The Relationship of Dietary Intake and Serum Levels of Retinol and Beta-Carotene With Breast Cancer

Results of a Case-Control Study

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The possible association between the risk of breast cancer, blood level, and dietary intake of preformed Vitamin A (retinol) and beta-carotene was investigated in a case-control study carried out from May 1982 to June 1985. The patients studied were 214 previously untreated individuals with T1–2, N0–1, M0 breast cancer admitted to the National Cancer Institute of Milan and 215 controls admitted for conditions other than neoplastic or metabolic disorders. Both cases and controls were selected from an age group ranging from 30 to 65 years old. Plasma levels of retinol and beta-carotene were tested from blood samples drawn during the first day after admission to the hospital. A questionnaire about diet was used to estimate the mean intake of 69 food items from which a daily dietary index of retinol and beta-carotene intake was computed. Information relating to the woman's history, socioeconomic status, and known risk factors for breast cancer was also collected. No association was found between beta-carotene (in the diet or blood) or dietary retinol and the risk of breast cancer. As for blood retinol, our data show a significant trend of increasing risk with higher levels; multivariate relative risk for subsequent serum levels based on the control quintiles, are 1, 1.5, 1.8, 1.7; (test for linear trend: chi-square = 8.26). Thus, these findings, together with the results of other studies,[47,48] suggest that retinol and beta-carotene are unlikely to be related to the risk of breast cancer.

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THE ANALYSIS OF DATA reported in the literature about the possible association between vitamin A and the risk of cancer[1–5] shows that the situation is rather confused, contradictory, and uncertain. In fact, while vitamin A and its precursor, beta-carotene play a protective role in several experimental tumors in animals,[6–12] its possible effect on various tumors in humans are extremely uncertain.[13–17] Consistent evidence concerns lung tumors,[14,18,19–21] especially microcytoma,[22,23] in which the protective role of vitamin A or its precursors emerges from several studies. In particular, beta-carotene (serum levels of which are reportedly influenced by dietary intake) attracts attention as a protective factor, which is commonly explained in terms of its "quenching" properties of free radicals.

Regarding tumors in other common sites and, in particular, breast cancer,[24,25] epidemiologic studies are few, the number of cases is not always appropriate for study, and the results are nearly always statistically not significant, especially when the dose-effect relationship is taken into consideration. Moreover, a great majority of researches have tried to evaluate the role of vitamin A and its precursors by information collected from questionnaires on diet. In only one paper[26] was the blood level of retinol and beta-carotene tested. Our case-control study[28] investigated the possible association between the risk of breast cancer and blood level as well as dietary intake of vitamin A and carotenoids. This simultaneously permitted the analysis of the possible relationship between dietary habits and blood level of vitamin A and beta-carotene.

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Patients and Methods

Our sample was made up of 214 cases of primary carcinoma of the breast (T1–2, N0–1, M0, according to the TNM classification[29]). They were not previously treated and were selected consecutively when admitted to the National Tumor Institute of Milan (I.N.T.) from May 1982 to June 1985. Two hundred and fifteen controls were selected from female patients consecutively admitted to San Raffaele, one of the major university hospitals of Milan, during the same period, with the exception of patients admitted for malignant tumors and for hepatic, vascular, and metabolic diseases.

Both cases and controls had the following characteristics: age between 30 and 65 years; residence in Milan or its province; negative medical history of breast cancer or other malignancies. With reference to Milan and its province, the "catchment" area of the two hospitals are comparable.

The day after patients were admitted, a blood sample was taken from each subject after a fast. Part of the plasma, frozen at −18°C, was sent to the Hoffman-La Roche laboratories at Basle to be tested for retinol, beta-carotene, vitamin E, vitamin C, and vitamin B_2 levels using high pressure liquid chromatography.[30] The plasma from both cases and controls was sent in one single parcel and could only be identified by the consignment number. Matching the results of these chemical analyses with the subject could only be carried out by the research group and not by people in charge of the analyses.

