormonal therapy plus chemotherapy
- Invasive disease free survival similar in both groups
- Overall survival similar in both groups

Tailor-X trial

- Chemotherapy may be avoided in 70% of women with hormone receptor positive, HER2-negative, node negative breast cancer
  - Older than 50 with recurrence score of 11-25
  - Any age with recurrence score of 0-10
  - ≤50 with recurrence score of 11-15
- Consider chemotherapy for remaining 30% of women
  - Any age with recurrence score 26-100
  - ≤50 with recurrence score 15-26

Hormonal Therapy

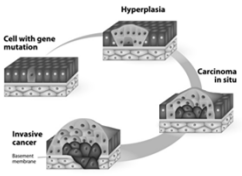
- Offered to women with estrogen or progesterone receptor positive breast cancer
- Reduce recurrence and new primary breast cancer
- Duration 5-10 years based on original prognosis, side effects, potential for toxicity
- Postmenopausal women
  - Aromatase inhibitor therapy
  - Tamoxifen

Hormonal Therapy

- Premenopausal Women
  - High risk
    - Ovarian suppression plus exemestane
      - Based on results of SOFT and TEXT trials
        - Demonstrated improved disease-free survival when ovarian suppression combined with aromatase inhibition
  - Risk features not present
    - Tamoxifen as single therapy

Why does breast cancer develop?

- Cancer occurs from a buildup of mutations in critical genes
  - Genes that control cell growth or division
  - Genes that repair damaged DNA
- These mutations allow cells to grow and divide uncontrollably
- A tumor is formed



Why does breast cancer develop?

- Somatic mutations
  - Acquired mutations in genes
  - Not inherited
- Genetic mutations
  - GERMLINE mutations
    - Inherited from a parent
  - In patients with genetic mutations, environmental and lifestyle factors contribute to development of breast cancer

Why does breast cancer develop?

» **Environmental/Lifestyle (Somatic) Causes**
  – **Obesity, estrogen exposure, alcohol exposure, advancing age, radiation exposure**
» **Genetic causes**
  – **Less than 10% of breast cancer**
  – **BRCA1/BRCA2 mutation**
  – **PTEN, CHD1, TP53, STK11 mutations**

High Risk Factors

- **BRCA mutation : lifetime risk 56-85%**
- **Other Genetic Mutations:**
  – **CDH1,ATM, PALB2, CHEK2**
- **Family History (primarily first degree)**
- **Radiation Exposure**
- **LCIS, ADH, ALH**

Gail Model

<u>Model for annual risk of breast cancer</u>

- **Age/race**
- **Family history**
- **Age at first birth and menarche**
- **Number of breast bx**
- **Hx of atypia**

Risk reduction strategies considered if >1.7 % 5-yr risk

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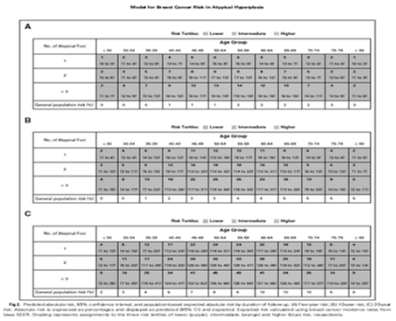
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Model for Predicting Breast Cancer Risk in Women With Atypical Hyperplasia

Amy C. Degnim, Stacey J. Winham, Ryan D. Frank, V. Shane Pankratz, William D. Dupont, Robert A. Vierkant, Marlene H. Frost, Tanya L. Hoskin, Celine M. Vachon, Karthik Ghosh, Tina J. Hieken, Jodi M. Carter, Lori A. Denison, Brendan Broderick, Lynn C. Hartmann, Daniel W. Visscher, and Derek C. Radisky



Risk Reduction Interventions

- **Chemoprevention (reduction of 50-86%)**
  – **Tamoxifen**
  – **Raloxifene**
- **Increased Screening (MRI/Mammo q 6 mons)**
- **Bilateral Mastectomy**
- **Lifestyle**
  – **HRT**
  – **Alcohol consumption**
  – **Exercise**
  – **Weight**

Benefit of screening mammography

Invitation to screening mammography results in a reduction in breast cancer mortality of approximately 20%

History of Screening Mammography Guidelines

Year	Organization(s)	Recommendation
1980	ACS	Baseline 35-40 Annually ≥ 50
1987	ACS, AMA,NCI, ACOG, ACS,	Baseline 35-40 (dropped in 1992) Every 1-2 years 40-49 Every year ≥ 50
1996	USPSTF	Every 1 to 2 years 50-69 (A rating) Individual choice ≥70 (C rating)
1997	ACS	Every year starting age 40, continuing while woman is in good health
2002	USPSTF	Every 1 to 2 years ≥ 40 (B rating)

American Cancer Society Breast Cancer Screening guidelines October 2015

- **Women with average risk should undergo regular screening mammography starting at age 45 (Strong recommendation)**
- **Women aged 45 to 55 should be screened annually (Qualified recommendation)**
- **At age 55, begin to transition to biennial screening or have the opportunity to continue annual screening (Qualified recommendation)**

