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Original Contribution

Overview of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

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The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) brought together 10 cohorts to conduct a prospective study of the association between vitamin D status, measured as serum concentrations of 25-hydroxyvitamin D (25(OH)D), and the development of 7 rarer cancer sites: endometrial, esophageal, gastric, kidney, non-Hodgkin lymphoma, ovarian, and pancreatic cancers. The cohorts come from 3 continents, with participants from a wide range of latitude who are racially diverse. Across each cancer site, there was no evidence of a protective association between higher concentrations of 25-hydroxyvitamin D (>75 nmol/L) and cancer outcome. An increased risk at very high levels (≥100 nmol/L) was noted for pancreatic cancer, confirming previous reports. The articles included in this issue detail the overall design and governance of the project, correlates of vitamin D status, and results from the cancer site-specific investigations. The Vitamin D Pooling Project realizes a major goal of consortium efforts, namely, to rigorously test hypotheses for rarer cancer outcomes that may not be adequately addressed in any one prospective cohort study. The results of this study have application for the planning and conduct of intervention trials, especially in determining potential risks.

case-control studies; neoplasms; prospective studies; vitamin D

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; VDPP, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.

Adequate vitamin D concentrations are necessary for bone health and prevention of rickets. The widespread prevalence of low concentrations of vitamin D has triggered great clinical, research, and public health interest in determining the amount of vitamin D required for optimal health. The interest in vitamin D as a cancer preventive agent arises from its biologic role in proliferation and apoptosis along with the presence of vitamin D in most tissues.

The main source of circulating vitamin D is conversion of 7-dehydrocholesterol in the skin to cholecalciferol (D_3) upon exposure to ultraviolet B radiation (1). Dietary sources, even with fortification of food, remain a minor contributor to vitamin D status. With the recognition of widespread prevalence of deficient or insufficient vitamin D concentrations, some have advocated increasing vitamin D through supplements. In May 2009, a committee was appointed by the Food and Nutrition Board, Institute of Medicine of the National Academies, to evaluate and update the dietary reference intake for vitamin D, as well as calcium (2). The Committee is charged with evaluating evidence of both the adequacy of current dietary vitamin D intake recommendations, including optimal dose and range of intake, and the potential harms from excess intake.

In 2008, the evidence pertaining to vitamin D and its association with cancer was reviewed by the International Agency for Research on Cancer (3). As part of that review, updated meta-analyses were conducted regarding the associations between serum levels of 25-hydroxyvitamin D (25(OH)D) and colorectal, breast, and prostate cancers. The results showed a statistically significant decrease in risk of colorectal cancer per 1-ng/mL increase in serum 25(OH)D concentration among prospective studies (relative risk = 0.984, 95% confidence interval (CI): 0.976, 0.991). For prospective breast cancer studies, results were heterogeneous, and the decreased risk observed was not statistically significant (relative risk = 0.994, 95% CI: 0.964,

Table 1. Participating Cohorts in the Vitamin D Pooling Project of Rarer Cancers and Number of Cases per Cancer Site

Cohort and Location	Population	Median Follow-up Time, years (25th, 75th Percentile of VDPP Cases)	No. of Cancer Cases Contributed by Cohort					
			Endometrial	Kidney	Lymphoma	Ovarian	Pancreatic	Upper GI (Esophageal and Gastric)
ATBC Study, Finland	Smokers	8.7 (4.9, 12.7)	0	286	208	0	313	416
CPS-II, United States—national	General	2.3 (1.3, 3.6)	51	58	135	27	65	40
CLUE, United States—Washington County, Maryland	General	10.1 (5.3, 14.7)	192	102	236	102	123	88
HPFS, United States—national	Health professionals	4.4 (2.6, 6.7)	0	0	133	0	0	0
MEC, United States—Hawaii and California	General	2.1 (1.1, 3.3)	39	64	96	18	109	82
NYU-WHS, United States—New York	Mammography screening	10.8 (6.0, 14.6)	139	35	73	94	73	27
NHS, United States—national	Registered nurses	7.0 (4.0, 9.5)	163	0	145	127	0	0
PLCO (32, 33), United States—national	General	4.5 (2.2, 6.8)	147	161	286	74	183	99
SMHS, China	General	1.7 (0.9, 2.7)	0	32	8	0	27	131
SWHS, China	General	4.7 (2.4, 6.6)	99	37	33	74	59	182
Total cancer cases			830	775	1,353	516	952	1,065

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; CPS-II, Cancer Prevention Study II Nutrition Cohort; GI, gastrointestinal; HPFS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort Study; NHS, Nurses' Health Study; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; VDPP, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.

