

Survivorship

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Overview

Issues to be addressed:

- ◆ Risk of disease recurrence
- ◆ Risk of associated malignancies
- ◆ Risk of late sequelae associated with treatment
- ◆ Impact on family members
- ◆ Psychiatric / psychosocial issues of survivorship

Disease Recurrence

■ Risk

- ◆ dependent on stage and tumor pathologic factors
- ◆ Sites of recurrence depend on tumor type
 - ◆ Breast – bone, liver, lung
 - ◆ Colon- liver
- ◆ Newer tools to help assess recurrence risk and impact of treatment

Breast:

- ◆ Adjuvantonline!
- ◆ Oncotype dx

Prognostic Factors - Breast

- Tumor size
- Lymph node status (#)
- Tumor grade
- Hormone receptor status
- Over expression of Her-2 neu
- Age
- Other factors
 - ◆ S phase / Dna index / Ploidy
- Gene array profiling – Stage I-II, Node -, ER+
- Circulating Tumor Cells – metastatic dx.

Oncotype DX™ Technology: Final Gene Set

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

HER2

GRB7
HER2

ESTROGEN

ER
PGR
Bcl2
SCUBE2

GSTM1

INVASION

Stromelysin 3
Cathepsin L2

CD68

BAG1

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

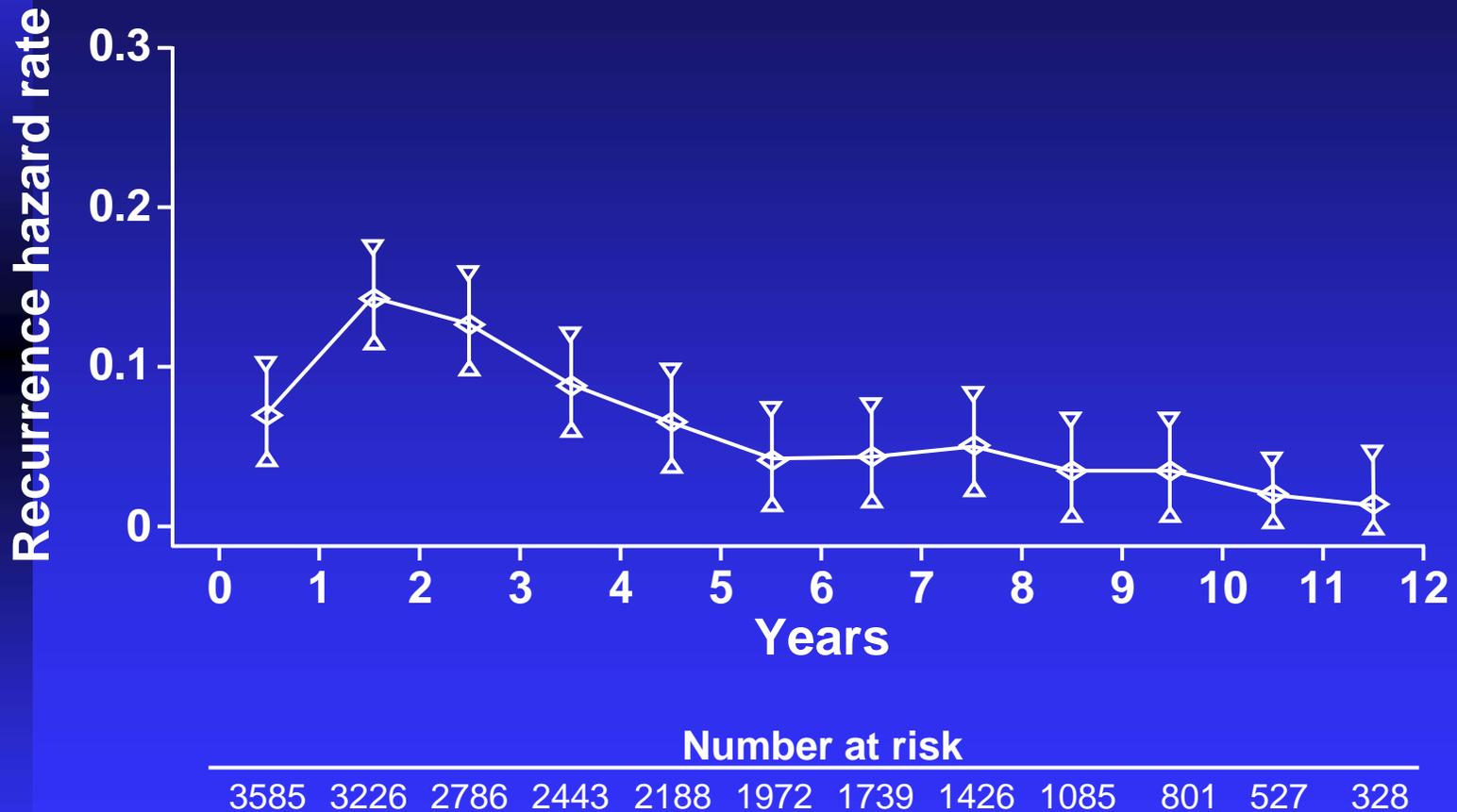
Oncotype DX™ Clinical Validation:

