Prediagnostic Hematocrit Values and Subsequent Cancer Risk

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Abstract
In this prospective study, the association between hematocrit values measured in 1965–68 and subsequent cancer incidence was studied among 7737 Japanese-American men in Hawaii. With an increase in hematocrit levels, there was an increasing risk for lung cancer, especially squamous or small cell type, and for kidney cancer. However, a statistically significant trend remained only for kidney cancer after adjusting for smoking history. The relative risk for kidney cancer was 4.94 (95% confidence interval, 1.03–23.63) for subjects with hematocrit values of 47 or higher compared with those with hematocrit values of 43 or lower. In contrast, the risk of oral-pharyngeal cancer decreased with increasing hematocrit levels. With adjustment for cigarette smoking and alcohol intake, the relative risk for oral-pharyngeal cancer was 0.20 (95% confidence interval, 0.04–0.88) for subjects with hematocrit values of 47 or higher compared with those with hematocrit values of 43 or lower. Association with kidney or oral-pharyngeal cancer was not affected by the time interval between examination and diagnosis of these cancers (≤10 and >10 years). Erythropoietin production by kidney tumors and micronutrient deficiencies in oral-pharyngeal cancer cases may partially account for these results.

Introduction
Hematocrit levels are affected by various endogenous and exogenous factors, including sex hormones, psychological stress, cigarette smoking, nutritional intake, and exposure to toxic substances (1). These factors have also been implicated in carcinogenesis. Therefore, hematocrit may be a useful biological marker to identify etiological factors of cancer and to evaluate the effects of various exposures.

In a ten-year mortality study, Waters et al. (2) reported that subjects with hemoglobin and hematocrit values near the mean had the lowest mortality rate. Subsequent studies found that an excess of cancer deaths occurred among those with low hemoglobin/hematocrit levels and an excess of cardiovascular deaths occurred among those with high hemoglobin/hematocrit levels (3–5). Because these studies usually had a relatively short period of follow-up (2–5), the anemia could be a consequence of the cancer.

Several specific cancers have been linked to anemia or low hematocrit values. Patients with Plummer-Vinson syndrome, who have iron deficiency anemia, have an increased risk for upper digestive tract cancer (6–9), and patients with pernicious anemia have an increased risk for gastric cancer (10–13). Otherwise, little is known about the association of hematocrit levels with the occurrence of other cancers.

An earlier report from the Honolulu Heart Program showed there was no association between hematocrit levels and total cancer deaths after 10 years of follow-up (14). However, the association of hematocrit values with cancer incidence by site has not been reported. These subjects have now been followed for more than 20 years, and the identification of a substantial number of incident cases of cancer permits us to assess the relation of hematocrit levels to cancer incidence by site.

Materials and Methods
The subjects for this study were American men of Japanese ancestry, born between 1900 and 1919, and residing on the Hawaiian island of Oahu. They were identified by the Honolulu Heart Program in 1965 with the use of the comprehensive 1942 Selective Service draft registration files (15). Of 11,148 identified men, 8,006 (71.8%) were interviewed and examined between 1965 and 1968. One hundred eighty men (1.6%) died before they could be examined, and 2962 (26.6%) did not participate in the program.

The subjects came to the baseline examination in a nonfasting state, and blood was drawn 1 h after a 50-g glucose load. Hematocrit levels were determined by the method of Guest and Siler (16). During the interview, information was collected on cigarette smoking history and alcohol intake (ounces/month).

Subsequent cases of cancer in the cohort have been identified by continuous surveillance of all general hospitals on Oahu and by linkage with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Each diagnosed case was confirmed by histological examination. Histological types of lung cancer (squamous and small cell carcinoma, adenocarcinoma, and others) were determined based on the classification of the World Health Organization (17). The slides from each case were reviewed by one of us. There were 81 prevalent cancer cases diagnosed before examination, 142 suspected cancer incident cases without histological confirmation, and 46 examinees without a hematocrit value. These subjects were excluded from the analysis. As a result, 7737 subjects remained in the study.

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Analysis of covariance (18) was used to calculate age-adjusted means of hematocrit. Cox proportional hazards regression models (19) were fitted to estimate age- and covariate-adjusted relative risks and associated 95% confidence intervals for specific sites of cancer according to levels of hematocrit. Adjustment was made for the following variables in addition to age: (a) for lung cancer, a detailed cigarette smoking history, i.e., current smoker status, age started smoking (current smokers), number of cigarettes smoked per day (current smokers), former smoker status, maximum number of cigarettes smoked per day (former smokers), and number of years this maximum amount was smoked (former smokers); (b) for oral-pharyngeal cancer, the detailed cigarette smoking history and total alcohol intake (ounces/month); (c) for kidney cancer, the detailed cigarette smoking history and use of cigar/pipe. A test for linear trend in the log of the relative hazard was also performed by Cox models. Each subject's time at risk was computed as the time from his examination to the diagnosis of cancer, death, or October 30, 1990, whichever occurred first. If more than one type of cancer was diagnosed in the same person, only the initially diagnosed cancer was considered.

### Results

A total of 1468 incident cases of cancer were identified during the follow-up period. The hematocrit levels of cancer cases and noncases are compared in Table 1. The cancer cases are separated by specific site and histological type. The age-adjusted mean hematocrit values were significantly higher (P < 0.05) in cases with lung cancer and kidney (renal cell) cancer. They were significantly lower in cases with oral-pharyngeal cancer. The association with lung cancer was limited to cases with squamous or small cell carcinoma.

