Published in final edited form as:
Am J Obstet Gynecol. 2008 January ; 198(1): 37.e1–37.e8. doi:10.1016/j.ajog.2007.05.033.

Lycopene and other carotenoid intake in relation to risk of uterine leiomyoma

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Abstract

Objective—Carotenoids have antioxidant properties and have been associated with reduced risks of some cancers. We hypothesized that carotenoid intake may reduce the risk of diagnosed uterine leiomyoma (UL).

Study design—We evaluated the associations between dietary carotenoids and risk of diagnosed UL in 82,512 premenopausal women ages 26–46 in 1991 in the Nurses' Health Study II over ten years of follow up. Diet was assessed every four years with a validated food frequency questionnaire, and incidence of UL was assessed biennially by questionnaire.

Results—Total lycopene intake was not associated with diagnosed UL risk. Intake of beta-carotene were associated with slightly increased risks of diagnosed UL; this association was restricted to current smokers (for highest vs. lowest quintile, RR = 1.36, 95% CI= 1.05–1.76; p_{trend} = 0.003).

Conclusions—Overall, our findings do not suggest that carotenoids reduce the risk of diagnosed UL. Among current smokers, high intake of beta-carotene may slightly increase risk of diagnosed UL.

Keywords

carotenoids; uterine leiomyoma; fibroids

INTRODUCTION

Uterine leiomyoma (UL), also known as fibroids, are benign tumors of the uterus and are the leading cause of hysterectomy in the U.S., accounting for 1.2 billion dollars in hospital expenditures annually (1). Approximately one in four women will have UL that come to clinical

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attention (2). Symptoms vary in severity and include pelvic pain, abnormal menstrual bleeding, and pregnancy complications (3).

Carotenoids are fat-soluble pigments responsible for the yellow, orange, and red colors in many fruits and vegetables. All the carotenoids have antioxidant properties, and some (e.g. alpha-carotene, beta-carotene, and beta-cryptoxanthin) have provitamin A activity that may facilitate cellular differentiation (4). Lycopene has the strongest antioxidant properties of the carotenoids and higher intake has been associated with a reduced risk of many cancer types, including prostate, lung, and stomach (5,6). Recent work in cancer cell lines and animal models has demonstrated that lycopene can reduce transcription of steroid-related genes, IGF-1 expression, and inflammatory signals, suggesting that these pathways may account in part for the inverse association between lycopene and risk of some cancers (7,8).

The administration of a lycopene supplement to quail results in reduced number and size of leiomyoma in the oviduct compared to quail who did not receive the lycopene supplement (9). To our knowledge, the relation between carotenoids and UL has not been investigated in humans.

Here we have evaluated the association between carotenoids and diagnosed uterine leiomyoma in a prospective cohort of young women with over 10 years of follow-up.

MATERIALS AND METHODS

Study population

In 1989, 116,609 female registered nurses aged 25 to 42 years and living in one of 14 US states responded to a baseline questionnaire about their medical histories and lifestyles. Follow-up questionnaires have been sent biennially to update information on risk factors and medical events. Follow-up for this cohort exceeds 90%. This study has been approved by the institutional review boards of the Brigham and Women's Hospital, Boston, MA, and the Harvard School of Public Health, Boston, MA.

This analysis includes only those women who answered the first dietary questionnaire distributed in 1991 (n=97,758). Women were excluded if their total energy was unrealistic (<600 or >3500 kcal/day), if two or more food sections on the dietary questionnaire were left entirely blank (aside from dairy and eggs/meat to accommodate vegans), or if more than 70 food items out of 145 were left blank (n=2,359). In addition, women were excluded at baseline (1991) if they had a history of fibroids (n=5744), an unknown date of fibroid diagnosis (n=763), a history of hysterectomy (n=4822), a history of cancer (n=893), or were postmenopausal (n=665). Women were censored during follow-up at the time of death, report of a fibroid (with or without confirmation by ultrasound or hysterectomy), hysterectomy, cancer diagnosis, or if they became menopausal.