1.024). No evidence for an association between 25(OH)D and prostate cancer risk was observed (3). Published data for other cancer sites were too sparse to conduct meta-analyses. Since that review by the International Agency for Research on Cancer, an additional prospective study of 25(OH)D concentrations and pancreatic cancer was published (4). Similar to the prior publication, an increased risk of pancreatic cancer was observed among individuals with the highest levels, but there was no dose-response association (4).

This issue contains a series of articles from the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP), a collaborative effort involving 10 cohorts that are members of the National Cancer Institute Cohort Consortium. The VDPP was undertaken to address the gap in knowledge of the association between vitamin D and cancer, in particular the rarer cancers sites (3, 5). The VDPP, using a central laboratory and standards provided by the National Institute of Standards and Technology, examined the associations between serum or plasma 25(OH)D concentrations, the main circulating form of vitamin D, and the development of 7 types of rarer cancer: endometrial, esophageal, gastric, kidney, non-Hodgkin lymphoma, ovarian, and pancreatic cancers (6–11). The project was a nested case-control study with the vast majority of samples assayed specifically for this project. The reports include an overall design paper, describing the governance of the consortium and detailing the design and statistical approaches used in the investigation, as well as a paper detailing the factors correlated with vitamin D status. The results for each cancer site are reported in separate papers except for gastric and esophageal cancers, which were combined as upper gastrointestinal cancers.

The Cohort Consortium (http://epi.grants.cancer.gov/Consortia/cohort.html) was established in 2000 to foster large collaborative studies to investigate gene-gene and gene-environment interactions with cancer. The first 2 Consortium projects focused on genetic studies of breast and prostate cancer. The VDPP realizes a major goal and advantage of the Cohort Consortium network, namely, the study of rare cancer outcomes that no one cohort alone may be able to examine. The VDPP brought together prospective cohort studies with stored blood samples, diverse in ethnicity and geographic distribution, to address the question of whether vitamin D concentrations are associated with the development of rarer cancer sites (Table 1). The cancer sites investigated were chosen because prior ecologic, preclinical studies or observational studies suggested possible associations with vitamin D. In addition, the consortium prospective approach has advantages for cancer sites that present at advanced stage at diagnosis and have high case-fatality rates, such as esophageal, pancreatic, and ovarian cancers. The considerable variation within and across cohorts in racial groups, latitude of residence, and vitamin D intake provided the opportunity to examine associations across a wide range of clinically relevant concentrations of vitamin D, measured as circulating 25(OH)D.

The overall design, description of the cohorts, and statistical methodology are outlined in the methods paper (12). A

nested case-control approach was used, with samples assayed in a central laboratory. A unique feature of the VDPP was the availability of the first serum standards for assays of 25(OH)D provided by the National Institute of Standards and Technology. The hypothesis being tested was that higher concentrations of vitamin D would be associated with a lower risk of developing the cancers being investigated.

