Physical Late and Long-Term Effects

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BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL
Mass General Brigham
Dana-Farber Cancer Institute
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Late and Long-Term Effects

- Late effects
  - Develop months to years after cancer treatment

- Long-term
  - Develop during treatment and continue for months to years following

Subsequent or Second Cancers

Subsequent Primary Cancers

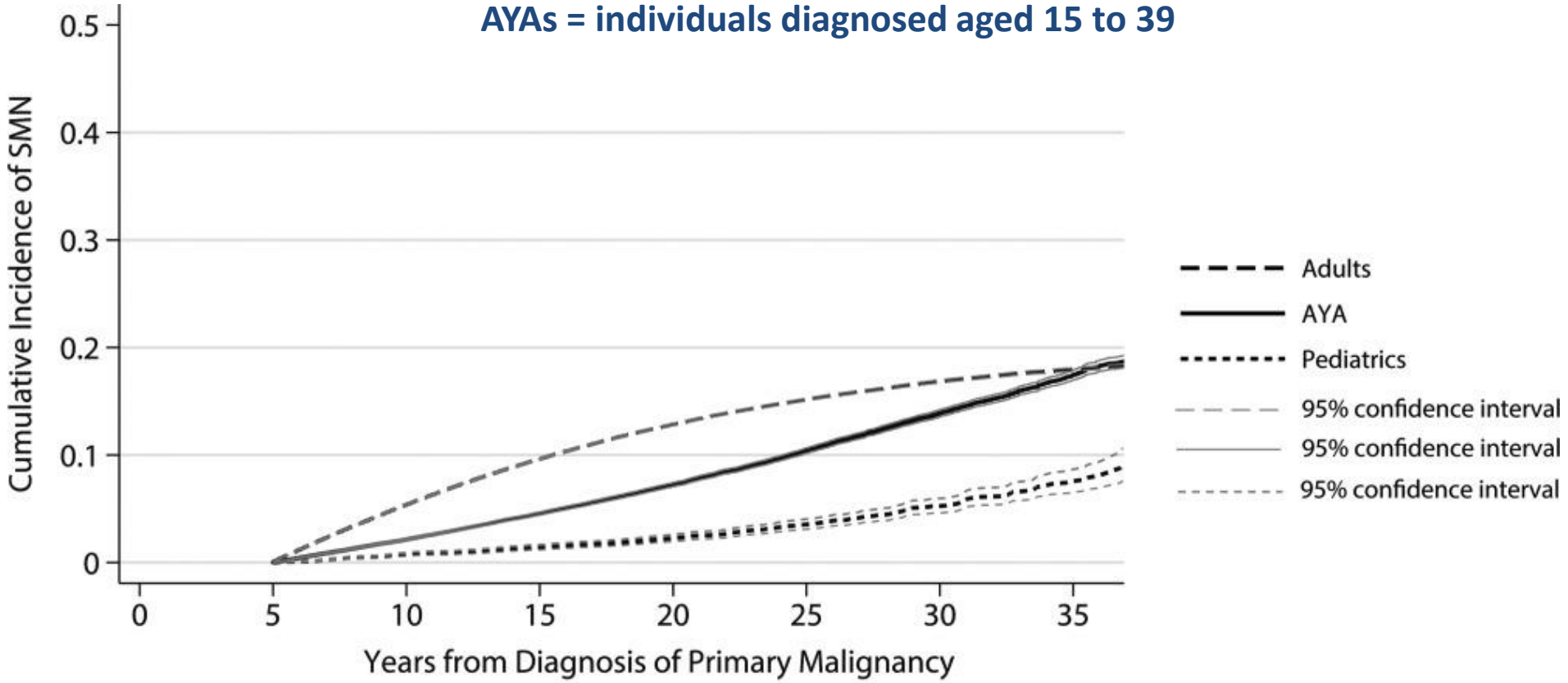
Using SEER data of 1.54 million cancer survivors (mean age, 60.4 years; 48.8% women), follow up 7.3 years.

- Male survivors (excluding those with prostate cancer)
  - Higher incidence (11%) and mortality (45%) from a subsequent primary cancer.
  - Most common subsequent cancers were lung, prostate, bladder/urinary, colorectal.
- Female cancer survivors
  - Higher incidence (10%) and mortality (33%) from a subsequent primary cancer.
  - Most common subsequent cancers were breast, colorectal, uterine.