The remaining plasma was sent to the central laboratory of the I.N.T. to determine total cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), copper, and zinc. The lipidic fraction was determined by means of enzymatic reaction while trace metals were determined through atomic adsorption spectrophotometry. Because of some troubles during blood collection and/or its transfer to the two laboratories, a few blood samples were missing.

All subjects were interviewed in the same standard way, during hospitalization, by previously trained interviewers. All subjects willingly cooperated.

Selection of Cases

Cases were chosen by means of a periodic check (usually weekly) from the patients admitted to the I.N.T. Those who were diagnosed at admission with primary breast cancer and with the required characteristics were randomly selected. Temporary admittance of patients into the study took place after the first clinical diagnosis. They were definitely included after histologic confirmation.

Two hundred fifty-eight women were interviewed. Forty-two patients were excluded because of a negative histologic diagnosis (benign breast diseases), and two patients were excluded because they had previous malignancies. The remaining 214 cases range in age from 31 to 65 (median age, 48).

Selection of Controls

Controls were chosen by means of a periodic examination (usually weekly) from patients admitted to the San Raffaele Hospital. They were chosen in such a way as to have an equal number of cases and controls during the same period of time.

The controls were hospitalized with the following illnesses: orthopedic illnesses, 46%; acute surgical conditions (strangulated hernia, acute appendicitis, perianal fistula), 22%; miscellaneous including peripheral venous diseases, benign tumors, and other similar conditions, 32%.

A total number of 222 controls were interviewed. Seven individuals were excluded because the diagnosis when they were discharged did not agree with the protocol. The remaining 215 controls ranged in age from 30 to 64 (median age, 47).

Questionnaire

Dietary information was collected by two dieticians who interviewed an approximately equal number of cases and controls. The interview was presented to the patients as a "study on the relationship between diet and health," in the hope that information about tumor and diet often disseminated by mass media would not influence the patients, especially cases.

The interview lasted about 50 minutes. The first part of the questionnaire dealt with general information regarding the socioeconomic situation of the subject and her medical history. The second part dealt with dietary information elicited through a dietary history questionnaire.[31–34] Subjects were asked to try to remember their usual weekly consumption of 69 foods. Breakfast, lunch, dinner, and morning and afternoon snacks were all mentioned to patients to remind them of their entire daily food consumption. If the patients' eating habits had changed during the past 12 months, they were asked to refer to the previous 12 months' consumption. For each meal considered, dieticians listed possible foods that were rarely consumed. They were particularly attentive while in collecting information about seasonal foods such as fruit and vegetables. To quantify their intake, patients were invited to report amounts of foods by showing the size of glasses, cups, spoons, or by refer-

TABLE 1. Estimates of Breast Cancer Odds Ratio Relative to Known Risk Factors

Factors		Cases	Controls	Odds ratio*	95% CI
Age at menarche (yr)					
Premenopause	≤12	40	59	1.1	(0.4–2.6)
	13–14	55	44	1.8	(0.7–4.6)
	≥15*	11	13	1.0†	
Postmenopause	≤12	42	36	1.2	(0.5–2.8)
	13–14	52	47	1.1	(0.5–2.6)
	≥15*	13	16	1.0†	
Age at first birth (yr)	≤24	32	42	1.0†	
	25–29	48	47	1.4	(0.7–2.6)
	≥30*	30	18	2.0	(0.9–4.3)
Parity‡	0	38	26	1.0†	
	1–2	100	85	0.9	(0.5–1.8)
	≥3*	12	22	0.3	(0.1–0.8)
Age at menopause (yr)	<50	65	64	1.0†	
	≥50	43	35	1.2	(0.7–2.1)
Quetelet index					
Premenopause	<20	24	17	1.0†	
	20–24	46	59	0.6	(0.3–1.2)
	25–28	25	29	0.6	(0.2–1.3)
	>28	11	11	0.6	(0.2–1.8)
Postmenopause	<20	6	11	1.0†	
	20–24	29	25	2.0	(0.3–5.9)
	25–28	48	34	2.4	(0.8–6.7)
	>28	24	28	1.5	(0.5–4.4)
Family history of breast cancer					
No		178	203	1.0†	
Yes		36	12	3.6	(1.8–7.3)
Education					
Licenza elementare§	(5 yr)	95	119	1.0†	
Licenza media inferiore‖	(3 yr)	56	56	1.5	(0.9–2.5)
Licenza media superiore¶ and university degree	(4–5 yr)	63	40	2.5	(1.5–4.2)

