on dietary and supplemental sources of vitamin D and related foods and nutrients, biomarkers of vitamin D, and genetic variation in the vitamin D receptor gene, all in relation to breast cancer risk (19). The review concluded that, despite some inconsistencies, increasing vitamin D concentrations were associated with decreasing breast cancer risk (19). Although these important findings have implications for primary breast cancer prevention, little is known about vitamin D status among breast cancer survivors. Understanding vitamin D status among cancer patients is critical because vitamin D influences important cellular events related to prognosis and survival (eg, apoptosis, cell-cycle regulation) (4, 6, 19). Here, we report on vitamin D status, assessed by circulating 25(OH)D concentrations, in a breast cancer survivor cohort. We also examine the relevance of breast cancer clinical characteristics and whether tamoxifen, which is used by many breast cancer patients, influences circulating concentrations of 25(OH)D (9, 20).

SUBJECTS AND METHODS

Study design, population, and recruitment

The Health, Eating, Activity, and Lifestyle (HEAL) study is a population-based, multicenter, multiethnic prospective cohort study of 1183 breast cancer patients that investigated whether weight, physical activity, diet, hormones, and other exposures affect breast cancer prognosis and survival. Details of the study design and procedures are published (21). Briefly, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries in New Mexico, Los Angeles County (CA), and western Washington state for study recruitment. In New Mexico, we recruited 615 women, aged $\geq$ 18 y, diagnosed with in situ to stage IIIA breast cancer between July 1996 and March 1999. In Western Washington, we recruited 202 women, aged 40–64 y, diagnosed with in situ to stage IIIA breast cancer between September 1997 and September 1998. In Los Angeles County, we recruited 366 African American women with stage 0–IIIA primary breast cancer who had previously participated in the Los Angeles portion of the Women's Contraceptive and Reproductive Experiences study or who had participated in a parallel case-control study of in situ breast cancer. Thus, the Los Angeles participants were a subset of women diagnosed with breast cancer between May 1995 and May 1998, aged 35–64 y at diagnosis, English speaking, and born in the United States. Procedures were approved by the institutional review boards of the participating centers, in accord with an assurance filed with and approved by the US Department of Health and Human Services; all participants gave written informed consent.

The HEAL participants completed extensive interviews within their first year after diagnosis (on average 7.5 mo after diagnosis) and 24 mo later (within their third year after diagnosis; on average 31.5 mo after diagnosis). Of the 1223 women initially enrolled in the study at baseline, 39 (3.2%) were later found to have had a prior breast cancer diagnosis (suggesting that the current diagnosis was either a recurrence or a second primary tumor) and 1 woman (<1.0%) was found to have metastatic disease at initial diagnosis. Because the women with recurrent or metastatic disease no longer met the HEAL eligibility criteria, they were subsequently excluded. Of the remaining 1183 women, 239 (20.2%) women did not return for the 24-mo visit. Reasons for not participating were death ($n = 44$), illness ($n = 2$), refusal ($n = 105$), moved ($n = 16$), and unable to contact or locate ($n = 72$). Nine hundred forty-four women completed the 24-mo follow-up questionnaires, which included detailed questions on health, menopausal status, diet, physical activity, and alcohol and tobacco use. Staff members also measured height and weight and collected a fasting blood specimen from all participants. We used the data and specimens collected at the 24-mo interview for this report, but we excluded those participants with no archived blood specimen ($n = 790$ available for analysis).

Breast cancer stage of disease and cancer treatment

Data on breast cancer stage of disease at diagnosis were obtained from the SEER registries. Participants were classified as having in situ, stage I, or stage II–IIIA breast cancer based on American Joint Committee on Cancer stage of disease classification. Treatment data were obtained during a review of medical records that provided more detailed information on chemotherapy, radiation, and hormonal therapy than that maintained by the registries. Adjuvant treatment was categorized into 4 mutually exclusive groups: *1*) surgery only, *2*) surgery and radiation, *3*) surgery and chemotherapy, and *4*) radiation and chemotherapy. Tamoxifen use was defined as self-reported current use at the 24-mo interview and blood draw.

Blood collection and 25(OH)D analysis

Fasting blood specimens were processed within 3 h of collection and stored at −70 to −80 °C until analysis. The biologically active form of vitamin D is 1,25(OH)D, but it is not a good biomarker because of its short half-life and tight homeostatic control (1, 22). Serum 25(OH)D is an excellent biomarker of vitamin D status, representing both cutaneous synthesis and dietary intake (1, 22). Serum 25(OH)D was assayed with the use of a radioimmunoabsorbant assay (DiaSorin Inc, Sillwater, MN). We included blinded duplicates in each assay, and the within- and between-assay CV was 3.7%.

Dietary assessment

Diet was assessed with the use of a validated self-administered food-frequency questionnaire that was designed for use in multiethnic postmenopausal women (23) This food-frequency questionnaire included 122 line items, 19 adjustment questions, and 4 summary questions. The database used to convert food information into nutrients is derived from the University of Minnesota's Nutrition Data Systems for Research (NDS-R, version 2005) and includes recent analytic food values for vitamin D. Information on vitamin D–containing dietary supplements was obtained by *1*) close-ended questions on the use of specific single supplements, including vitamin D and *2*) open-ended questions (New Mexico and Washington only) on the use of any other dietary supplements used at least weekly. We defined vitamin D–containing supplements as either single supplements or combination supplements (eg, vitamin D and calcium–type mixtures). Multivitamins were not included because we had no information on specific brands or formulations. However, because a high proportion of women reported use of multivitamins (72.9%), additional adjustments would not likely provide meaningful information.