Table 1 shows the age-adjusted relative risks for selected sites of cancer according to approximate tertiles of hematocrit values, based on all study subjects (≤43, 44-46, ≥47). There was an increase in risk for all types
of lung cancer with the increase in hematocrit levels. The significant trend was mainly due to the squamous or small cell histological type. A progressive increase in risk with ascending hematocrit values was also observed for kidney (renal cell) cancer. In contrast, there was a decrease in the risk for oral-pharyngeal cancer with increasing hematocrit levels.

The effects of simultaneous adjustment for confounding factors are shown in Table 3. After adjusting for cigarette smoking history, the positive association between the hematocrit and lung cancer was no longer statistically significant. The positive association between renal cell carcinoma and hematocrit levels remained significant with adjustment for cigarette and cigar/pipe smoking history. The decreasing trends in risk for oral-pharyngeal cancer also remained significant with adjustment for covariates.

Next, the relative risks for oral-pharyngeal and kidney cancer by time interval from examination to diagnosis of cancer were determined (Table 4). The decreasing trend in risk of oral-pharyngeal cancer and the increasing trend in risk of kidney cancer with increasing hematocrit levels were observed for cases diagnosed during the first 10 years and after 10 years, but none of these associations was statistically significant.

Discussion

Although an elevated hematocrit was associated with an increased risk of lung cancer, the association was no longer significant after adjustment for cigarette smoking. An earlier prospective study also found that the mean hemoglobin levels were similar between lung cancer patients and cancer-free subjects with adjustment for smoking status (20). Smokers are continuously exposed to elevated levels of carbon monoxide (21, 22), which binds to hemoglobin to form carboxyhemoglobin, an inactive form of hemoglobin that has no oxygen-carrying capacity (22, 23). Therefore, smokers maintain higher hemoglobin and hematocrit levels than nonsmokers to compensate for the decreased oxygen delivery capacity (24–27). Carbon monoxide also increases vascular permeability (28), which decreases plasma volume and increases hematocrit levels in smokers. Furthermore, the decreased pulmonary function caused by cigarette smoking may have accelerated hypoxemia leading to further stimulation of erythropoiesis. This view is consistent with the finding that the association with hematocrit levels was limited to squamous and small cell carcinomas, which are more strongly associated with cigarette smoking than other cell types of lung cancer (29–31).

Hematocrit levels were also elevated in cases of renal cell carcinoma. Although several case-control studies have demonstrated an increased risk of renal cell carcinoma in cigarette smokers (32–35), it is unlikely that the association with hematocrit observed in the present study is due to confounding from cigarette smoking. There was no difference in the cigarette smoking history between cases and noncases. Adjustment for the percentage of other tobacco users, which was significantly higher in kidney cancer cases than in noncases, did not change the results. Renal carcinoma is one of several types of malignant and benign tumors that produce erythropoietin (36–38). In addition to neoplasms, other chronic renal diseases, such as hydronephrosis, cystic kidney disease, and glomerulonephritis, have been associated with secondary polycythemia (38, 39). Therefore, the elevated levels of hematocrit in cases of kidney cancer may be related to secondary polycythemia due to preclinical tumors.

The inverse association of the hematocrit levels with cancer of the oral cavity and pharynx in this cohort resembles the association of these tumors with the Plummer-Vinson syndrome (6–8). This syndrome occurs almost exclusively in women and has been attributed to the combination of iron and multivitamin deficiency (9). Although this is a male cohort, the same principles may apply. In addition, a defect in cell-mediated immunity has been reported in patients with iron-deficiency anemia (40). Smoking and alcohol are also important risk factors for this site of cancer. However, adjustment for these factors did not affect the results.

Sex hormones have a significant role in erythropoiesis. Men usually have higher hemoglobin/hematocrit

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Table 4  Age-adjusted relative risks and 95% confidence intervals for cancers of the oral-pharynx and kidney according to hematocrit levels by time interval from initial exam to diagnosis of cancer

<table>
<thead>
<tr>
<th>Interval (years)</th>
<th>Type of cancer</th>
<th>Hematocrit level</th>
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<tr>
<td></td>
<td></td>
<td>≤43*</td>
<td>44–46</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RR*</td>
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<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>0.14–2.58</td>
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<td>Kidney (renal cell)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RR</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>0.22–8.17</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Oral-pharynx</td>
<td>No.</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>0.17–1.60</td>
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<tr>
<td></td>
<td>Kidney (renal cell)</td>
<td>No.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
</tbody>
</table>

* Referent group.

* RR, relative risk; CI, confidence interval; NA, not applicable.
levels than women (41). Testosterone deficiency in men and castration or estrogen administration to a male reduce the hemoglobin level (1). It has been suggested that endogenous and exogenous sex hormones are involved in the etiology of some sites of cancer in men including cancers of the prostate (42) and colon (43, 44), especially the proximal colon. However, we did not find any association between hematocrit levels and suspected hormone-related cancers.

One limitation of this study was that data were not collected on other hematological parameters. The physiological basis for our findings could be assessed more accurately if the RBC, hemoglobin, serum iron, transferrin, and ferritin levels were also known. Another point of consideration is that the absolute values of hematocrit in our study subjects may be artificially elevated by a glucose load, since the red cell acts as an osmometer (1). However, this effect should be similar for cases and noncases.

In summary, this prospective study showed that prediagnosed hematocrit levels were positively associated with the risk of lung and renal cancer and inversely associated with oral-pharyngeal cancer. The association with lung cancer was largely attributable to cigarette smoking. The association between hematocrit levels and the other two types of cancer was not affected by the interval from examination to diagnosis. However, because of the small number of cases and their relatively poor prognosis (45), the findings could still be a consequence of the disease process. Further studies are required to establish the association.

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References