Sung H et al. JAMA 2021

Increased risk of second malignant neoplasms in children and AYA survivors

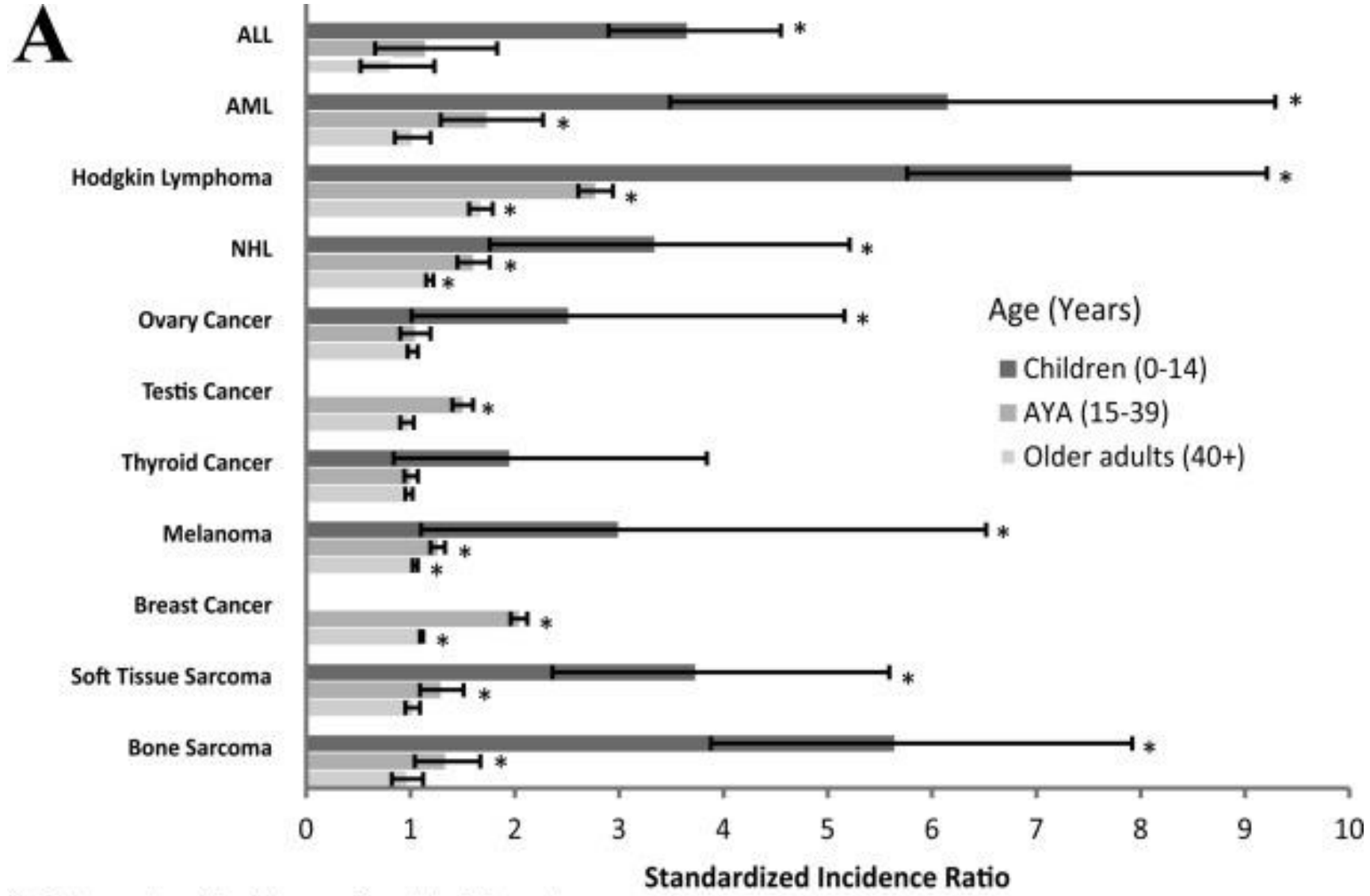
AYAs = individuals diagnosed aged 15 to 39



Persons at risk	10	20	30
Younger	7369	3734	1282
AYA	71429	34713	10228
Older	245611	66921	11590

Lee JS. Cancer 2016

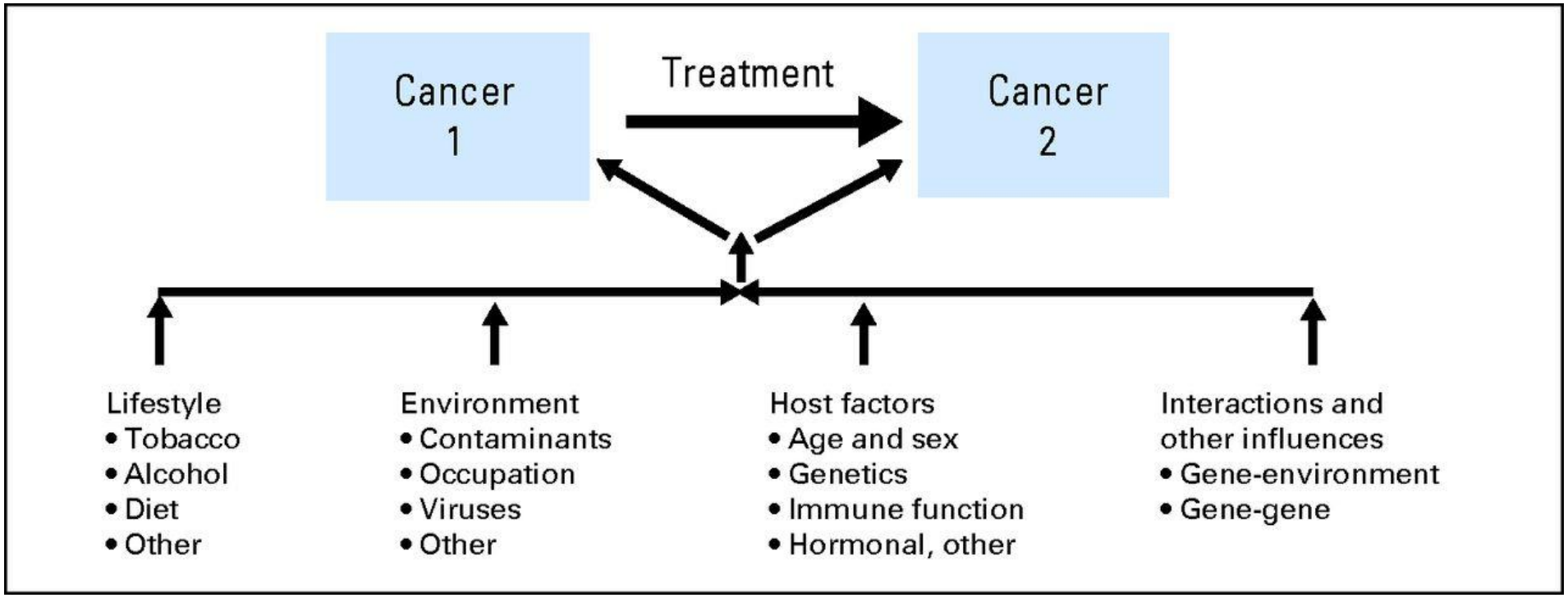
Increased risk of second malignant neoplasms in children and AYA survivors



$ - SMN occurring at least 5 years after original diagnosis
*p<0.05

Lee JS. Cancer 2016.