CI: confidence intervals.
* Allowance was made for decade of age by means of the Mantel-Haenszel Procedure for all relative risk estimates.
† Reference category.
‡ Analysis was confined to women whose parity was equal to gravidity.
§ Analagous to primary school completion.
‖ Analagous to junior high school completion.
¶ Analagous to high school diploma.

ring to the weight of commercial packages. If patients were unable to quantify food consumption, dieticians recorded weights of foods according to a list of standard weights prepared ad hoc.

From the 69 foods or groups of foods, the amount of weekly consumption was transformed into the daily intake of nutrients by means of tables derived from different sources.[35,36]

Statistical Methods

The role of known risk factors (age at menarche, parity, age at first birth) was investigated by using the Mantel-Haenszel procedure.[37] The effect of retinol and beta-carotene on the risk for breast cancer adjusted for age and all factors mentioned in Table 1 was evaluated by multiple logistic models fitted by the Generalized Linear Interactive Modelling package (GLIM).[38] Furthermore, retinol and beta-carotene blood levels were adjusted for cholesterol and triglyceride blood levels, while retinol and beta-carotene dietary indices were adjusted for total calories and alcohol intake.

In these analyses all the continuous variables (age, cholesterol, triglycerides, total calories, and alcohol intake excluded) were divided into classes. In particular, both blood and dietary values of beta-carotene and retinol were arranged into five classes according to the quintiles determined by the distribution of controls; the first quintile was taken as the reference class. Variables, the roles of which had to be investigated together with the main effects of covariates, were inserted in the logistic models as explanatory variables.