[中譯文]

研究目標與研究方法

研究設計、母體及徵求參加者

健康狀態、飲食型態、運動執行和休閒暨社會活動(HEAL)研究法，是針對1183位乳癌病患的母體基礎，以多中心、多種族的前瞻性世代研究(prospective cohort study)法，調查體重、運動情形、飲食、荷爾蒙和其他曝曬活動，對乳癌預後和存活率的影響。本研究的設計細節和過程業已發表(21)。簡而言之，我們採用國立癌症研究所之監視系統、流行病學和最終結果研究(SEER)登記資料，徵求新墨西哥、洛杉磯(CA)、和西華盛頓地區的參加者。於新墨西哥地區，我們招募615位婦女，年齡≧18歲，在1996年7月至1999年3月之間，被診斷出原位癌～第IIIA期乳癌。於西華盛頓地區，我們招募202位婦女，年齡40-64歲，在1997年9月至1998年9月之間，被診斷出原位癌～第IIIA期原發性乳癌。於洛杉磯地區，我們招募366位非裔美人，患有第0期～第IIIA期乳癌，曾經參與洛杉磯婦女避孕劑和生產經驗研究，或曾經參與類似的原位乳癌病例控制研究。因而，洛杉磯的參加者，是在1995年5月到1998年5月之間被診斷出乳癌，當時年齡界於35-64歲，操英文，並在美國出生婦女的一個子集合。研究過程經參與中心的公共機構審查會核准，並經提交給美國人類健康服務部取得擔保一致同意；所有參加者均簽有同意書。

針對HEAL參加者，於確診後的第一年內(平均爲確診後7.5個月)，及在24個月後(在確診後第三年內；平均爲確診後31.5個月)，完成大規模訪談。最初在基線期有1223位婦女登記參加，有39位(3.2%)之後被診斷出先前即罹乳癌(即當前的診斷不是復發即爲第2個原發性腫瘤)，及1名婦女(<1.0%)在最初診斷時，被發現有新陳代謝疾病。這些婦女因爲復發或新陳代謝疾病，便不再符合HEAL的資格標準，自然必須予以排除。而剩下的1183位婦女，有239位(20.2%)在24個月後並未回來訪談。其原因包括死亡(n=44)、生病(n=2)、拒絕(n=105)、搬家(n=16)，及無法取得聯繫或找不到人(n=72)。有944位婦女完成24個月後的追蹤問卷，問題細節包括健康狀況、經期情形、飲食、運動和煙酒用量。研究人員也測量所有參加者的身高和體重，並採集空腹血液樣本。本報告係使用由24個月後之面談所蒐集到的數據和樣本，而且排除採血未歸檔的參加者 (可分析樣本數n=790)。

乳癌期別及治療方式

乳癌期別的診斷數據係來自SEER登記資料。根據美國共同委員會的癌症期別分類，將參加者分類成原位癌、第I期或II–IIIA期。治療方式則是檢視病歷，取得有關化療、放射線療法和荷爾蒙療法之資料，較登記資料更多且詳細。輔助治療被分類成4組彼此獨立的群組：1)僅手術、2)接受手術和放療、3)手術和化療及4)放療和化療。抗雌激素的使用定義爲在主動回報時，於第24個月訪談時正在使用及有採血。

血樣蒐集與 25(OH)D 分析

空腹血液樣本在採血3小時內處理，於分析前儲存在-70℃到-80℃。1,25(OH)D是維他命D的生物活性形式，但它並非一個好的生物標誌，因其半衰期短，而且體內自我平衡控制嚴格(1, 22)。血清25(OH)D則是維他命D狀態的一個極佳生物標誌，可經由皮膚合成或飲食攝取(1,22)。血清25(OH)D係使用放射免疫測定法(radioimmunoabsorbant)分析(DiaSorin Inc, Sillwater, MN)。在每個分析過程中，我們包含盲目複製，而批內分析和批間分析CV爲3.7%。

飲食評估

飲食係使用針對多種族的經後期婦女設計，讓其自行管理的評估飲食頻率問卷(23)。這項飲食頻率問卷包括122個條項，19個調整性問題，和4個摘要性問題。將食品資料轉成營養成分的資料庫，係使用明尼蘇達大學的營養數據系統(NDS-R、2005版本)，並且包括新近分析的食品維他命D值。關於維他命D的資訊，包括來自日常飲食補充品的 1)使用含特定維他命D單一補充劑的封閉型問題，和2)至少每週使用一種飲食補充劑的開放式問題(僅新墨西哥和華盛頓地區)。我們將維他命補充劑，定義爲單一種或組合式補充劑(例如，維他命D和鈣混合型)。其中並未包括綜合維他命在內，因爲我們並未指定品牌或規劃構想。然而有很高比例的婦女回報有服用多種維他命(72.9%)的情形，再做其他額外調整，可能也得不到有意義的資訊。