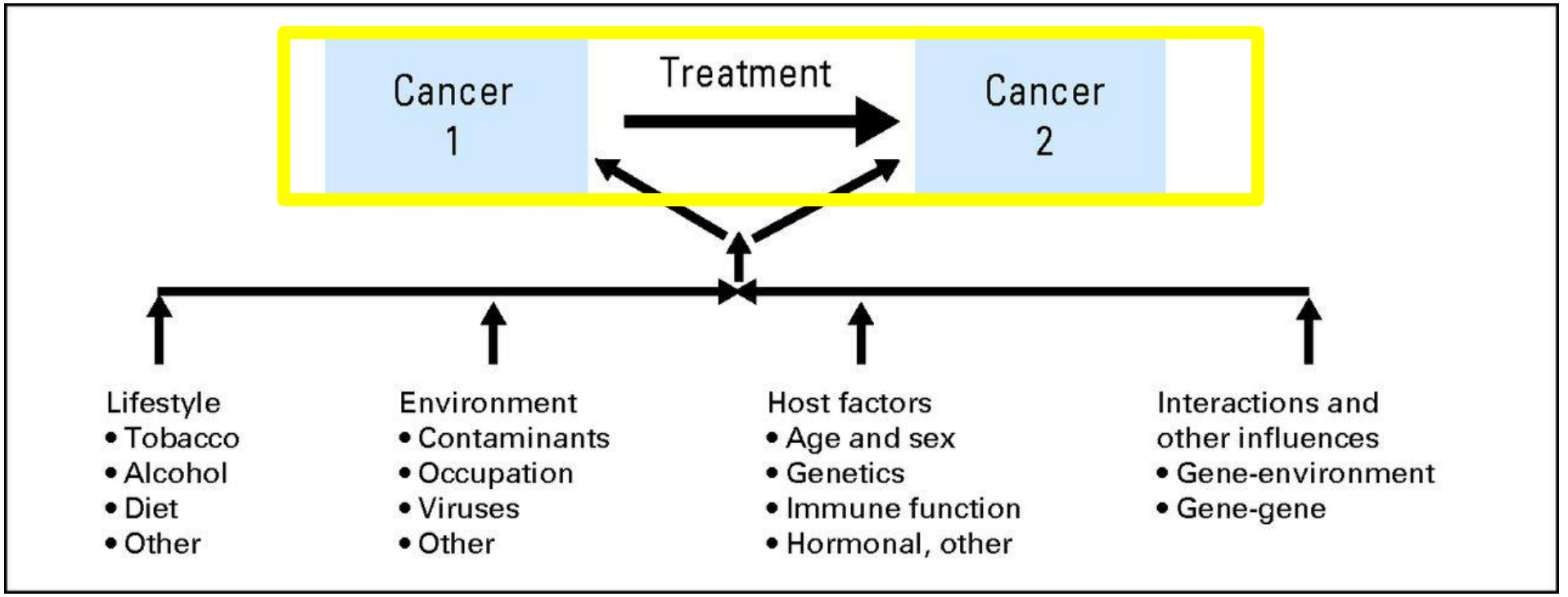
Multiple primary cancers etiologic factors



Wood M E et al. JCO 2012;30:3734-3745

JOURNAL OF CLINICAL ONCOLOGY

Multiple primary cancers etiologic factors



Wood M E et al. JCO 2012;30:3734-3745

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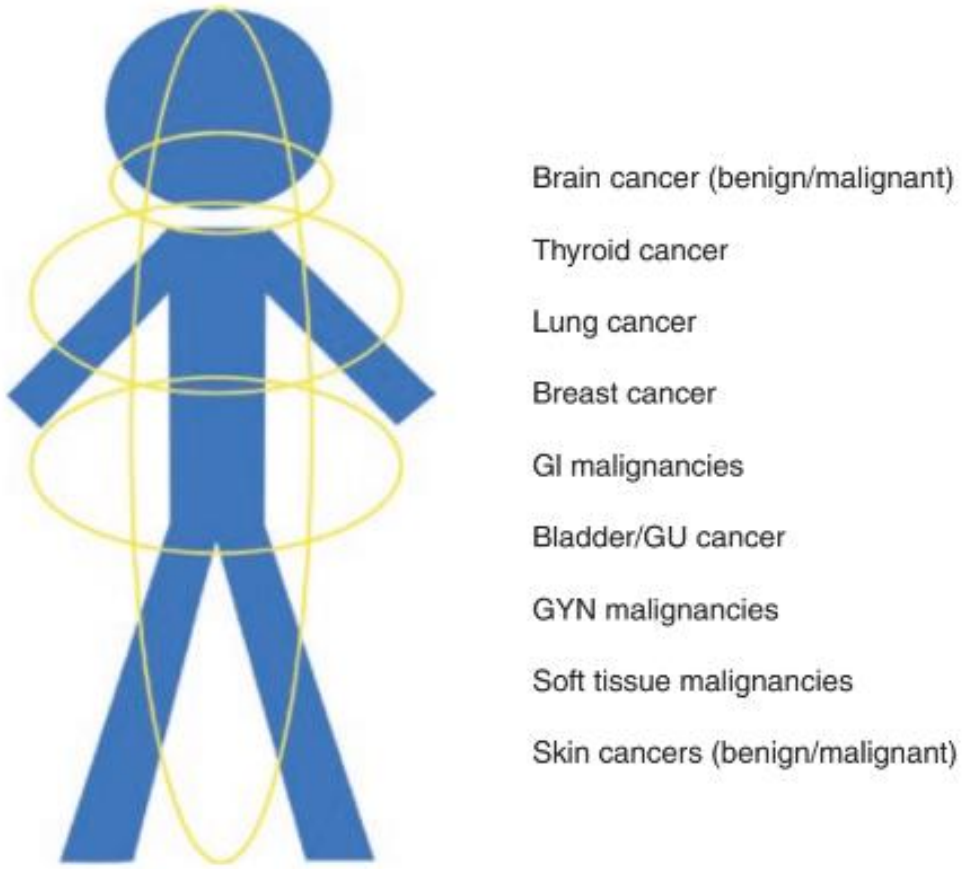
Treatment-Related Risks of Subsequent Cancers

- Chemotherapy
  - Early to late risk of leukemias, solid tumors
    - Type of drug
    - Higher drug doses
    - Longer treatment time
    - Higher dose intensity
- Radiation therapy
  - Most are not seen for at least 10 years after XRT
    - Dose of radiation
    - Area treated
    - Age at treatment
    - Chemotherapy
    - Smoking
    - Years since XRT

http://www.cancer.org/acs/groups/cid/documents/webcontent/002043-pdf.pdf

Radiation therapy and Subsequent Cancer



Brain cancer (benign/malignant)

Thyroid cancer

Lung cancer

Breast cancer

GI malignancies

Bladder/GU cancer

GYN malignancies

Soft tissue malignancies

Skin cancers (benign/malignant)

FIGURE 6.2 Subsequent cancers associated with radiation. Circles represent fields of radiation

Nekhlyudov et al. Caring for Patients Across the Cancer Care Continuum: Essentials for Primary Care. Springer 2019.