American Cancer Society Breast Cancer Screening Guidelines October 2015

- **Women should have the opportunity to begin annual screening at age 40** ***(Qualified recommendation)***
- **Continue screening as long as woman is in good health with a life expectancy of at least 10 years** ***(Qualified recommendation)***
- **Does not recommend clinical breast exam for average risk women (***Qualified recommendation)*

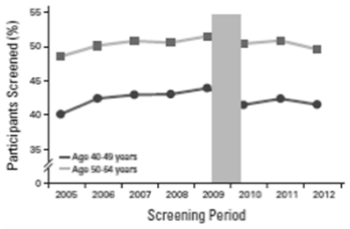
Screening recommendations United States Preventive Services Task Force (USPTF) 2016

- **Screening mammography biennial: age 50 -74 (Grade B recommendation)**
- **Against routine screening mammography for women 40-49 (Grade C recommendation)**
- **Insufficient evidence to recommend for or against screening mammography for women > 74**

Meta-analysis of screening trials
–mortality reduction by age

- **15% women 40-49**
- **14% women 50-59**
- **32% women 60-69**

Mammography Rates after USPSTF 2009



Wharamet al JCO 2015;33:1067

Annals of Internal Medicine | Clinical Guidelines

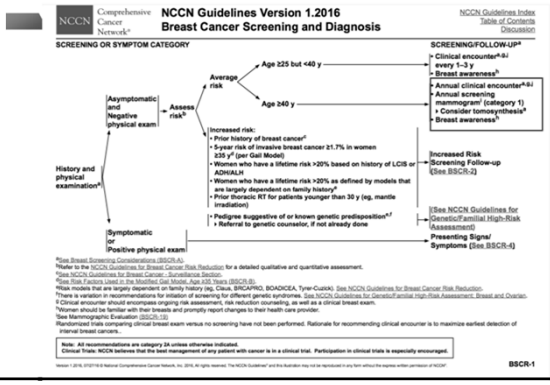
Screening Mammography in Women 40 to 49 Years of Age: A Systematic Review for the American College of Physicians

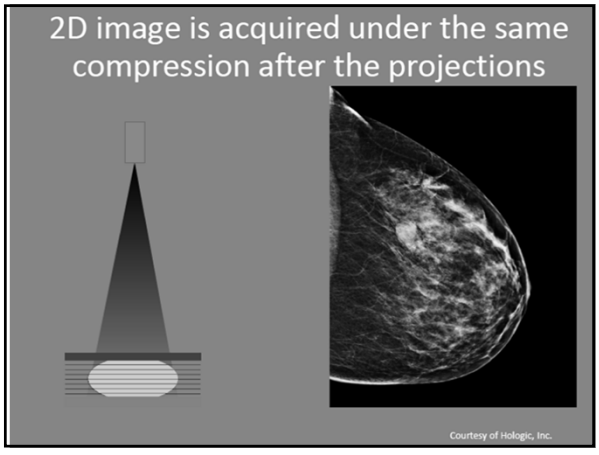
Armstrong et al Ann Int Med 2007;146:516

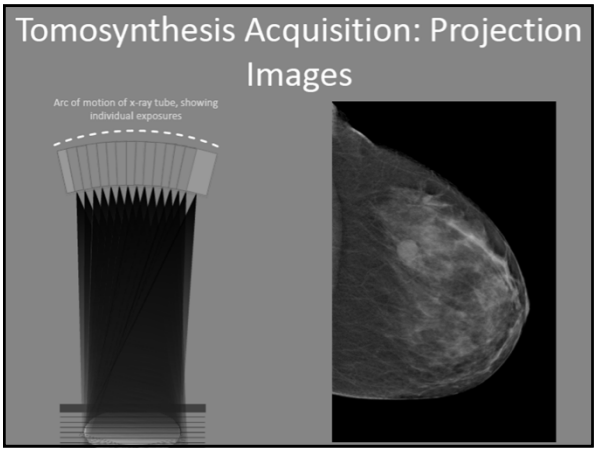
- Mortality reduction 7% to 23%
- Cumulative risk of false positive 20% to 56% after 10 mammograms

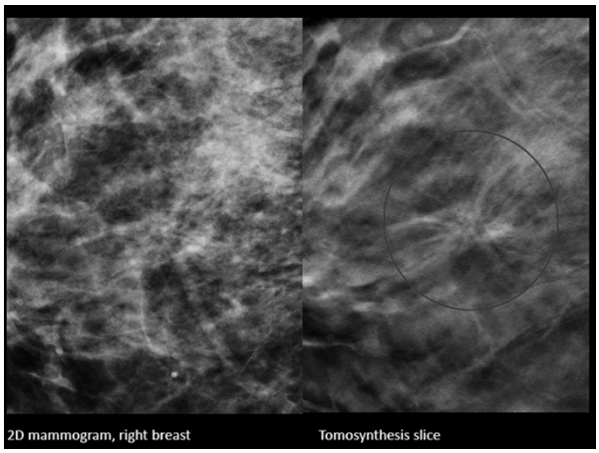
Current Guidelines

- Annual starting at 40 (NCCN, ACOG, ACR)
  - costs $4 billion/yr
- Biennial age 50-74 (USPSTF)
- Annual starting 45-55, over 55 biennial (ACS)
  - costs $3.6 billion/yr









» **Thank you very much for your time!**

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