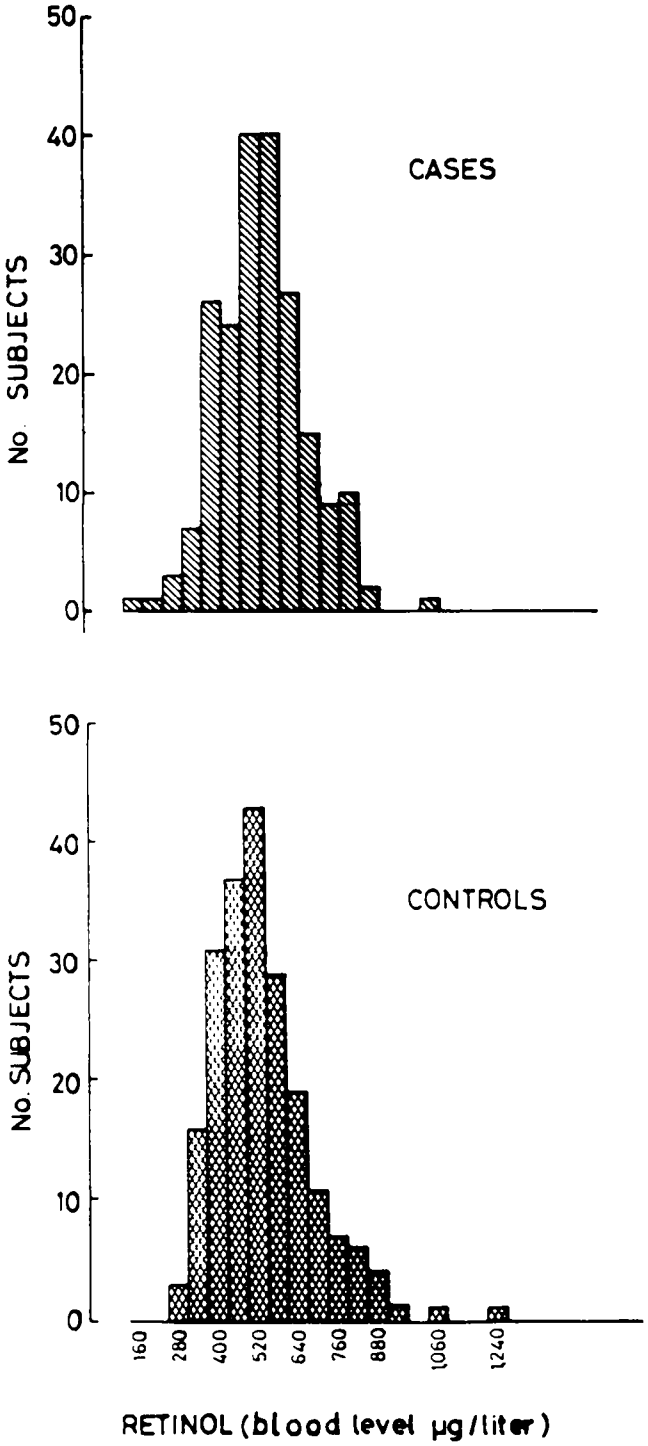

FIG. 1. Distribution of retinol blood levels (µg/l) in cases and controls.

Results

The estimated odds ratios (OR) relative to known risk factors are reported in Table 1. Significant values were obtained for parity, family history (only mother and her female relatives) age at first birth, and educational level. Figures 1 and 2 show the frequency distribution of retinol and beta-carotene blood levels for cases and controls.

After testing for heteroschedasticity and skewness, the statistical analyses suitable for comparing cases and controls were carried out by using the logarithmic transformation of these variables. Table 2 reports sample size (in brackets) median, mean, standard deviation of original data, and results of the *t* tests on the logarithmic metameter.

A significant difference was found for blood retinol—the mean level of cases was higher than for controls. The mean blood level of beta-carotene was higher in cases than in controls, but the averages were not significantly different. After excluding the one patient whose beta-carotene blood level was 4330, one obtains a mean of 418.44 and a standard deviation of 263.17. Cholesterol and triglyceride blood levels in controls were lower than in cases; after allowing for this, no significant difference between mean levels of blood retinol and beta-carotene in cases and controls emerged.

Regarding the dietary intake of retinol and beta-carotene, no significant difference was found. However, the mean dietary intake of retinol seems to be lower in the cases, while beta-carotene seems to be higher. The same results were achieved after adjusting for total calories and alcohol intakes.

The association between dietary intake of retinol and beta-carotene and the corresponding blood levels has also been investigated both for cases and controls. Only correlation coefficients between the dietary beta-carotene index and the corresponding blood level in cases and controls ($r = 0.27$ and $r = 0.20$, respectively) are statistically significant ($P < 0.01$).

Data referring to the possible association between breast cancer and retinol and beta-carotene are shown in Tables 3 and 4. The odds ratio tends to increase with the blood levels of retinol showing a statistically significant linear trend, while no significant result appears in relation to dietary levels of retinol (Table 3). The values of the odds ratio relative to blood levels of beta-carotene are not significantly different in all the classes (Table 4). In terms of the dietary beta-carotene index, the increase of the estimated OR is statistically significant only in the next to last quintile, although the chi-square for trend is far from significant.

In light of the possibility that dietary factors influence postmenopausal breast cancer to a greater extent than premenopausal breast cancer, the analyses that were performed on the whole series were also performed after