Screening For Subsequent Cancers

- Breast cancer screening if prior chest wall radiation as child
  - Earlier start for mammography – age 25 or 8 years post XRT whichever is later
  - Addition of breast MRI
- Colorectal cancer – start at age 30 if childhood XRT to abdomen
- Lung cancer
  - *?CT scan, especially for head/neck cancers and smokers*
- Thyroid – clinical examination, ?thyroid US
- Patients and physicians need to be vigilant about symptoms!!!

Non-cancer Late and Long-term Effects

Non-cancer late and long-term effects

Surgery

- Lymphedema
- Pain
- Functional limitations
- Sexual dysfunction
- Body image
- Infertility
- Ostomy

Non-cancer late and long-term effects

Chemotherapy (examples)

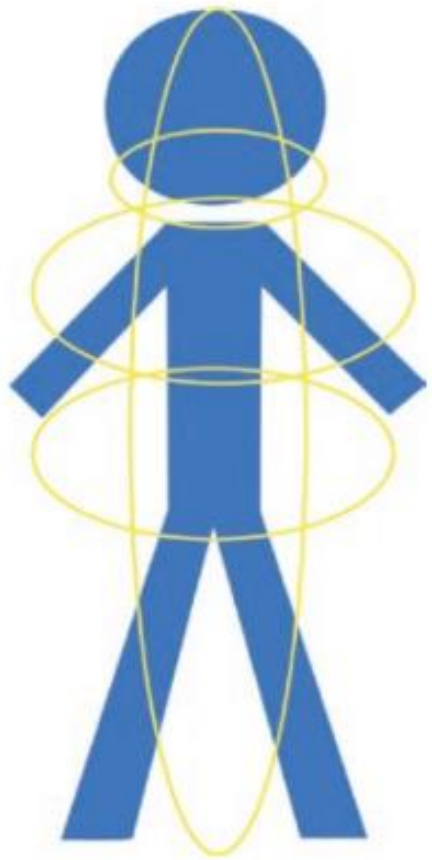
- Cardiac dysfunction (doxorubicin, daunorubicin, trastuzumab)
- Pulmonary fibrosis (bleomycin)
- Neuropathy (vincristine, vinblastine, paclitaxel, docetaxel, oxaliplatin, cisplatin)
- Hearing loss (cisplatin)
- Premature menopause, infertility (cyclophosphamide, nitrogen mustard)

Late and Long-Term Effects

Hormonal therapy

- Tamoxifen
  - Clotting, uterine cancer, hot flashes, vaginal dryness
- Aromatase inhibitors
  - Osteoporosis, musculoskeletal pain
- Androgen deprivation
  - Hot flashes, osteoporosis, metabolic syndrome, breast tenderness, reduced libido/ED, fatigue