Exposure assessment

In 1991, 1995, and 1999 participants were asked to complete a food frequency questionnaire. Women were asked their average consumption of more than 130 different food items over the past year; nine possible responses ranged from "never/less than 1 per month" to "6 or more per day". Participants were also asked about use of multivitamins or other supplements, including information on dose and duration. The reliability and reproducibility of dietary measurements collected using the FFQ has been assessed in the Nurses' Health Study (NHS) and is described elsewhere (10).

The carotenoid intake for each woman was estimated by multiplying consumption frequency of each food, as reported on the dietary questionnaire, by the carotenoid content in that food

item determined primarily from the USDA-National Cancer Institute carotenoid database (11,12). The correlations between dietary and plasma carotenoid levels were assessed previously in a sample of non-smoking women in the Nurses' Health Study cohort and suggest a reasonable correlation between dietary intake and blood levels (covariate-adjusted Pearson correlations were 0.21 for lycopene, 0.48 for alpha-carotene, 0.27 for beta-carotene and lutein, and 0.32 for beta-cryptoxanthin) (13).

Since the amount of carotenoid consumed and the amount that is actually absorbed and used by the body differs among foods, we estimated the amount of bioavailable carotenoid using plasma data available from a similar cohort of women, the first NHS cohort (1976 – present), to determine the association between each carotenoid-containing food and plasma carotenoid levels. Previously, carotenoid levels were measured in the sera of selected participants in the original NHS study to evaluate the association between lycopene and risk of breast cancer (14). Nurses in the original NHS study completed dietary questionnaires virtually identical to those used in the NHSII. Using only the plasma carotenoid data from NHS controls (n=992), we used multivariate linear regression analysis with blood carotenoid levels as the dependent variable and all individual food contributors of carotenoid as the independent variables to estimate the contribution of each food item to measurable carotenoid levels in blood. The beta coefficients from these models were then used to weight the carotenoid contribution of each food (categorized as servings per week) to estimate the carotenoid level in the blood for participants of the entire NHSII cohort. A similar approach has been used to investigate the relation between lycopene intake and risk of prostate cancer (15).

Potential confounders including medical and reproductive history, lifestyle, and demographic characteristics were assessed at baseline and at 2-year intervals during follow-up.

Outcome assessment

Incidence of uterine leiomyoma was first assessed in 1993 when the participants were asked if they had ever had uterine fibroids diagnosed by a physician. If a participant answered "yes", she was asked when she was first diagnosed (before September 1989, September 1989 to May 1991, June 1991 to May 1993, after June 1, 1993), whether the diagnosis was confirmed by pelvic exam, and whether the diagnosis was confirmed by ultrasound or hysterectomy. For all subsequent questionnaires, women were asked if they had been diagnosed with a fibroid before, during, or after the current two-year study period. A woman was considered a case only if she reported a UL confirmed by an ultrasound or hysterectomy. Women who reported a new fibroid that had not been confirmed by ultrasound or hysterectomy (diagnosed by pelvic exam only) did not contribute person-time to that time period but were allowed to reenter the analysis in the future if the fibroid was confirmed. Methods utilized in other studies (16,17) include censoring unconfirmed cases (those identified by pelvic exam only) at first report and keeping them in the analysis as non-cases. We estimated hazard ratios using these two approaches and observed no substantive differences between the results of these methods and our own results. The midpoint between the receipt of the questionnaire before diagnosis and the receipt of the questionnaire after diagnosis was assigned as the date of diagnosis.

Marshall and colleagues examined the validity of self-reported diagnosis of UL in this cohort (16). Briefly, 243 (100 Caucasian, 143 African-American) randomly selected women with newly diagnosed UL by ultrasound or hysterectomy after 1989 were mailed a supplemental questionnaire including questions on symptoms and a request to review medical records. Of the 216 (89%) who responded, 6% denied the diagnosis and 34% confirmed the diagnosis but did not release their medical records. Among those cases in which medical records could be obtained, 93% were confirmed. The proportion diagnosed by hysterectomy, myomectomy, examination under anesthesia, or ultrasound did not differ between those who did and did not

give permission for medical record release, and the proportion confirmed by medical record did not vary significantly between white (94%) and black (92%) participants.

