Screening for Breast Cancer in Patients with Uterine Corpus Cancer and for Uterine Corpus Cancer in Patients with Breast Cancer

Thesis
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List of Abbreviations

AUB	Abnormal uterine bleeding.
BMI	Body mass index.
CEP	Combination Estrogen-Progesterone.
CFDI	Color flow Doppler imaging.
CI	Confidence interval.
CMF	Cyclophsphamide, methotrexate and flurouracil.
COC	Combination oral contraception.
DCIS	Ductal carcinoma in situ.
E	Expected number of subsequent primary cancers.
EAR	Excess absolute risk per 10,000 person-years = [(O-E)/PYR] _ 10,000.
EBCTCG	Early Breast Cancer Trialists' Collaborative Group.
EC	Endometrial cancer.
ECS	Endometrial cancer-specific.
ERT	Estrogen replacement therapy.
HNPCC	Hereditary nonpolyposis colorectal cancer.
HRT	Hormone replacement therapy.
HT	Hormone therapy.
IBIS-1	International Breast Cancer Intervention Study-1.
IGF-1	Insulin-like growth factor 1.
LCIS	Lobular carcinoma in situ.
NSABP	National Surgical Adjuvant Breast & Bowel Project.
O	Observed number of subsequent (2nd, 3rd, etc.) primary cancers.
O/E	O/E = ratio of observed to expected cancers.
OR	Odds ratio.
PEPI	Postmenopausal Estrogen Progestin Interventions.

List of Abbreviations

RB	Retinoblastoma.
RR	Relative risk.
SEER	Surveillance Epidemiological and End Result.
SERM	Selective estrogen receptor modulator.
SHBG	Sex hormone-binding globulin.
SHG	Sonohystography.
SIR	Standardized incidence ratio.
TAM	Tamoxifen.
TGF b	Transforming growth factor B.
TVUS	Transvaginal ultrasonography.
UCC	Uterine corpus cancer.

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Introduction

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The 5-year relative survival rate after a diagnosis of cancer has increased steadily over the last few decades to reach almost 64% in the mid-1990s **(Ries et al., 2003).**

As of 2001, there were almost 10 million cancer survivors in the United States, representing 3.5% of the population. Because of advances in early detection, supportive care, and treatment, the number of cancer survivors has tripled since 1971 and is growing by 2% each year **(Ries et al., 2003).**

This growing and heterogeneous population provides important opportunities for clinical and epidemiologic research into cancer biology, long-term treatment effects, and prevention. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. The number of second- or higher-order cancers is burgeoning and accounted for about 16% of incident cancers in 2003 **(Ries et al., 2003).** In addition, second cancers which have become a leading cause of death among long-term survivors of Hodgkin lymphoma **(Dores et al., 2005).**

Second cancers can reflect the late squeal of treatment; the influence of lifestyle factors, environmental exposures, and host factors; and combinations of influences, including gene–environment and gene–gene interactions. Second primary cancers were categorized according to major identified etiologic influences: syndromic, cancer treatment, and shared etiologic exposures. The categories were recognized as not

mutually exclusive, because multiple factors influence the risk of second cancers (Fig. 1); including interactions between treatment and other exposures, such as tobacco use **(Travis et al, 2002).**

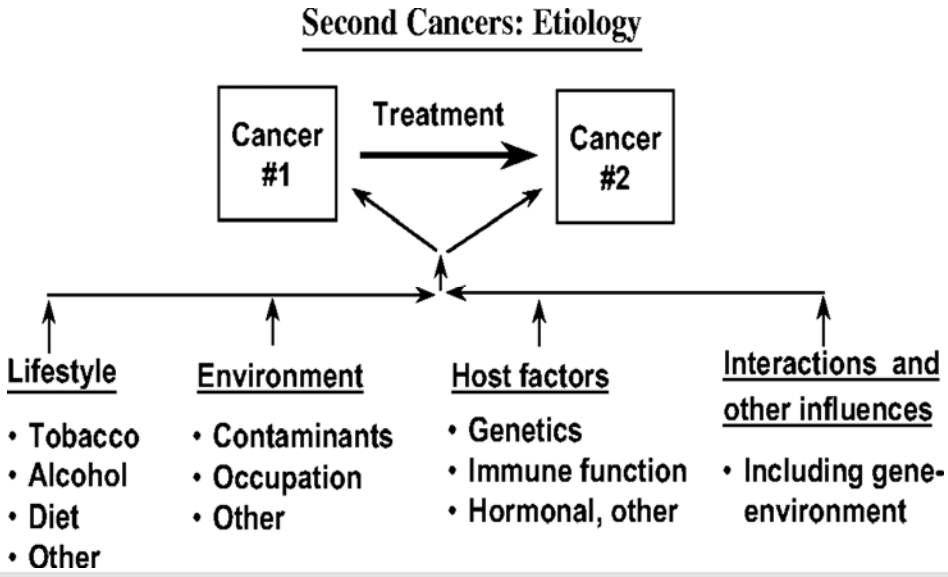

Fig. 1. Risk factors for second primary cancers. Many nfluences, some of which are diagrammed here, may contribute to the development of multiple primary cancers, including interactions between exposures.