Radiation therapy and Non-Cancer Effects

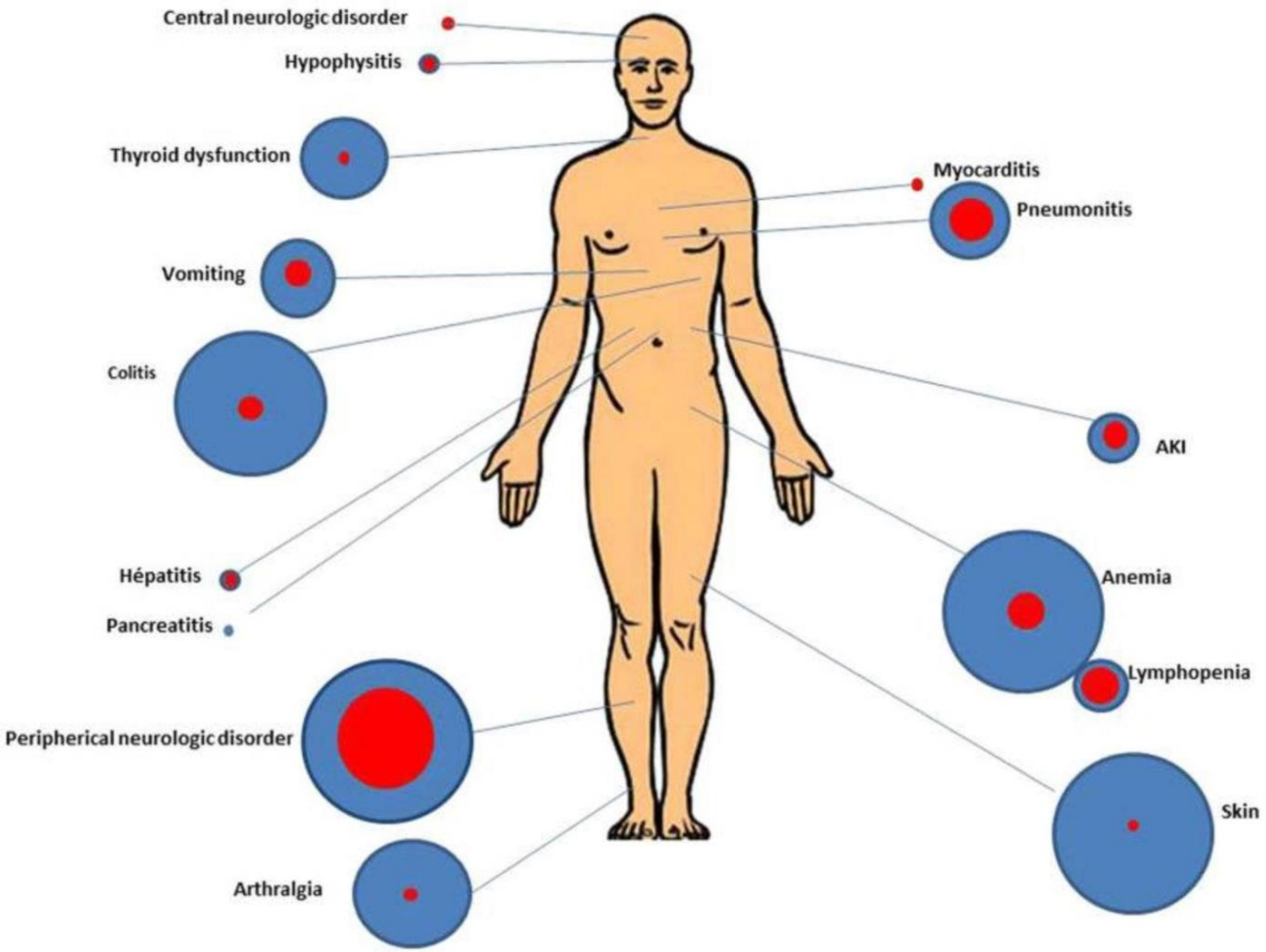


CNS vascular disease
Neurocognitive effects
CNS hormonal imbalances
Hypothyroid/nodules
Cervical/shoulder syndrome
Carotid stenosis
Neuropathy/plexopathy
Pulmonary fibrosis
Coronary/vascular/valvular disease
Gastritis/colitis/ileitis
Proctitis
Cystitis
Vaginal stenosis
Benign skin conditions

FIGURE 6.1 Secondary non-cancer effects associated with radiation. Circles represent fields of radiation

Nekhlyudov et al. Caring for Patients Across the Cancer Care Continuum: Essentials for Primary Care. Springer 2019.

Immunotherapy



https://www.cancer.gov/news-events/cancer-currents-blog/2019/cancer-immunotherapy-investigating-side-effects

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

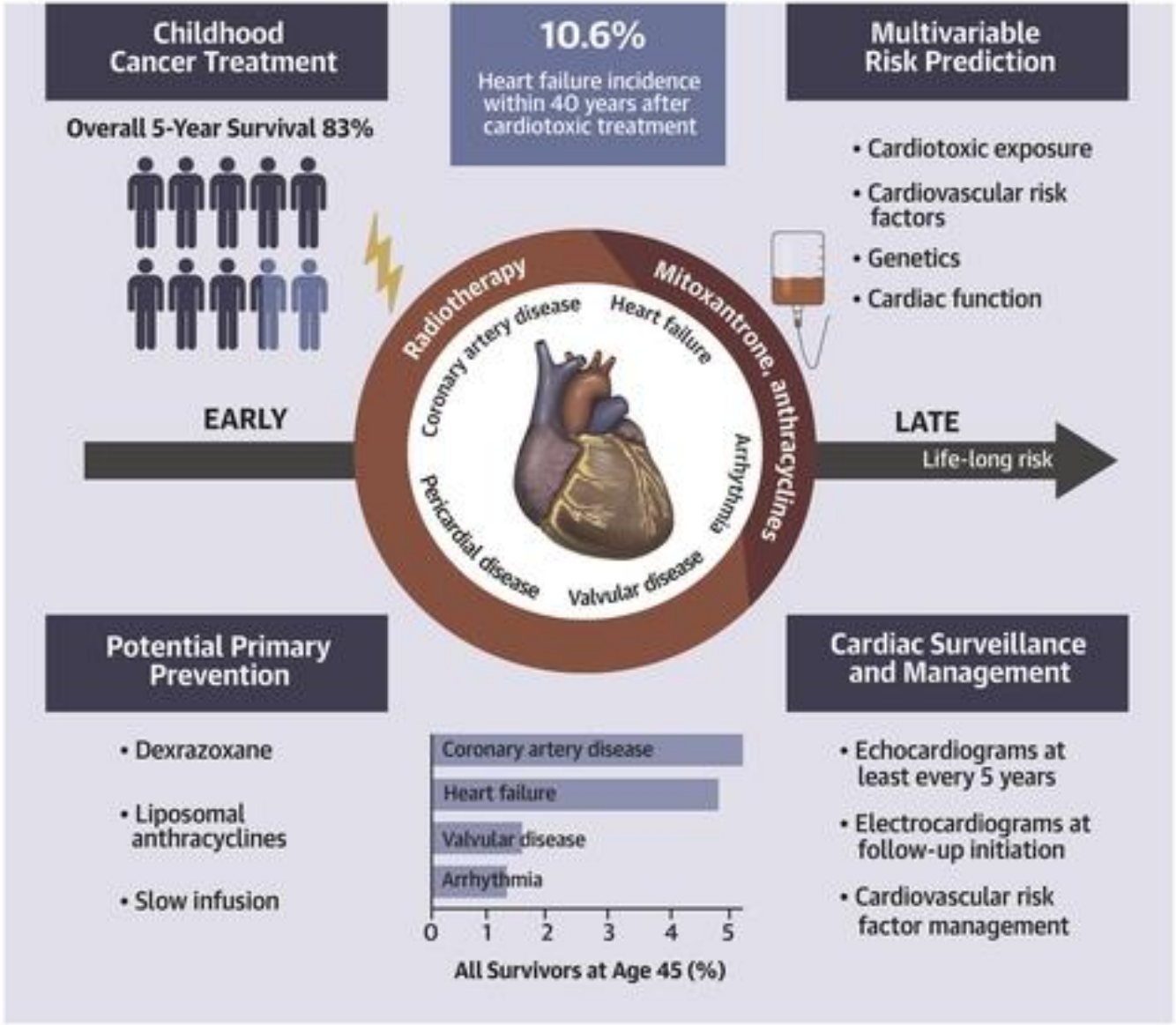
Condition	Survivors (N=10,397)	Siblings (N=3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

* For survivors, major joint replacement was not included if it was part of cancer therapy.
† For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.
‡ Values are for women only.

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Oeffinger et al. NEJM 2006

CENTRAL ILLUSTRATION: Overview of Clinical Practice in Childhood Cancer Survivors at Risk for Cardiotoxicity



Leerink, J.M. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):363-78.