Statistical analysis

Each participant contributed follow-up time, measured in months, from the return of the 1991 questionnaire until report of a fibroid, death, the return of the 2001 questionnaire, or the last returned questionnaire if lost to follow-up. We used Cox proportional hazards regression models to estimate the hazard ratio of diagnosed UL while controlling for potential confounding variables. Covariate-adjusted models included age in months, age at menarche (≤10, 11, 12, 13, 14–15, ≥16, missing), infertility (yes, no, missing), marital status (ever, never, missing), ancestry (Caucasian, African American, Hispanic, Asian, Other), parity (nulliparous versus 1, 2, 3, or 4 pregnancies lasting 6 or more months), age at first birth (≤ 24, 25–30, >30 years, missing), time since last birth (<1 year, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, ≥16, missing), age at first oral contraceptive use (13–16, 17–20, 21–24, ≥25, missing), current body mass index (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, ≥30, missing), diastolic blood pressure (<65, 65–74, 75–84, 85–89, ≥90), antihypertensive therapy (yes, no), and total energy intake (continuous). Categories cutpoints for body mass index were chosen based on World Health Organization guidelines (18). We used the midpoint of the categories to perform a trend test.

We were able to reduce measurement error by updating dietary intake over time. To incorporate all measurements, we used a cumulative average in which all the data for a particular carotenoid up to that point is averaged. In addition, we used baseline carotenoid intake alone to assess whether a longer latency period is important.

Furthermore, we performed stratified analyses to evaluate whether the association between carotenoids and fibroids differs across subgroups. We stratified by recent breast or pelvic exam (no, yes for screening, yes for symptoms, missing) and fertility status (infertile, no reported infertility, missing) in order to assess whether the association between carotenoids and diagnosed UL differed among women with greater medical surveillance since observations in this subgroup are less susceptible to bias from asymptomatic UL. In addition, we were interested in evaluating the associations by smoking status (never, past, current) since previous epidemiologic studies suggest that smoking may influence the absorption of carotenoids (19) and smoking may modify the effect of carotenoids (20–21). Stratification variables (recent breast/pelvic exam, fertility, and smoking status) were updated with data from the most recent questionnaire. To test for heterogeneity between the strata, we conducted one-degree likelihood ratio tests comparing the model having both the main effects and the interaction terms with the model containing only the main effects. Interaction terms were created by multiplying a linear trend term for the carotenoids (based on the midpoints of each quintile) and a term indicating the stratum (for instance current smoker vs. past or never smokers).

In addition, we assessed the influence of misclassification of the outcome using methods proposed by Duffy and colleagues (22). Briefly, we determined the corrected log HR by dividing the uncorrected log HR by sum of the of the positive predictive value, the negative predictive value and negative one. In these analyses, we assumed self-reported UL had a positive predictive value of 93% based on the validation study performed earlier in this study population (16) and a negative predictive value of 51% based on a study by Baird and colleagues that showed half of the women in a randomly selected population who reported no UL had UL on ultrasound screening (23).

RESULTS

Between 1991 and 2001, the 82,512 women who provided dietary information contributed nearly 692,203 person-years of observation. During this time, there were 6,302 new diagnoses of uterine leiomyoma confirmed by ultrasound or hysterectomy. The distributions of uterine leiomyoma risk factors do not differ by baseline intake of lycopene (Table 1).

Overall, we observed no association between the cumulative average intake of lycopene and risk of diagnosed UL (Figure 1). Compared to women in the lowest quintile of cumulative average lycopene intake, the corrected HRs for women in the second, third, fourth, and fifth quintiles of cumulative lycopene intake were 1.01 (95% CI= 0.86–1.18), 1.11 (95% CI=0.94–1.31), 0.90 (95% CI=0.75–1.08), 0.97 (95% CI=0.79–1.20). With regard to baseline intake of lycopene (in 1991), women in the highest quintile had a 7% lower risk of diagnosed UL of borderline significance, but there was no association with other levels of lycopene use and no trend in the association (Table 2).