The results of the VDPP do not suggest a benefit from higher concentrations of vitamin D, nor do they suggest an increased risk from lower concentrations with respect to the cancer sites studied (Figure 1). The observations from the study of pancreatic cancer were consistent with prior reports of an excess risk associated with concentrations of 25(OH)D greater than 100 nmol/L (adjusted odds ratio = 2.12, 95% CI: 1.23, 3.64) (11). Because the previously reported studies of 25(OH)D and pancreatic cancer also participated in the VDPP, analyses were conducted excluding these cohorts. A similar point estimate of risk was observed in association with concentrations exceeding 100 nmol/L, although the estimate was no longer statistically significant (odds ratio = 2.23, 95% CI: 0.82, 6.08). Even in this large collaborative study, the numbers of cases and controls were limited at the extreme high end of the distribution, emphasizing the challenge of studying both rare cancers and the associations with the extremes of exposures. These results, though not conclusive, raise concern about recommendations for use of high-dose supplementation with vitamin D that may result in high serum concentrations of vitamin D. The observation of a decreased risk of upper gastrointestinal cancer with low concentrations of 25(OH)D among Asians was also consistent with previously published studies among Asian populations that observed a lower risk of cancer among individuals in the low range of vitamin D (7, 13, 14). Although data are sparse at the extremes of 25(OH)D concentrations and in population subgroups, the consistency with other reports in different populations makes it likely that these results are not by chance. However, these results should be confirmed in other collaborative prospective cohort projects.

As part of the project, an analysis of correlates of 25(OH)D was conducted to both guide analyses of site-specific papers and to take advantage of the wide spectrum of populations represented in the VDPP (15). Consistent with other reports, individuals with higher 25(OH)D levels tended to be male and to be lean, to engage in vigorous physical activity, to have a greater dietary intake of vitamin D, and to have greater use of multivitamin and calcium supplements.

The current recommended daily intake according to the Food and Nutrition Board of the Institute of Medicine, National Academies, is age dependent and ranges from 200 to 600 IU, with the highest dose recommendations for elderly women. The tolerable upper limit of intake, defined as the amount that is likely to pose no overall risk of adverse effects, varies from 1,000 IU in infants to 2,000 IU in adults (16). These recommendations are currently under review by the Food and Nutrition Board (Institute of Medicine) and may be altered. Finding the optimal dose of vitamin D is important, as there appears to be risk at both extremes of the distribution of vitamin D concentrations. Higher mortality rates occur at the extreme low concentrations, as well as at the high end of the distribution (3, 17). The VDPP suggests a possible increased risk for pancreatic cancer at higher vitamin D concentrations.

As the safety of high-dose supplementation for prolonged periods is uncertain and reports of harm have surfaced at the high end of 25(OH)D concentrations, caution should be exercised in using high-dose supplementation in both clinical practice and research settings. If high doses are to be used, serum 25(OH)D concentrations should be monitored. Clinically, high-dose supplementation may be recommended when measured vitamin D concentrations are very low. Research studies may also use doses at the higher end of the tolerable safe upper limit in order to maximize the ability to detect effects. A search of the Clinical Trials Registry maintained by the National Institutes of Health (http://clinicaltrials.gov/), with vitamin D as the key term and limitation to interventional studies, yielded 360 open studies. Further search with key terms of ''vitamin D and prevention'' and ''vitamin D as an intervention'' yielded 59 open studies. The populations being studied included pregnant women, children, and adults. Among those studies that listed the dose of vitamin D, 28 studies had at least 1 intervention arm with a vitamin D dose of 2,000 IU per day or higher. For example, a weekly dose of 20,000 IU of vitamin D (for an average daily dose exceeding 2,500 IU) is being investigated in a 5-year intervention trial among individuals with impaired glucose tolerance. A study with recruitment beginning in January 2010 per the study website is the Vitamin D and Omega-3 Trial (referred to as ''VITAL''), which plans to recruit 20,000 individuals to test vitamin D supplementation at a dose of 2,000 IU per day (http://www.vitalstudy.org/). Participants are asked to limit their supplement intake to no more than 800 IU per day for a potential supplementation dose of 2,800 IU per day. As noted previously, the safety of these doses, especially with prolonged supplementation of 1 year or more, is uncertain. Given the current information on risks at extreme levels, trial participants should have regular monitoring of blood concentrations.