B-14 Results – DRFS (cont)

<u>Risk Group</u>	<u>% of Patients</u>	<u>10-yr Rate Recurrence</u>	<u>95% CI</u>
Low (RS <18)	51%	6.8%	4.0%, 9.6%
Intermediate (RS 18-30)	22%	14.3%	8.3%, 20.3%
High (RS ≥31)	27%	30.5%	23.6%, 37.4%

Test for the 10-year DRFS comparison between the low and high risk groups
p <0.00001

Recurrence Hazard Rates for Breast Cancer After Primary Therapy



Management of Recurrence Risk

Risk Modification

Adjuvant therapy – chemotherapy, hormone rx
Chemoprevention- Tamoxifen
Lifestyle modification - ????

Surveillance

Goal: Cure or Palliation

Cure – local recurrence, isolated metastasis

Palliation – diffuse metastasis

Guidelines: NCCN Guidelines

Examples:

Breast Cancer

Colon Cancer

Surveillance for Disease Recurrence

TESTS:

X-rays, CT's, MRI's, PET scan,

Nuclear studies – bone scans, CEA scans

Tumor markers:

Breast – ca27-29

Colon - cea

Ovarian- ca125

Prostate – PSA

Others

Molecular genetic markers (p53, Kras)

Surveillance for Disease Recurrence

Breast Cancer - “Minimalism”

Surveillance for Disease Recurrence

Colon Cancer - “Intensivist”

Risk of Secondary Malignancies

Malignancies due to treatment

- ◆ Carcinogenicity of individual treatment modality varies

Associated Malignancies

- ◆ Shared environmental exposures

Hereditary Syndromes

Aging process

Secondary Malignancies - Impact

- **# Cancers diagnosed 1998** **1,200,000**
 - **# 2nd cancers / all cancers** **6.6%**
 - **Estimated 2nd cancers 1998** **80,000**
- ∴ 5th most common “Cancer”**

Fred Li, ASCO 1998

Secondary Malignancies - Effects of Treatment

- Combination Therapy
- SARCOMA – XRT
- Bladder Cancer – Cyclophosphamide
- Endometrial Cancer - Tamoxifen
- AML - CHEMOTHERAPY
 - ◆ Topo II Inhibitors (Etoposide, Adria)
 - ◆ Short Latency
 - ◆ Alkylating Agents
 - ◆ Latency > 5 years

Risk of Secondary Malignancies

- Varies with agent used
- Varies with total dose, duration of exposure, time of exposure in life cycle
- Endometrial Cancer & Tamoxifen use:
 - ◆ Ever use – RR 1.5
 - ◆ ≥ 5 years – RR 6.6

Risk of Secondary Malignancies

- Risk of Leukemia based on cumulative dose of platinum, duration of Rx, & specific agent

<u>Dose</u>	<u>RR</u>	<u>Duration</u>	<u>RR</u>
<500mg	1.9	<6 month	1.2
500-749	2.1	6-12month	4.3
750-999	4.1	>12 month	7.0
>1000	7.6		

<u>Specific Drug</u>	<u>RR</u>
Cisplatin	3.3
Carboplatin	6.5
Both	9.0

Travis et al. NEJM 1999;340:351

Risk of Secondary Malignancies

- Risk of secondary cancer in 1253 patients with Hodgkin's Disease according to age at start of treatment, type of 2nd cancer & age at dx of HD