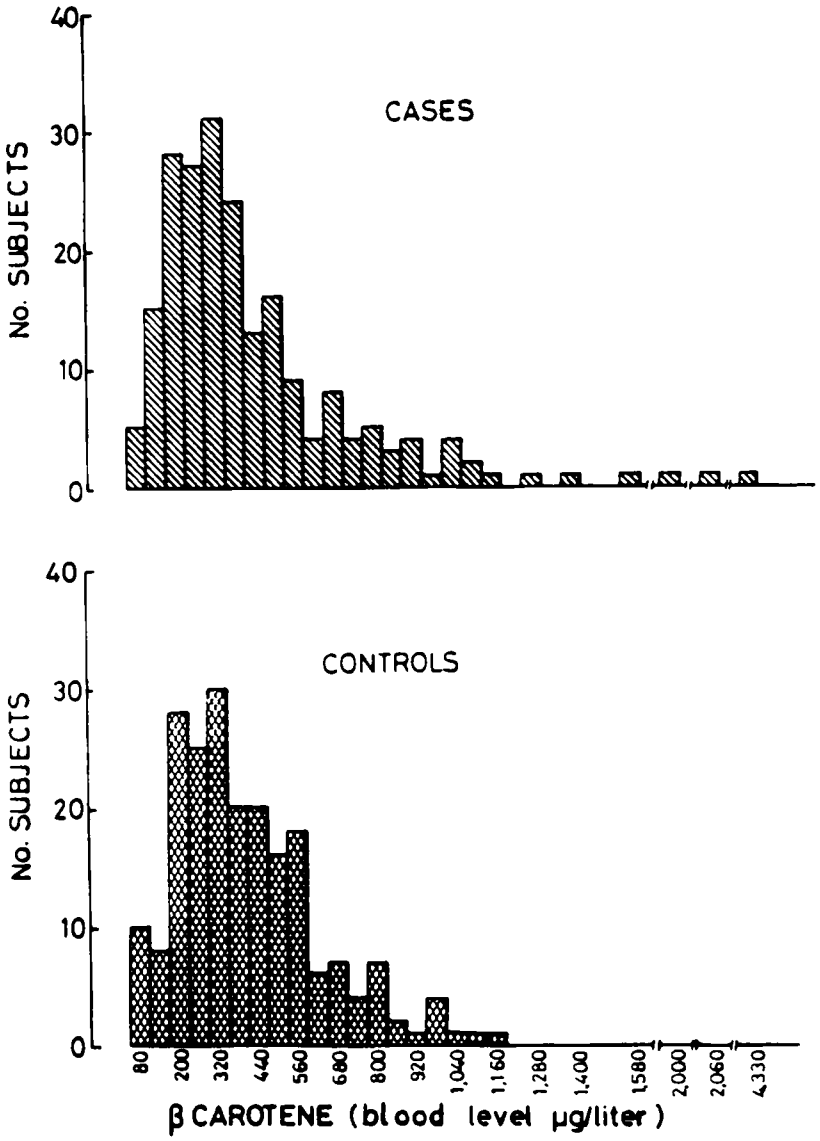

FIG. 2. Distribution of beta-carotene blood levels (µg/l) in cases and controls.

dividing the data into premenopausal and postmenopausal categories. We found no difference between the two categories with regard to the retinol/beta-carotene hypotheses.

Discussion

The results of this study indicate that higher serum levels and dietary intake of preformed vitamin A, retinol, or its precursor, beta-carotene, do not appear to protect against the risk of breast cancer. We were unable to show that these findings were incidental because cases and controls were drawn from comparable areas, participation rate was total, and allowance for a large number of identified potential confounding factors (including the major known or suspected correlates of breast cancer) failed to modify any of the results.

In this study the values of the odds ratios relating to well-known risk factors of breast cancer tend to be the same as those already published.[39-42] Parity, family history, and education are risk factors that emerged in a statistically significant way. The level of education is higher in cases, and data seem to suggest that cases belong to a higher social class than controls.[39,43,44]

Because we are aware of the controversy about information collected by dietary questionnaires, we used the "Dietary History" type questionnaire. This has been shown to compare favorably with other types of questionnaires in case-control studies.[32,33] Moreover, in our opinion, reference to the overall dietary history of the

TABLE 2. Blood Levels and Daily Dietary Intake of Retinol and Beta-Carotene in Cases and Controls: Median, Mean, Standard Deviation, and *t* Test After Logarithmic Transformation

	Retinol blood level (μg/l)		β-carotene blood level (μg/l)		Retinol dietary index (IU/day)		Beta-carotene dietary index (IU/day)	
	Cases (210)*	Controls (209)	Cases (210)	Controls (209)	Cases (214)	Controls (215)	Cases (214)	Controls (215)
Median	550.50	510.00	345.25	355.00	1,205.32	1,245.07	7,777.55	6,900.70
Mean	556.78	530.06	455.22	404.41	2,691.12	2,961.06	9,023.06	8,550.07
Standard deviation	133.79	144.36	419.31	219.50	3,209.97	3,150.07	7,029.01	5,364.00
t test after logarithmic transformation	2.12†		0.68‡		1.13‡		0.82‡	

* Numbers in parentheses indicate sample size.
† $P < 0.05$.
‡ Not significant.