1. Cancer Syndromes and genetic factors:

Some syndromic cancers are associated with nonmalignant phenotypes that identify individuals at increased risk, such as Fanconi anemia or Cowden disease, whereas others exhibit only malignant phenotypes, such as BRCA1- and/or BRCA2-related breast and/or ovarian cancer or Li Fraumeni syndrome **(Garber et al., 2005; Lindor et al., 1998).**

Some syndromes are autosomal dominant (e.g., Li Fraumeni syndrome and Cowden disease); others are autosomal recessive (e.g., Fanconi anemia, Bloom syndrome, and xeroderma pigmentosum). These syndromes are most recognizable in the familial setting, and the major

susceptibility genes for many of these syndromes have been identified. Factors that affect gene penetrance are complex, include the nature and location of the specific mutation, and presumed gene–environment and gene–gene interactions. Although hereditary susceptibility explains only a small proportion of all second cancers, an increased risk of primary tumors arising in multiple sites is a distinguishing feature of kindred's carrying germline genetic predispositions and can provide unique insights into underlying mechanisms **(Garber et al., 2005)**.

The overall burden of the risk of multiple primary cancers associated with the common hereditary breast and colon cancer syndromes is noteworthy. If we assume that there are more than 5 million survivors of breast or colon cancer in the U.S**. (Rowland et al., 2004)**, of which 5%–10 % may be caused by genetic factors **(Offit et al., 2004)**, and up to half a million of these patients may be at risk of secondary hereditary neoplasms. The historic observation of twofold to fivefold increased risks of cancers of the ovary, thyroid, and connective tissue after breast cancer presaged the later syndromic association of these tumors with inherited mutations of BRCA1, BRCA2, PTEN, and p53 **(Garber JE et al., 2005)**. By far the largest cumulative risk of a secondary cancer in BRCA mutation carriers is associated with cancer in the contralateral breast, which may reach a risk of 29.5% at 10 years **(Metcalfe et al., 2004)**.

The Breast Cancer Linkage Consortium also documented threefold to fivefold increased risks of subsequent cancers of prostate, pancreas, gallbladder, stomach, skin (melanoma), and uterus in BRCA2 mutation carriers and twofold increased risks of prostate and pancreas cancer in

BRCA1 mutation carriers; these results are based largely on self-reported family history information **(Thompson et al., 2002)**.

By use of the technique of direct mutation detection in the Ashkenazim, in whom genotyping is facilitated by the predominance of three founder mutations, the excess risk of prostate and pancreatic cancer was observed only in BRCA2 mutation carriers **(Kirchhoff et al., 2004),** and no increased risk of colon cancer or lymphoma was observed in BRCA1 or BRCA2 mutation carriers **(Kirchhoff et al., 2004; Kauff et al., 2002).**

Hereditary nonpolyposis colorectal cancer, which is associated with excess cancers of colon, endometrium, stomach, small intestine, hepatobiliary system, kidney, ureter, and ovary, was linked to germline mutations in a family of DNA mismatch repair genes (e.g., MH1L, MSH2, MSH6) **(Lynch et al., 2003).**

Relationships between cancers of breast, colon, and possibly other sites may also exist through inherited mutations of CHEK2 **(Cybulski et al., 2004).**

2. **Treatment-related cancers :**

A large body of research supports the role of chemotherapy or radiotherapy in the development of second cancers after adult or pediatric cancer **(Van Leeuwen et al., 2005)**.

Second malignant neoplasms are one of the most serious sequelae of successful cancer treatment and are the leading cause of death in long-term survivors of Hodgkin lymphoma **(Dores et al., 2005).**

Analytic studies have documented dose–response relations between radiotherapy for Hodgkin lymphoma and subsequent breast **(Travis et al., 2003*)*** and lung cancer (**Travis et al., 2002)** and between radiation and chemotherapy for breast cancer and lung cancer **(Inskip et al., 1994)** and leukemia **(Curtis et al., 1992).**

Late effects of treatment may be modified by moderate- or low-penetrance genetic traits or by other gene–environment and gene–gene interactions. The importance of pharmacogenomics has been increasingly recognized, with estimates that genetics contributes 20%–95% of the variability in cytotoxic drug disposition and effects **(Watters et al., 2004)**. Genetic polymorphisms in proteins involved in drug metabolism and transport are clinically relevant, as are variations in genes that encode receptors for target proteins of drugs **(Evans et al., 2003)** and epidermal growth factor receptor tyrosine kinase inhibitors **(Lynch et al., 2004).**

Advances in molecular genetics and pharmacogenomics have linked polymorphisms in genes encoding selected drug-metabolizing enzymes, such as glutathione *S*-transferase, cytochrome P450s, and thiopurine methyltransferases, with the development of therapy-related cancer (**Evan et al., 2004)**.

For example, patients who have deficient activity of thiopurine methyltransferase are at increased risk of epipodophyllotoxin-related acute myeloid leukemia **(Relling et al., 1998)** or irradiation-induced brain tumor **(Relling et al., 1999).** In fact, acute myeloid leukemia has been reported in these patients even when treatment consisted primarily of antimetabolites **(Thomsen et al., 1999).**

Retinoblastoma (RB) serves as a prominent example of how genetic mutations can influence the risk of radiotherapy-related cancers. Patients with hereditary RB have germline mutations in the RB-1 gene that predispose them to a high risk of osteosarcomas, soft-tissue sarcomas, melanoma, as well as cancers of the brain, nasal cavities, eye, and orbit; and radiation therapy further enhances the risk of tumors arising in the radiation field **(Kleinerman et al., 2005).**

3. Second cancers caused by shared etiologic factors.

Tobacco use is one of the major causes of multiple primary cancers, with strong well-established associations with tumors of lung and upper aerodigestive tract (oral cavity, pharynx, larynx, and esophagus) **(Begg et al., 1999)**.

Patients with lung cancer also demonstrate increased risks of cancers of lip, bladder, and second primary lung cancers **(Caporaso et al., 2005),** indicating the shared etiologic role of tobacco use. Often, increased reciprocal risks of lung cancer follow first primary cancers at these other sites **(Begg et al., 1999)**.