SECTION 4
OUTCOME CLASSIFICATIONS:
CANCER OUTCOMES

INTRODUCTION

Breast and colorectal cancers are primary outcomes of the Dietary Modification (DM) trial and secondary outcomes of the Calcium and Vitamin D (CaD) trial. Endometrial, ovarian and other cancers are secondary outcomes of all three clinical trial interventions.

4.1 Cancer Outcomes - Overview

The following incident cancer diagnoses will be monitored during the Women's Health Initiative (WHI):

- Breast cancer
- Endometrial cancer
- Ovarian cancer
- Colon cancer
- Rectal cancer

→ Referred to as the **five major cancers** for WHI.

- Other cancers (exclusive of non-melanoma skin cancer)

All WHI participants (Clinical Trial [CT] and Observational Study [OS]) will be asked to self-report any physician diagnosis of new cancer, a malignant tumor, or growth of any type. Clinical Trial participants complete a *Form 33 - Medical History Update* at each semi-annual contact; OS participants complete this form annually.

For **each** self-report of a new cancer diagnosis in CT or OS participants, the following data sources are to be requested by the CC:

- pathology/cytology report
- hospital Face Sheet with ICD-9-CM codes
- operative report
- hospital discharge summary
- outpatient, day surgery, or short stay recode

In addition, for the **five** major cancer outcomes, copies of the following are to be requested by the CC:

- history and physical
- oncology consult/treatment summary
- radiology report (diagnostic)
- tumor registry abstract
- estrogen and progesterone receptor assay report (for breast cancer only)
- TNM staging form.

For **the five major cancers**, the above documentation is required for a new diagnosis of **primary** breast, endometrial, ovarian, colon or rectal cancer in CT and OS participants. Appendix is not included as a sub-site for colon. It is coded independently as "other cancer" (see *Appendix C, Coding Reference*). CCs are responsible for documenting the occurrence of cancer, the primary site, including the 2-digit ICD-0-2 code, date of diagnosis, whether the cancer was pathologically confirmed, and the type of reporting source.

When requested by the CCC, CCs will forward all documents relevant to the cancer diagnosis (including *Form 122 - Report of Cancer Outcome)* to the CCC for centralized review. The Fred Hutchinson Cancer Research Center (FHCRC) Cancer Surveillance System (CSS) staff will code site, date of diagnosis, confirmation, laterality, and source, as well as anatomic sub-site, tumor morphology, and stage of disease at diagnosis. Cancer cases where the CSS staff cannot assign a final diagnosis will be forwarded to the CSS reference pathologist for the definitive diagnoses. If CSS requires further documentation or information in order to code a specific cancer case, a "query" will be sent to the CC for response. For all hospitalized cancer occurrences, *Form 125 - Report of Hospitalization Diagnosis* should also be completed.

For **all other cancers** (i.e., other than the five major cancer outcomes of interest to WHI), the CCs will be responsible for documenting the occurrence of a cancer in **CT and OS** participants, the primary site, date of diagnosis, whether the cancer was pathologically confirmed, and the type of reporting source. These data will be recorded by the CCs, and a copy of the pathology report and other relevant documents will be included in the adjudicator case packet and filed in the participant's outcomes file.

4.1.1 First vs. Recurrent Disease

Only information on **newly** diagnosed incident cancers is of interest to WHI. Information on recurrent disease or metastasis from a previously diagnosed cancer(s) is not collected. A cancer metastases from a primary cancer site that has already been adjudicated would not require adjudication. However, a second primary cancer would require local and central adjudication, as this would be considered a new cancer, and not a metastasis. For example, a second cancer in the breast (even if the same breast) would be considered a new primary, unless stated to be recurrent or metastatic (i.e., *Form 125 – Summary of hospitalization Diagnoses*). Subsequent (recurrent) cancer requiring hospitalization will be documented as are other hospitalization's, and adjudicated as such locally and will not require the extensive documentation that is required for the first occurrence.

4.1.2 Occurrence (Definition)

Cancer is defined as a physician diagnosis of any primary malignant tumor. Invasive and *in situ* cancers of all histologic subtypes will be included, as well as borderline malignant ovarian tumors. The definition of cancer and procedures for defining and coding a new primary tumor will be based on those utilized by the Surveillance, Epidemiology, and End Results (SEER) program (The SEER Program Code Manual, June 1992). Both pathologically (biopsy-proven) confirmed and not pathologically confirmed tumors will be recorded.