<u>All Malignancies</u>	<u>observed cases</u>	<u>RR</u>
≤20	28	13.3
21-30	61	8.2
31-39	48	4.9
<u>Solid Tumors</u>		
≤20	25	13.9
21-30	43	6.5
31-39	38	4.2
<u>Breast Cancer</u>		
≤20	9	16.9
21-30	12	5.6
31-39	6	2.4
<u>Leukemia</u>		
≤20	2	27.6
21-30	14	7.3
31-39	2	9.3

Risk of Secondary Malignancies

- Risk of Bladder Cancer & cumulative dose & duration of cyclophosphamide

<u>Cumulative Dose</u>	<u>Cases</u>	<u>RR</u>
<20 grams	8	2.4
20-49	5	6.3
<u>≥50</u>	5	14.5
 <u>Duration of Therapy</u>		
<1 year	8	2.5
1-2 yrs	3	3.7
>2 yrs	7	11.8

Causes of Hereditary Susceptibility to Breast Cancer

Gene	Contribution to Hereditary Breast Cancer
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<u>Brca1</u>	<u>20-40%</u>
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<u>Brca2</u>	<u>10-30%</u>
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<u>TP53</u>	<u><1%</u>
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<u>PTEN</u>	<u><1%</u>
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<u>CHK2</u>	<u><1%</u>
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<u>Undiscovered genes</u>	<u>30-70%</u>
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Hereditary Syndromes

Breast Cancer

BRCA1/2 - 60% lifetime risk 2nd breast cancer
20-60% lifetime risk ovarian cancer

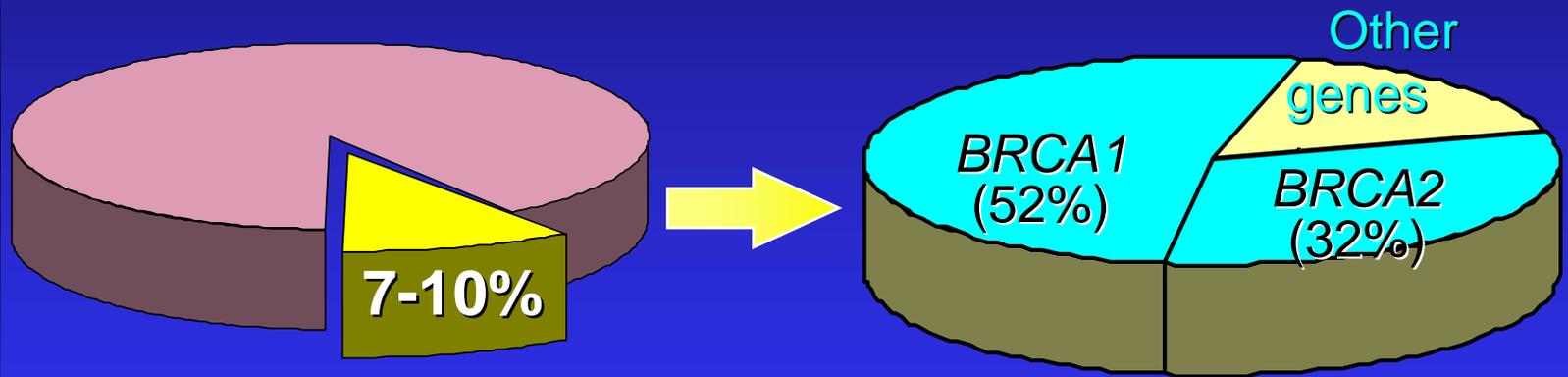
SPORATIC - 20% lifetime risk 2nd breast cancer