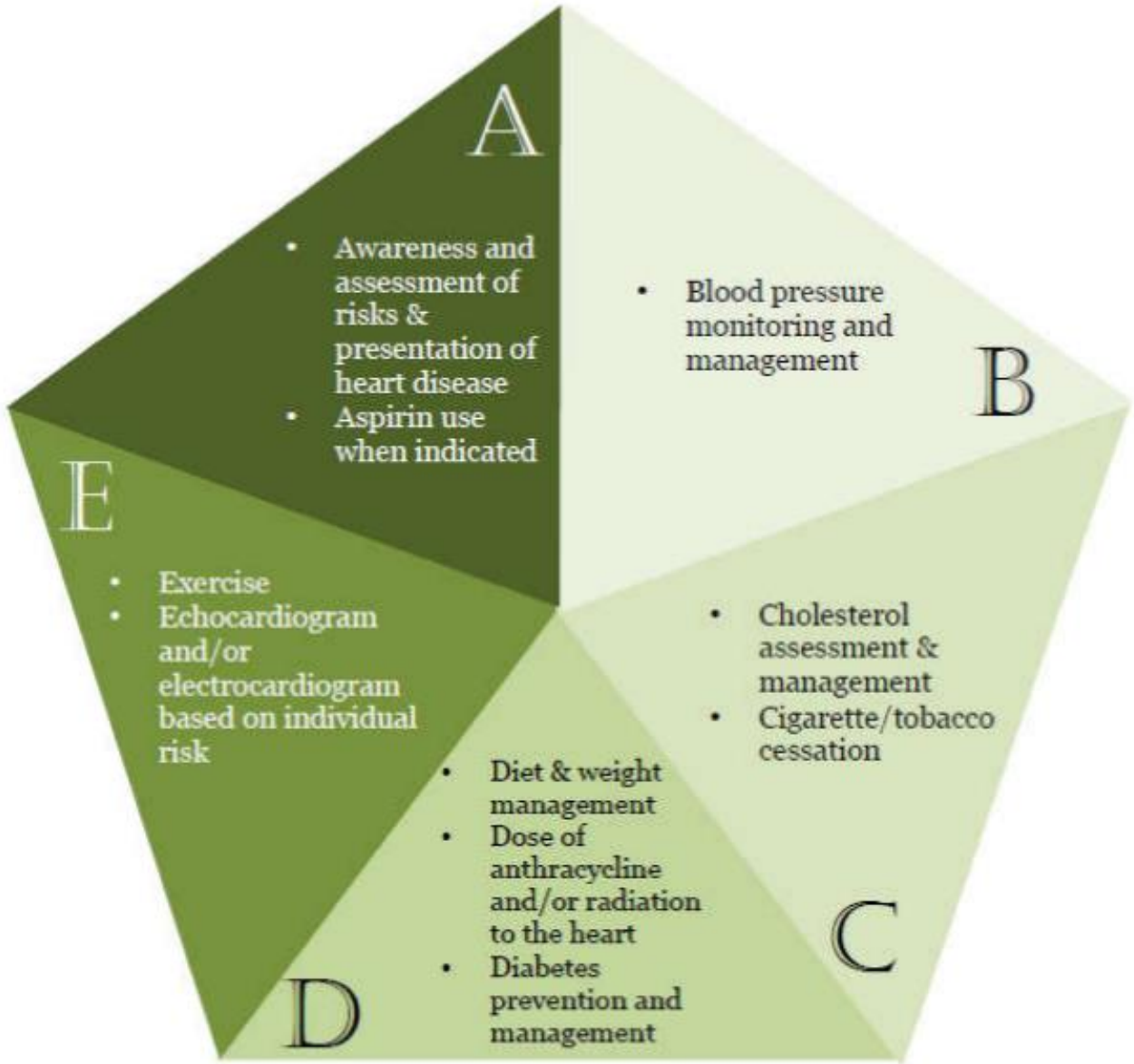


Figure 1. ABCDEs to promote Cardiovascular Health in Cancer Survivors.

Figure from Ruddy et al. Cancers **2020**, *12*(12), 3737

Surveillance: Systems Based Approach

Evaluate symptoms/physical exam/educate!

- CNS
  - Radiation
  - Chemotherapy

  → **Consider imaging**
- Visual
  - Radiation/prednisone

  → **Regular eye examinations**
- Endocrine
  - Radiation (CNS/thyroid)

  → **Consider labs (TSH/FT4), cortisol, GH, thyroid US, DEXA**
- Pulmonary
  - Radiation
  - Chemotherapy (bleomycin)

  → **Consider PFTs, CXR, ?Lung CT**
- Cardiovascular
  - Radiation
  - Chemotherapy (doxorubicin)

  → **Echo, EKG, stress test, consider carotid US, lipids, manage risk factors**

**Stem cell transplant – any/all of the effects based on pre-conditioning regimen*

Surveillance: Systems Based Approach

Evaluate symptoms/physical exam/educate!

- Gastrointestinal
  - Radiation
  - Chemotherapy (alkylators)

  → **Consider EGD, early colonoscopy**
- Hematologic
  - Chemotherapy (alkylators)

  → **Yearly CBC to follow counts/MCV (?10 yrs)**
- Genitourinary/renal
  - Radiation
  - Chemotherapy (alkylators)

  → **Consider urinalysis, BMP, minerals**
- Reproductive
  - Surgery
  - Chemotherapy (alkylators)

  → **Consider labs (testosterone, LH/FSH, AMH), referral to reproductive endocrinology**

**Stem cell transplant – any/all of the effects based on pre-conditioning regimen*

Surveillance: Systems Based Approach

Evaluate symptoms/physical exam/educate!

- Breasts
  - Radiation → **Mammogram, MRI**
- Neurological/CIPN
  - Chemotherapy
  - Radiation → **Duloxetene, PT**
- Muscular
  - Radiation
  - Surgery → **Physical therapy, exercise program**
- Psychological
  - Chemotherapy
  - Radiation
  - Surgery → **Mental health evaluation, treatment, lifestyle**

**Stem cell transplant – any/all of the effects based on pre-conditioning regimen*

Surveillance: Systems Based Approach

Evaluate symptoms/physical exam/educate!