A. *Pathologically confirmed*: is defined as a pathology report that clearly states the diagnosis in specific terms that are synonymous with cancer (e.g., malignancy, malignant tumor, malignant neoplasm, carcinoma, CA, or a specific histology that defines malignant tumor morphology). Ambiguous terms "probable, suspect, suspicious, compatible with, most likely, and consistent with" cancer ARE considered to be diagnostic of cancer. Ambiguous terms "questionable, possible, suggests, worrisome, and equivocal" ARE NOT considered to be diagnostic of cancer. The term *"neoplasm"* or *"tumor"* alone does not constitute a cancer diagnosis; the word *"malignant"* usually precedes these terms to indicate a diagnosis of cancer except for cancers with specific terms (e.g., Burkitt's lymphoma, Hodgkin's disease, hepatoma, etc.).

B. *Not pathologically confirmed*: a physician diagnosis of cancer based on direct visual observation, radiography, positive laboratory test/marker study or clinical examination only.

4.1.3 Primary Site/Histology (ICD-0-2 Codes)

The CC Physician Adjudicator should determine whether the cancer site is primary or secondary and which site would be the most definitive one. The WHI identifies "cases" of cancer according to the **primary** site. If the site of origin cannot be determined exactly, it may be possible to use the NOS category of an organ system or the Ill-Defined Sites.

Form 122 – Report of Cancer Outcome lists cancers by site. The CC Physician Adjudicator checks the appropriate box for the primary site. The codes listed beside tumor site correspond to the ICD-0-2-coding LC system. If the primary site cannot be determined, check box 00 and write in the cancer site. Then, use *Appendix C – Cancer coding reference (alphabetical index)* to identify the appropriate ICD-0-2-code and document this on *Form 122*.

For example: A case pathology report states the primary site is "breast" carcinoma. This site is looked up in the Alphabetic Index, and is found to be 50. In coding, the two-character code, '50' will be recorded.

In addition to the ICD-0-2 codes on *Form 122 – Report of Cancer*, the ICD-9-CM code from the woman's cancer diagnosis on the hospital Face Sheet is to be recorded on *Form 125 - Summary of Hospitalization Diagnosis*. (See *Appendix C* for detailed lists of ICD-9-CM codes.)

4.1.4 Date of Diagnosis

The date of diagnosis of the cancer will be defined according to the method of confirmation (see *Section 4.1.6 - Confirmation*). The following rules apply:

a. Microscopically-confirmed cancer -- the date of diagnosis is the date the tissue, that resulted in the positive pathology (histology), was removed. For microscopic confirmation based on a positive cytology report (no positive histology), the date of diagnosis will be the date the sample that resulted in the positive cytology was taken.

b. Not microscopically-confirmed cancer -- the date of diagnosis will be the date of first hospitalization for the cancer. If no hospitalization, the date of diagnoses will be (ordered hierarchically) the date of a positive laboratory test or marker study, the date of a positive radiography or other imaging technique study, the date of direct visualization of the cancer by the physician, or, lastly, the date the physician made the clinical diagnosis (in the absence of any of the above).

c. Autopsy-only cancer - date of diagnosis is the date of death.

d. Death certificate-only cancer - date of diagnosis is the date of death.

e. Self-report only cancer - date of diagnosis is the date reported by the participant.

4.1.5 Tumor Behavior

The usual behavior codes are listed in both the numeric and alphabetic indices of ICD-0-2, following the histology code.

The following codes are used for defining tumor behavior:

0 = benign

1 = uncertain whether benign or malignant; borderline malignancy; low malignant potential; indeterminate malignancy.

2 = carcinoma *in situ*; intraepithelial; non-infiltrating; non-invasive; Bowen's disease; CINIII; Clark's level 1 for melanoma; confined to epithelium; intraductal; intraepidermal NOS; lobular neoplasia; no stromal invasion; VAINIII; VIN III.

3 = malignant (invasive), primary site

4.1.6 Confirmation

Diagnostic confirmation indicates whether AT ANY TIME there was microscopic confirmation of the morphology of the cancer. Data on confirmation will be sought for each cancer that is self-reported by WHI participants, but will be limited to cancers occurring after enrollment in WHI (i.e., during follow-up). The confirmation recorded on *Form 122 – Report of Cancer* indicates not only the fact of microscopic confirmation, but the nature of the BEST evidence available. Thus, the codes are in a priority series with code '1' (one) taking precedence.