Retinoblastoma

HEREDITARY RB - 51% LR 2nd cancer by age 50

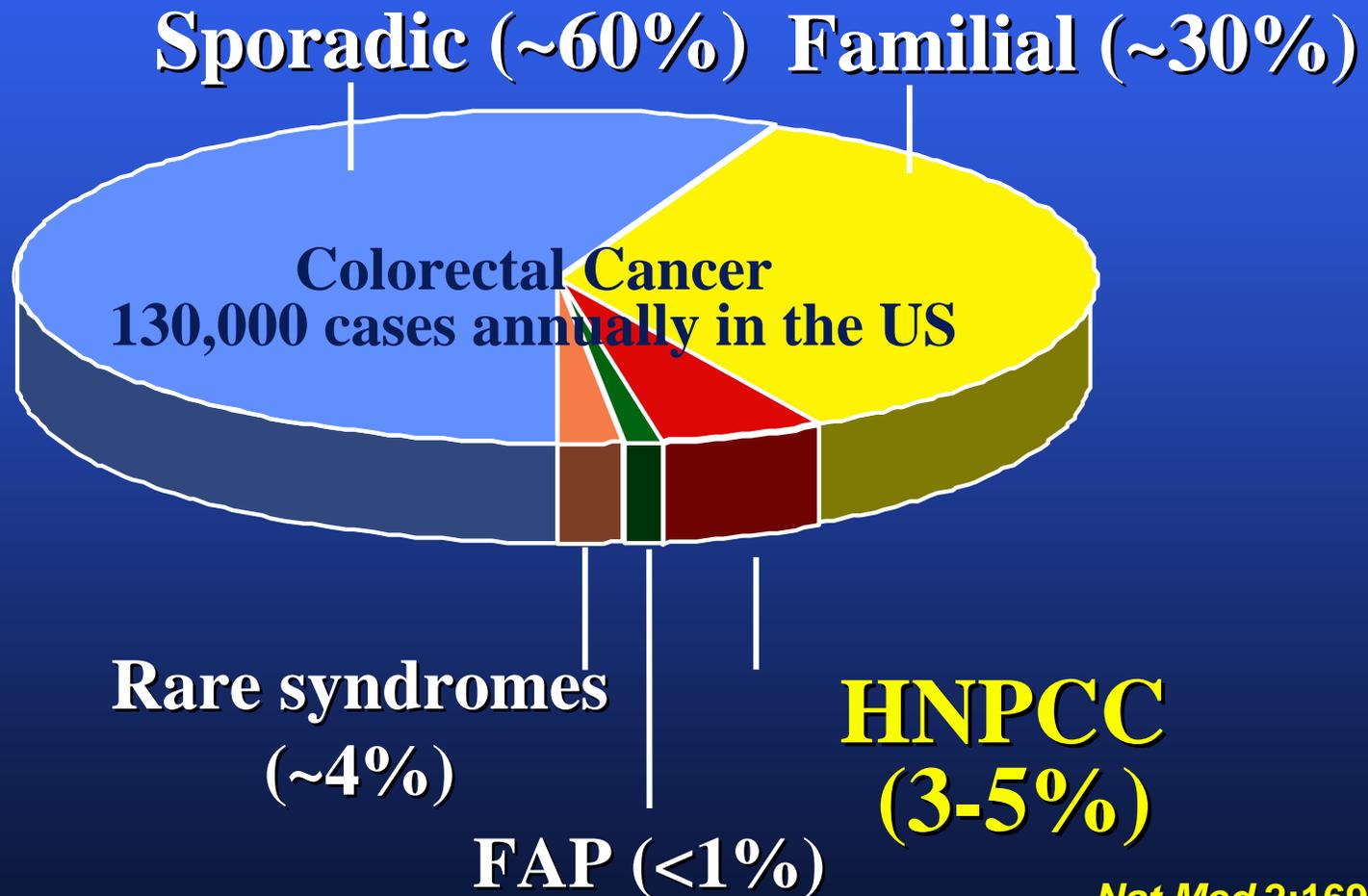
SPORATIC RB - 5% LR 2nd cancer

Hereditary Breast and Ovarian Cancer



- Sporadic
- Hereditary

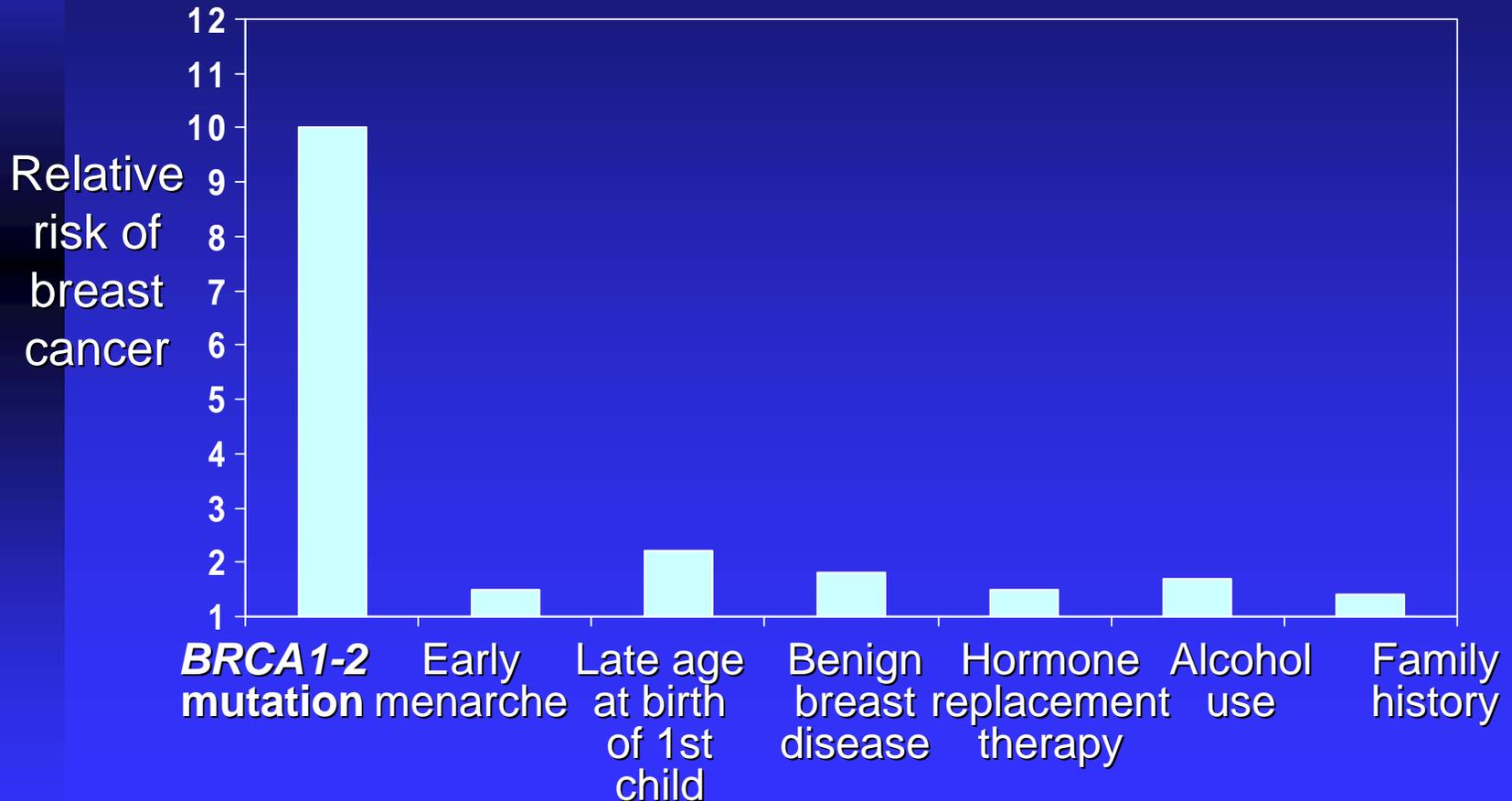
Colorectal Cancer – Hereditary Aspects



Risk of Colorectal Cancer (lifetime risk)

- General Population -----5%
- Personal Hx Colorectal Neoplasia-----15%
- Inflammatory Bowel Disease-----15-40%
- HNPCC Mutation-----70-80%
- FAP-----→95%

BRCA1-2 Mutations Increase the Risk of Cancer More Than Other Factors



Risk Associated with BRCA1/2

■ Breast Cancer

	Population risk	Carrier risk
By age 40	.5%	10-20%
By age 50	2%	33-50%
By age 70	7%	56-87%

■ Ovarian Cancer

1%	44% BRCA1
	27% BRCA2

Ford. Lancet 1994;343:692-695

Struewing. NEJM 1997;336:1401-1408

Easton. AJHG 1995;56:265-271

BRCA1 and BRCA2 Mutations Increase the Risk of a Second Cancer

- Increased risk of ovarian cancer following breast cancer
 - ◆ 10-fold increase in risk compared to women without mutations
 - ◆ lifetime risk is at least 16%
- Increased risk of contralateral breast cancer
 - ◆ 20% (*BRCA1*) or 12% (*BRCA2*) within 5 yrs
 - ◆ Up to 64% (*BRCA1*) or 52% (*BRCA2*) by age 70
- Increased risk of new cancer in lumpectomy/xrt treated breast (not local recurrence)

JNCI 1999;15:1310-6
J Clin Oncol 1998;16:2417-25
Lancet 1998;351:316-21
J Clin Oncol 1999;17:3396-402
Lancet 1994;3343:692-5