The predicted vitamin D levels have been suggested as a surrogate for serum measures of 25(OH)D, but these may not be sufficiently reliable for safety monitoring (3). The Women's Health Initiative observed a statistically significant but very modest correlation between reported diet and supplement intake and measured 25(OH)D concentrations ($r = 0.19$; $P < 0.001$) (18). Indeed, only 3% of women in the upper fifth of the distribution (cutpoint, 67.6 nmol/L) reported intakes greater than 1,000 IU per day. Among controls in the VDPP, a similarly low correlation between total vitamin D intake and serum levels was observed ($r = 0.26$; $P < 0.0001$). This relatively poor prediction of serum concentrations from reported diet and supplement intake emphasizes the need for clinical monitoring in practice and on research studies. The need for monitoring may be particularly critical for research participants with baseline pretrial 25(OH)D concentrations in the nondeficient range. In the VDPP study, increments of intake of 1,000 IU were associated with 18 nmol/L higher 25(OH)D. Therefore, an

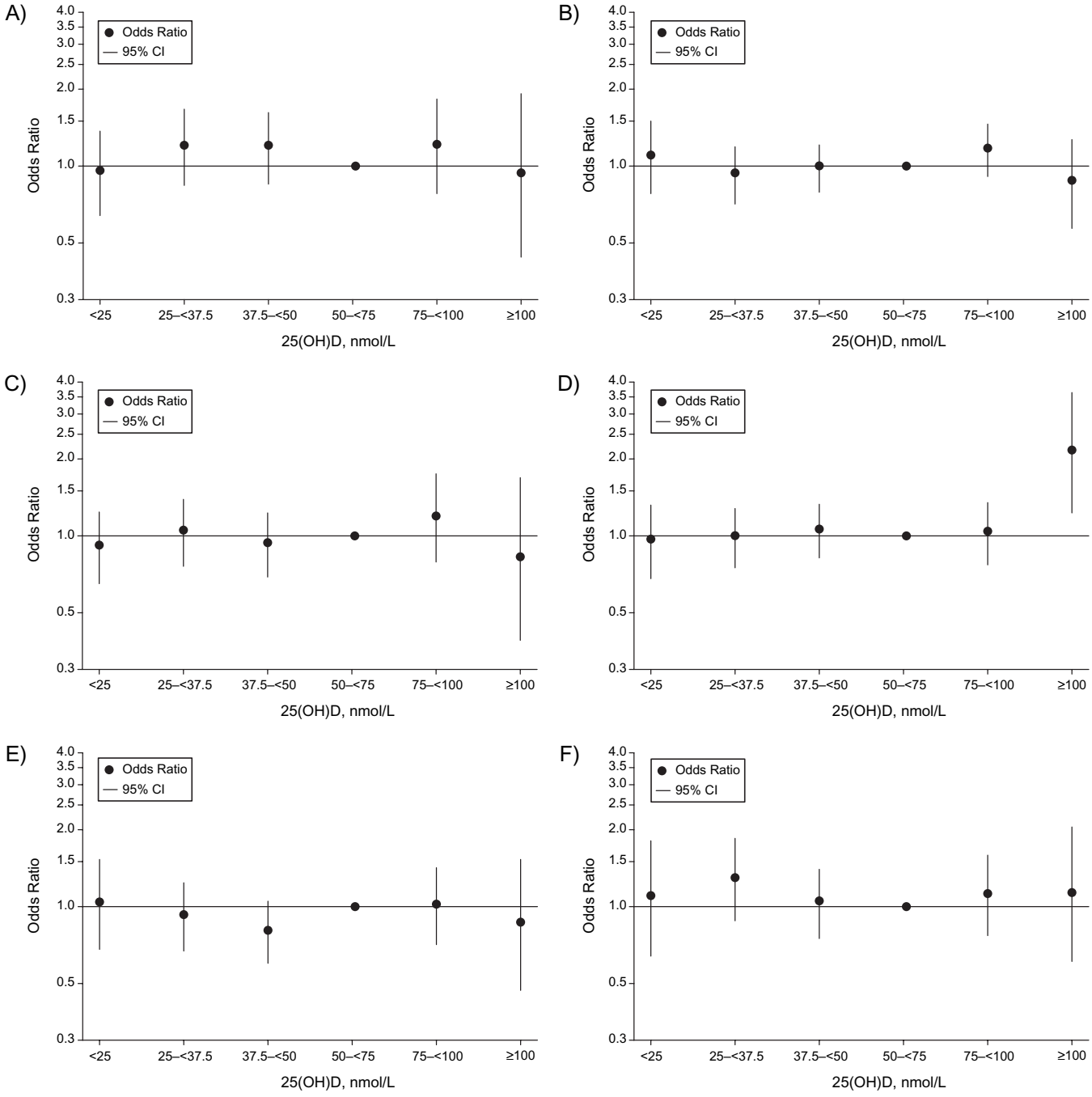

Figure 1. Odds ratios and 95% confidence intervals for cancer risk by site across categories of circulating levels of 25-hydroxyvitamin D (nmol/L), Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Odds ratios were derived from conditional logistic regression models. Reference category: 50–<75 nmol/L 25(OH)D. A, kidney cancer adjusted for education, body mass index, height, smoking status at blood draw, history of high blood pressure at blood draw, history of diabetes at blood draw, and alcohol use at blood draw. B, non-Hodgkin lymphoma adjusted for height (≤165, >165–171, >171–177.781, >177.781 cm). C, upper gastrointestinal (combined esophageal and gastric) cancers adjusted for alcohol, smoking, education, and history of gastric surgery. D, pancreatic cancer adjusted for body mass index (<18.5, 18.5–<25.0, 25.0–<30.0, 30.0–<35.0, ≥35.0 kg/m^2 (WHO categories), missing), smoking (never, former quit ≥15 years ago, former quit 1–<15 years ago, former quit <1 year or currently smoking <20 cigarettes per day, and former quit <1 year or currently smoking ≥20 cigarettes per day), and diabetes (yes, no, missing). The highest category of vitamin D and association with pancreatic cancer is statistically significant (95% confidence interval: 1.23, 3.64). E, endometrial cancer adjusted for education (less than high school, completed high school, vocational school, some college, college graduate, graduate studies, missing), menopausal status (pre-, peri-, post-, missing), age at menarche (<13, ≥13 years of age, missing), parity (0, 1, 2, 3, ≥4, missing), oral contraceptive use (never, ever, missing), hormone replacement therapy (never, ever, missing), smoking (never, former, current, missing), history of high blood pressure (yes, no, missing), history of diabetes (yes, no, missing), and body mass index (<25, 25–<30, ≥30 kg/m^2, missing). F, ovarian cancer adjusted for duration of oral contraceptive use and number of pregnancies. CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; WHO, World Health Organization.

individual in the adequate range of vitamin D concentrations (e.g., >75 nmol/L) who is taking more than 2,000 IU per day of total vitamin D intake may have vitamin D concentrations in the range associated with increased risk of pancreatic cancer (11, 15).

The report from the International Agency for Research on Cancer examining the association between vitamin D status and cancer risk calls for randomized trials of vitamin D for cancer prevention, stating that observational studies are unlikely to ''disentangle the complex relationships between vitamin D and known cancer risk factors'' (3, p. 1). The report also points to contradictory results between observational studies and randomized trials as further evidence for the need to conduct more trials rather than additional observational studies (3). However, observational studies examine a broad range of exposures and can evaluate multiple health outcomes and potential harms, including rare outcomes. Clinical trials are unlikely to be large enough or to be conducted long enough to detect rare adverse events. In the relatively short history of cancer chemoprevention, unwarranted harms have occurred in intervention trials with doses of supplements previously considered safe (19–21). Cancer prevention trials require large sample sizes because cancer outcomes are rare, even for the more common cancer sites. As a consequence, many individuals are exposed, but relatively few can derive the actual benefit of a cancer prevented, if the intervention does indeed decrease the risk of cancer. Thus, under the principle of ''first do no harm'' as well as the wise expenditure of research dollars, it is critical to have compelling evidence of potential benefit for a proposed preventive intervention that far outweighs harms, before embarking on large-scale trials. Observational studies may provide such evidence, especially when outcomes are rare. The results of the VDPP study should be included in the overall evaluation of potential risks and benefits of vitamin D supplementation proposed for future trials or being used in ongoing prevention trials.

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