Specifics:

Code: Microscopically confirmed

- Code 1 - Positive histology (pathology), primary site: Microscopic diagnosis based upon tissue specimens from biopsy, frozen section, surgery, autopsy, or dilatation and curettage (D & C). Positive hematologic findings relative to leukemia are also included. Bone marrow specimens (including bone marrow aspiration biopsies) are also coded as '1'.
- Code 2 - Positive exfoliative cytology, no positive histology: Cytologic diagnosis based on microscopic examination of cells as contrasted with tissues. Included are smears from sputum, bronchial brushings, bronchial washings, tracheal washings, breast secretions, gastric fluid, spinal fluid, peritoneal fluid, pleural fluid, endometrial aspiration, urinary sediment, cervical and vaginal smears. Also included are diagnoses based upon paraffin block specimens from concentrated spinal, pleural, or peritoneal fluid.
- Code 3 - Positive histology (pathology), distant metastatic site only: Microscopic diagnosis based upon a tissue specimen from a metastatic site *only* (code to "1" if histologic confirmation is also done on the primary site or a regional site).
- Code 4 - Positive microscopic confirmation, method not specified: Diagnosis stated to be microscopically-confirmed, but with no detailed information on method.

Code 5: Not Microscopically confirmed

- Code 5 - Positive laboratory test/marker study: Clinical diagnosis of cancer based on certain laboratory tests or marker studies which are clinically diagnostic for cancer. Examples are the presence of alpha fetoprotein for liver cancer and an abnormal electrophoretic spike for multiple myeloma and Waldenstrom's macroglobulinemia.
- Code 6 - Direct visualization without microscopic confirmation: Visualization includes diagnosis made at surgical exploration or by use of the various endoscopes (including colposcope, mediastinoscope, peritoneoscope). However, use this code only if such visualization is not supplemented by positive histology or positive cytology reports. Also use this code when gross autopsy findings are the only positive information.
- Code 7 – Positive laboratory test/marker study: Cases with diagnostic radiology for which there is neither a positive histology nor a positive cytology report. "Other imaging techniques" include procedures such as ultrasound, computerized (axial) tomography (CT or CAT scans), and magnetic resonance imaging (MRI).
- Code 8 – Clinical diagnosis only (other than 5, 6, or 7): Cases diagnosed by clinical methods not mentioned above and for which there were no positive microscopic findings.

Code: Confirmation Unknown:

- Code 9 – Unknown whether or not microscopically-confirmed: Cases for which it is unknown whether or not they have been microscopically confirmed. Also included are all "self-report only" and "death certificate only" cancers.

4.1.7 Reporting Source

This data item provides information to help assess the completeness and reliability of the data in other fields; to indicate the number of patients who were not hospitalized as inpatients or outpatients for their cancers; and to identify the cases diagnosed by autopsy or death certificate only. The code should be based on all source documents used to prepare *Form 122 - Report of Cancer Outcome*, rather than only the source of the original diagnosis, and should be assigned hierarchically in the order shown.

Code:

1 Hospital inpatient (with or without any of the following)

2 Hospital outpatient/radiation or chemotherapy facility, surgical center, or clinic - includes outpatient services of HMO's and large multi-specialty physician group practices where at a minimum the reports from multiple physicians and laboratories are filed in a single medical record for the patient.

3 Laboratory only (hospital or private)

4 Physician's office/private medical practitioner (LMD)

5 Nursing/convalescent home/hospice

6 Autopsy only - means that the cancer was not diagnosed even as a clinical diagnosis while the patient was alive. If the patient was an inpatient with another admitting diagnosis and an autopsy disclosed the cancer for the first time, code '6' is proper. Autopsy findings take precedence over death certificate information (i.e., code '6' takes precedence over code '7'). However, a clinical diagnosis of cancer at any of the sources coded '1'-'5' has priority over confirmation at autopsy.

7 Death certificate only (including Coroners' case) - used only when "follow-back" activities have produced no other medical reports--the death certificate is truly the **only** source of information. Often a case is reported first via the death certificate, but later action yields previously - missing or additional medical reports. Such additional reports take precedence

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