Risks of Other Cancers

- Male breast cancer (*BRCA1*, *BRCA2*)
 - ◆ $\leq 6\%$ by age 70
- Prostate (*BRCA2*, possibly *BRCA1*)
 - ◆ 20% by age 80; 3- to 7-fold increase RR
- Pancreatic cancer (*BRCA2*)
 - ◆ 2-3% by age 80; 3- to 4-fold increase RR
- Colon
 - ◆ Little or no increased risk

Am J Hum Genet 1997;61: 120-8

JNCI 1999;15:1310-6

Dis Colon Rectum 1999;42:1041-5

HNPCC – Cancer Risk

	Population risk	HNPCC risk
<u>Colon</u>		
By age 50	0.2%	>25%
By age 70	2%	80%
<u>Endometrial</u>		
By age 50	0.2%	20%
By age 70	1.5%	60%

Gastroenterology 1996;110:1020-7

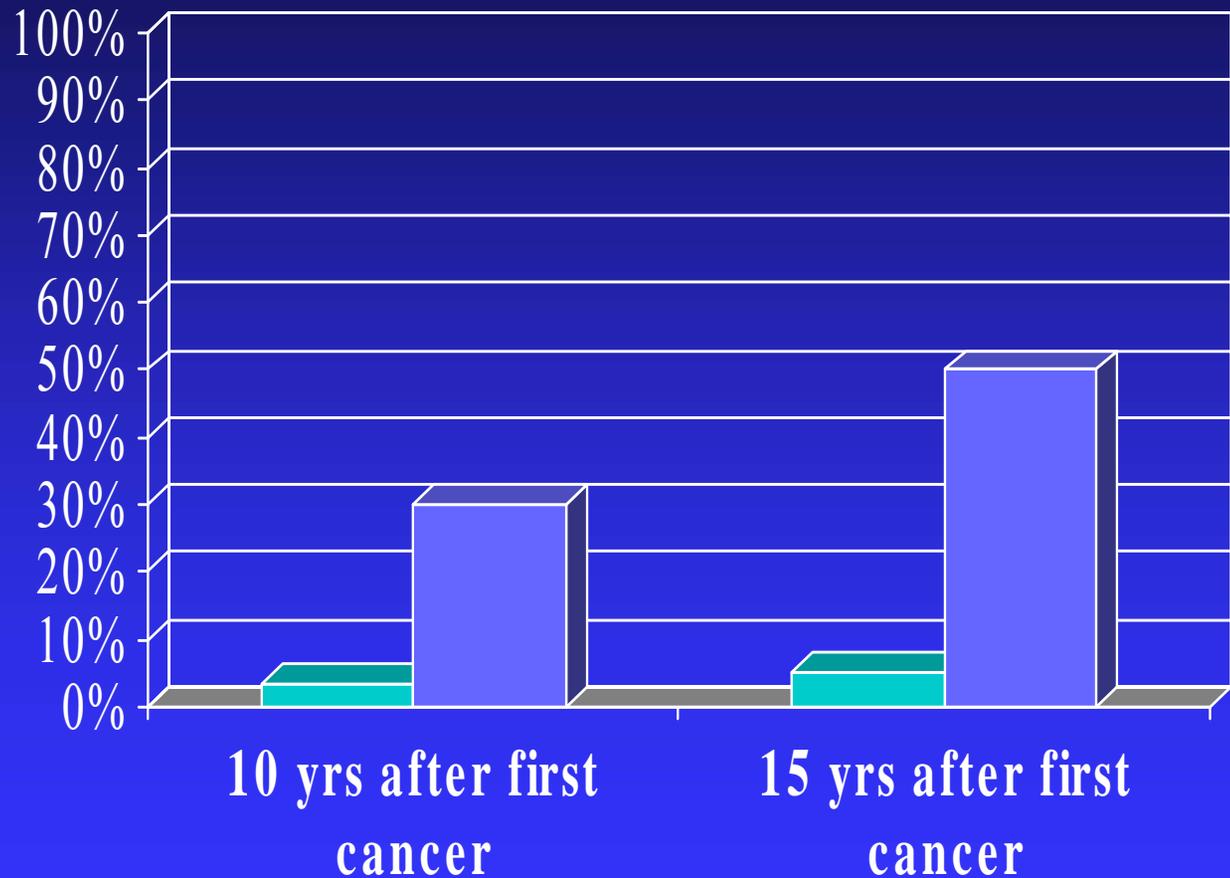
Int J Cancer 1999;81:214-8

HNPPC – Risk of other cancers

- Ovary
 - ◆ 12% by age 70
- Stomach
 - ◆ 13% by age 70
- Other
 - ◆ Urinary tract (4% by age 70)
 - ◆ Small intestine (100-fold relative risk, but < 5%)
 - ◆ Biliary tract (2% by age 70)
 - ◆ Brain (~4% by age 70)