- Sexual
  - Surgery
  - Chemotherapy
  - Radiation

→ **Referral to sexual therapy, mental health, specialized GYN**

- Dental
  - Chemotherapy
  - Radiation

→ **Regular dental care**

- Dermatologic
  - Radiation

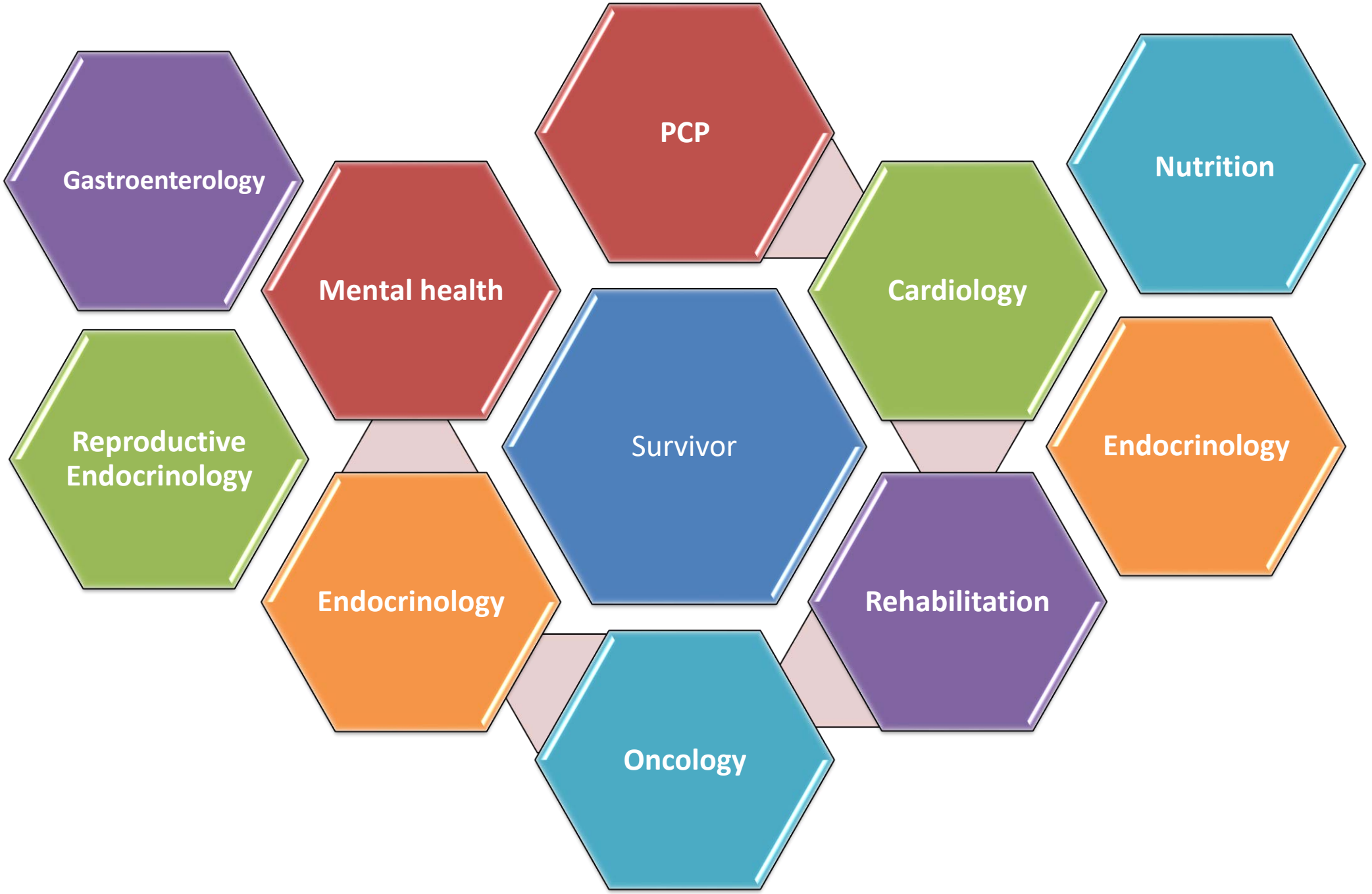
→ **Regular skin examination**

- Immunological
  - Splenectomy
  - Radiation, BMT

→ **Vaccination, early treatment of infections**

**Stem cell transplant – any/all of the effects based on pre-conditioning regimen*

Collaboration and Communication


Gastroenterology
PCP
Nutrition
Mental health
Cardiology
Reproductive Endocrinology
Survivor
Endocrinology
Endocrinology
Rehabilitation
Oncology

Health Care Deja vu

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MONOGRAPHS

Toward Improving the Quality of Cancer Care: Addressing the Interfaces of Primary and Oncology Related Subspecialty Care

2010
Number 40

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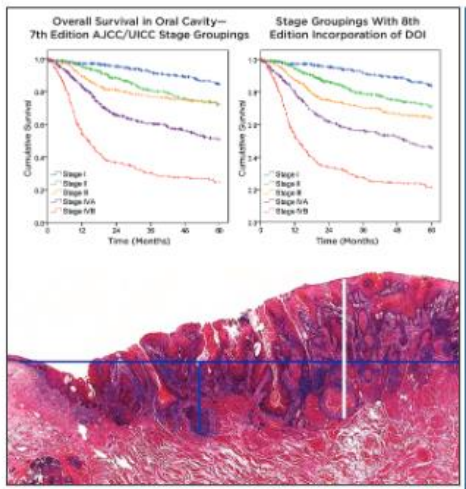
A Cancer Journal for Clinicians



In This Issue:

The Lancet Oncology Commission

The expanding role of primary care in cancer control

Greg Rubin, Annette Berendsen, S Michael Crawford, Rachel Dommett, Craig Earle, Jon Emery, Tom Fahey, Luigi Grassi, Eva Grunfeld, Sumit Gupta, Willie Hamilton, Sara Hiom, David Hunter, Georgios Lyratzopoulos, Una Macleod, Robert Mason, Geoffrey Mitchell, Richard D Neal, Michael Peake, Martin Roland, Bohumil Seifert, Jeff Sisler, Jonathan Sussman, Stephen Taplin, Peter Vedsted, Teja Voruganti, Fiona Walter, Jane Wardle, Eila Watson, David Weller, Richard Wender, Jeremy Whelan, James Whitlock, Clare Wilkinson, Niek de Wit, Camilla Zimmermann