Intake of alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and zeaxanthin at baseline were not associated with diagnosed UL risk (data not shown). However, we observed a weak positive association between diagnosed UL risk and cumulative average intake of both beta-carotene and lutein/zeaxanthin (Table 3).

When we evaluated the association between beta-carotene and lutein/zeaxanthin and diagnosed UL by smoking status, we observed the strongest association among current smokers. Women who smoked had an increased risk of diagnosed UL with increasing beta-carotene intake ($p = 0.003$), while women who had never smoked or had smoked in the past had no increase in risk with beta-carotene intake ($p_{interaction} = 0.06$). We observed the same differences by smoking status for lutein/zeaxathin. When we included beta-carotene and lutein/zeaxanthin in the same model, the association among current smokers between beta-carotene and diagnosed UL remained (covariate adjusted HR for top to bottom quintile = 1.41, 95% CI: 0.98, 2.03) while the association between lutein/zeaxanthin and diagnosed UL was attenuated (covariate adjusted HR for top to bottom quintile = 0.96, 95% CI: 0.67, 1.38), suggesting that previously observed association between lutein/zeaxanthin and diagnosed UL was due to the correlation between beta-carotene and lutein/zeaxanthin. We observed no differences in the association between carotenoids and UL when we stratified by recent breast/pelvic exam or by fertility status (data not shown).

Overall, we observed little association between the carotenoid bioavailability scores and risk of diagnosed UL. Bioavailable alpha-carotene was associated with a slightly reduced risk of diagnosed UL but this association was attenuated after adjustment for confounders.

Our results regarding the association between carotenoids and diagnosed UL did not change appreciably when we corrected our estimates for misclassification of the outcome (assuming that half of the women who did not report UL actually had undiagnosed UL).

COMMENT

We observed no overall association between carotenoids and risk of diagnosed UL. Among smokers, we observed a modest increased risk of diagnosed UL with cumulatively averaged intake of beta-carotene.

To our knowledge, there are no previous studies in humans regarding carotenoid intake and risk of diagnosed uterine leiomyoma. One study in Japanese quail demonstrated that supplementation with lycopene reduces the incidence of leiomyoma in these animals (9). However, lycopene action in an animal model may not accurately represent lycopene action

in humans. Lycopene intake has been inversely associated with the risk of prostate, lung, stomach, and possibly other cancers (reviewed in 6), but UL are benign tumors and consequently may have a different etiologic path than malignant tumors.

Although we hypothesized that other carotenoids would reduce the risk of diagnosed UL due to their antioxidant properties, we observed that cumulative average intake of beta-carotene may slightly increase risk among smokers. This is consistent with randomized trials and observational studies that have shown an increased risk of various cancers among smokers with beta-carotene supplementation (24–29)) . Furthermore, data from animal models show that high dose beta-carotene in smoke-exposed animals results in multiple events that could increase cancer risk, including increasing the number of transient oxidative metabolites, diminishing retinoid signaling, and enhancing cellular proliferation (30). However, our observations regarding beta-carotene and UL risk may be due to bias or chance, particularly since the association is relatively weak.

Strengths of this study include its large sample size (over 6000 cases of diagnosed UL) and prospective design (alleviating concerns about selection or recall bias). In addition, our biennial collection of updated covariate information allows careful control for confounding and assessment of diet over an extended period. This is particularly important in this setting, since these nutrients may have protective or growth-promoting effects depending on proximity of intake to tumor development.

There are several limitations in this study, including our reliance on self-reported UL. Although we are confident that women who report a UL diagnosis actually have UL based on the validation study performed by Marshall and colleagues (16), we do not know how many women in the reference population have UL that have not come to clinical attention. Baird et al. performed ultrasounds on a random sample of women who had no UL diagnosis and found that approximately 50% had UL (23), suggesting that many UL are undiagnosed. Given that the undiagnosed UL are asymptomatic (or at least not symptomatic enough to come to clinical attention), these may not be important in terms of public health. When we consider misclassification of the outcome in our analyses, the observed associations remain the same, suggesting that despite these limitations our data are useful in describing UL risk. However, our misclassification correction cannot correct for systematic biases that may arise if women who have symptoms evaluated are more or less likely to eat carotenoids than women who do not have symptoms evaluated. For instance, busy women may eat fewer fruits and vegetables (and therefore fewer carotenoids) and may be less likely to have potential UL symptoms evaluated by a physician than women who are not busy. If this were true, then carotenoid intake may falsely appear to increase UL risk or may mask a protective effect of carotenoids.