HNPCC- Risk of Second Cancer

Percent
diagnosed with
a second
cancer



■ General Population ■ HNPCC

Cancer 1977;40:1849
Dis Colon Rectum
1993;36:388

Management of Hereditary Risk

- Early detection
- Chemoprevention
- Prophylactic surgery
- ??Lifestyle change

Preventive Strategies

■ Modifiable Risk Factors

- Diet
- Obesity
- Tobacco
- Etoh

■ Chemopreventive Strategies

For disease recurrence & 2ndary malignancies

- Breast
- Prostate
- Colorectal
- Cervix

Late Effects of Therapy

- Risks of late effects vary by tissue and age of patient at time of exposure
- Dose, modality & time specific
- Additive effect of combined modality Rx.
- Important for future management
 - ◆ Screening
 - ◆ Risk reduction strategies
 - ◆ Lifestyle changes
 - ◆ exposures

Late Effects of Treatment

- Fatigue
- Pain
- Menopausal symptoms
- Reproductive & fertility concerns
- Growth / development effects
- End-organ dysfunction
 - pulmonary toxicity
 - cardiac toxicity
 - neurotoxicity
 - nephrotoxicity
 - vascular toxicity

Late Effects of Surgery

- Limb Amputation
- Abdominal Surgery
- Lymphadenectomy (Breast, Melanoma)
- Splenectomy (HD)
- Pelvic Surgery (male & female effects)

Late Effects of Chemotherapy

- Cardiac (Anthracyclines, High dose C, Herceptin)
- Pulmonary (Bleomycin)
- Cns (Mtx)
- Peripheral Nervous System (Cisplatin, Vincas, Taxol)
- Renal (Cisplatin, Mtx)
- Hematologic (AML, MDS, Neutropenia)
- Gonadal

Late Effects of Radiotherapy

- Bone & soft tissue -- growth effects
- Dental / oral
- Eye
- Cardiovascular (HD)
- Pulmonary
- CNS
- Hematologic
- Gi / Gu

Fertility Effects of Therapy

- Planning for this issue needs to begin at time of diagnosis and treatment – when possible!!!
- Preservation of Fertility, hormone levels & sexual function
 - ◆ Choice of regimens
 - ◆ Gonadal shielding
 - ◆ Sperm/egg cryopreservation
 - ◆ Pharmacologic attempts to preserve fertility – lupron
 - ◆ Assisted reproductive techniques
- Outcomes of Pregnancy
 - ◆ No increased birth defects or genetic diseases in offspring conceived after cytotoxic therapy (baseline population level 4%)

Risk to Family Members

- Spectrum of cancers
- Risk due to extent of family history
- Hereditary cancer syndromes
 - ◆ Breast / ovary syndrome
 - ◆ Colorectal cancer syndromes
 - ◆ Role of genetic testing

When to Suspect Hereditary Factors

- Young age at onset
- Bilateral disease
- Multiple cancers in one organ
- Cluster of cancers in individual or family
 - ◆ Breast / Ovary – BRCA1
 - ◆ Breast/Ovary/melanoma/Pancreas – BRCA2
- Multiple generations affected
- Male breast cancer
- Precursor lesions

Benefits and Limitations

■ Benefits

- ◆ Provides risk information for individuals and families
- ◆ Provides information useful in health care
- ◆ Results alleviate uncertainty and anxiety

■ Limitations

- ◆ A negative result is most definitive if there is a known mutation in the family
- ◆ Some genetic variants are of unknown clinical significance

Guidelines for Cancer Predisposition Testing

- *American Society of Clinical Oncology: “Cancer predisposition testing should be offered when...”*
 - ◆ The individual has personal *or* family history features suggestive of a genetic cancer susceptibility condition
 - ◆ The results will aid in the diagnosis or influence the medical/surgical management of the patient *or* family members at hereditary risk of cancer