The nature of cancer control is changing, with an increasing emphasis, fuelled by public and political demand, on prevention, early diagnosis, and patient experience during and after treatment. At the same time, primary care is increasingly promoted, by governments and health funders worldwide, as the preferred setting for most health care for reasons of increasing need, to stabilise health-care costs, and to accommodate patient preference for care close to home. It is timely, then, to consider how this expanding role for primary care can work for cancer control, which has long been dominated by highly technical interventions centred on treatment, and in which the contribution of primary care has been largely perceived as marginal. In this Commission, expert opinion from primary care and public health professionals with academic and clinical cancer expertise—from epidemiologists, psychologists, policy makers, and cancer specialists—has contributed to a detailed consideration of the evidence for cancer control provided in primary care and community care settings. Ranging from primary prevention to end-of-life care, the scope for new models of care is explored, and the actions needed to effect change are outlined. The strengths of primary care—its continuous, coordinated, and comprehensive care for individuals and families—are particularly evident in prevention and diagnosis, in shared follow-up and survivorship care, and in end-of-life care. A strong theme of integration of care runs throughout, and its elements (clinical, vertical, and functional) and the tools needed for integrated working are described in detail. All of this change, as it evolves, will need to be underpinned by new research and by continuing and shared multiprofessional development.

Lancet Oncol 2015; 16: 123
See Comment pages 1225–3

School of Medicine, Pharm and Health, Durham Unive Stockton on Tees, UK (Prof G Rubin FRCGP, Prof D Hunter PhD); **Department of General Practice, University of Groningen, Groningen, Netherlands** (A Berendsen I **Airedale National Health Service Foundation Trust, Keighley, UK** (S M Crawford MD); **School Clinical Sciences, Universit Bristol, Bristol, UK** (R Dommett PhD); **Ontario Institute for Cancer Resear Toronto, ON, Canada**

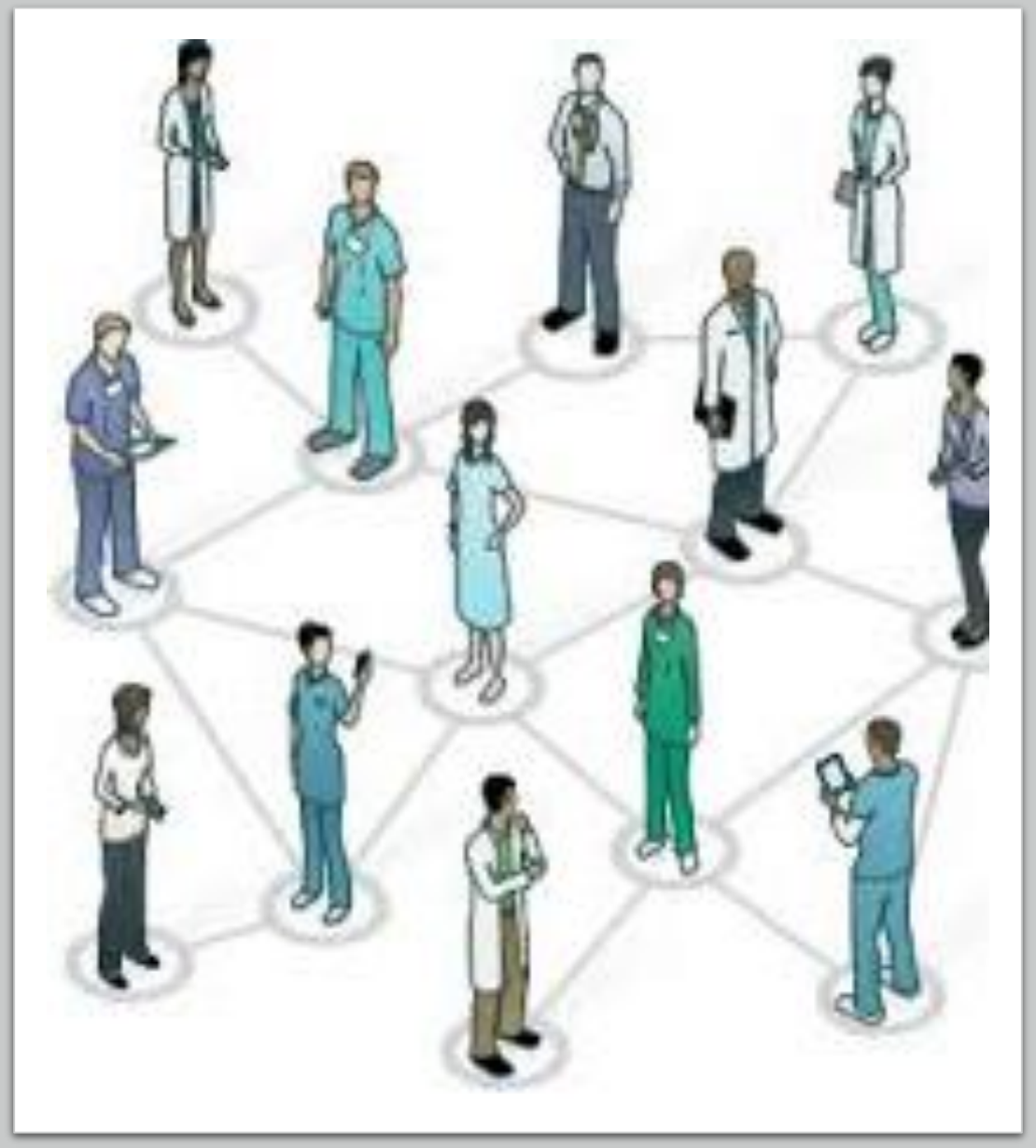
Primary and Cancer Specialists Relationship

- poor and delayed communication between PCPs and cancer specialists
- cancer specialists' endorsement of a specialist-based model of care
- PCPs' belief that they play an important role in the cancer care continuum
- PCPs' willingness to participate in the cancer care continuum
- cancer specialists' and PCPs' uncertainty regarding the knowledge or training of the PCP to provide care, and
- discrepancies between PCPs and oncologists regarding roles and expectations

Dosett et al. The Primary Care Provider (PCP)-Cancer Specialist Relationship: A Systematic Review and Mixed-Methods Meta-Synthesis. CA Cancer J Clin 2017;67:156–169

Possible Solutions

- Electronic medical records
- Use of standardized communication strategies
- Practicing in one healthcare delivery system
- Direct communication (i.e. telephone, email)
- Existing relationship



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Thank you!

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