TABLE 3. Distribution of Cases and Controls According to Blood Levels and Dietary Intake of Retinol in Groups Defined by Control's Quintiles Together With Pertinent Odds Ratios, Their 95% Confidence Intervals, and Chi-Square Test for Trend

	Quintiles					
	1	2	3	4	5	Total
Retinol blood levels						
Cases	27	32	40	57	54	210
Controls	44	41	43	39	42	209
Multivariate OR* (95% CI)	1.0†	1.3 (0.6–2.8)	1.7 (0.8–3.5)	2.2 (1.1–4.5)	2.0 (1.0–4.0)	$\chi^2_{trend} = 5.03$ ($P < 0.05$)
Retinol dietary intake						
Cases	41	41	68	32	32	214
Controls	43	44	42	43	43	215
Multivariate OR* (95% CI)	1.0†	1.1 (0.5–2.2)	1.5 (0.8–2.8)	0.9 (0.4–1.7)	0.7 (0.4–1.5)	$\chi^2_{trend} = 1.10$ (NS)

CI: confidence intervals; NS: not significant.
* Multivariate odds ratio adjusted for age, cholesterol, triglyceride blood level, and all factors in Table 1.
† Reference category.

TABLE 4. Distribution of Cases and Controls According to Blood Levels and Dietary Intake of Beta-Carotene in Groups Defined by Control's Quintiles Together With Pertinent Odds Ratios, Their 95% Confidence Intervals, and Chi-Square Test for Trend

	Quintiles					
	1	2	3	4	5	Total
Beta-Carotene dietary intake						
Cases	46	39	49	28	48	210
Controls	46	41	41	43	38	209
Multivariate OR* (95% CI)	1.0†	1.2 (0.6–2.4)	1.3 (0.7–2.4)	0.7 (0.4–1.4)	1.2 (0.6–2.3)	$\chi^2_{trend} = 0.03$ (NS)
Beta-Carotene dietary intake						
Cases	28	48	38	65	35	214
Controls	42	44	43	44	42	215
Multivariate OR* (95% CI)	1.0†	1.6 (0.8–3.2)	1.4 (0.7–2.9)	2.0 (1.1–4.0)	1.2 (0.6–2.5)	$\chi^2_{trend} = 0.72$ (NS)

CI: confidence intervals; NS: not significant.
* Multivariate odds ratio adjusted for age, cholesterol, triglyceride blood level, and all factors in Table 1.
† Reference category.

patient rather than to limited periods makes collected data more reliable because it tends to eliminate the risk of overestimating consumption of unusual foods.[45,46]

Since blood samples from cases were taken at the time of diagnosis, one could argue that the serum level of retinol and beta-carotene could be influenced by the already developed tumor and possible changes it might induce. To our knowledge, however, there are no data that support the hypothesis that the tumor may influence the blood level of retinol and beta-carotene.

An interesting aspect of our study is that it includes the simultaneous analysis of dietary and blood values of retinol and beta-carotene. The results obtained show a significant but low correlation between diet and blood values of beta-carotene, as Willett[47] already assessed in a smaller number of cases.

The few epidemiologic data available on breast cancer and retinol appear to be discordant. Graham *et al.*,[25] investigating the ingestion of foods containing retinol in 2720 women in a case-control context, found a statistically significant, though extremely weak, increase of risk that was related to a diminished dietary intake of retinol. In contrast, Wald *et al.*[26] concluded that blood retinol levels were not related to subsequent risk of breast cancer. Similarly, a large case-control study performed in northern Italy using an extremely simplified 14-item frequency questionnaire showed no association between estimated measures of retinol or beta-carotene intake and breast cancer risk.[48] Thus, in our opinion, it appears that dietary intake[47,48] and serum levels of vitamin A and its precursor, beta-carotene, are unlikely to be related to the risk of breast cancer.

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