Another limitation of our study is the small number of minorities in our population. Diagnosed UL are three times more common in African-American women than Caucasians and therefore pose a more serious public health concern in African-American populations (19,16). The small number of African-American women in our population limits our power to evaluate associations with diagnosed UL in this subgroup; this deserves to be evaluated in other studies.

Acknowledgements

We would like to thank Dr. Edward Giovannucci for his insightful comments.

Supported by DSM nutritional products Inc. Parsippany, NJ, National Cancer Institute grants CA50385, CA67262, T32 CA009001 (KLT), American Cancer Society research scholar grant RSG-00-061-04-CCE (ID)

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Table 1

Age-adjusted distribution of potential risk factors for uterine leiomyoma according to lycopene quntiles at baseline, NHSII 1991 – 2001

Characteristic	Quintiles of lycopene Q1 (low)	Q2	Q3	Q4	Q5 (high)
Median lycopene intake	3027	4737	6095	8230	13687
n	16466	16595	16513	16492	16446
Mean age (years)	35.7	35.7	35.7	35.7	35.7
Age at menarche (%)					
≤ 10 years	7	7	7	8	8
11 years	16	17	16	17	16
12 years	30	30	31	30	30
13 years	27	28	28	28	28
14–15	15	15	15	14	15
≥ 16	3	3	3	3	3
Missing	<1	<1	<1	<1	<1
Ever used oral contraceptives (%)	82	84	85	84	84
Age at first oral contraceptive use (%)					
<13 years	18	16	15	16	16
13–16 years	5	5	5	5	5
17–20 years	38	40	40	40	40
21–24 years	27	28	28	28	27
≥ 25 years	10	9	9	9	9
Missing	3	2	2	2	3
Infertile (%)	6	6	6	6	6
Ever married (%)	86	90	91	91	91
Parity					
0	32	26	26	26	27
1	19	18	18	17	16
2	30	35	35	35	34
3	14	16	16	16	16
≥4	4	5	5	5	5
Missing	2	2	2	2	2
Age at first birth (% among parous women)					
<24 years	36	35	36	37	38
25–30 years	50	52	52	51	50
>30 years	15	13	12	12	12
Time since last birth (% among parous women)					
<1 year	7	6	6	6	6
1–3 years	31	30	28	28	29
4–5 years	14	15	16	15	15
6–7 years	11	12	12	12	12
8–9 years	9	10	10	10	10
10–12 years	11	12	13	12	13
13–15 years	8	8	8	8	8
>16 years	9	8	7	8	8
Ancestry (%)					
White	89	93	93	94	94
Black	3	1	1	1	1
Hispanic	1	1	1	1	2
Asian	3	2	1	1	1
Other	4	3	3	3	3
Smoking (%)					
Never	68	67	66	65	65
Past	19	21	21	21	23
Current	13	12	12	13	12
Missing	< 1	< 1	< 1	< 1	< 1
Body Mass Index					

Characteristic	Quintiles of lycopene Q1 (low)	Q2	Q3	Q4	Q5 (high)
<20	14	13	13	12	13
20–21.9	24	24	25	24	24
22–23.9	18	20	20	20	20
24–24.9	8	8	8	8	8
25–26.9	10	10	10	11	10
27–29.9	9	9	9	9	9
>30	14	12	12	13	12
Missing	3	3	3	3	3
Diastolic Blood Pressure					
<65	22	22	22	22	23
65–74	47	48	48	48	47
75–84	24	24	23	23	23
85–89	4	4	4	4	4
≥90	3	2	2	2	2
Missing	<1	<1	<1	<1	<1
Antihypertension medication (%)	3	3	3	3	3

Table 2

Association between quintiles of lycopene* intake and incidence of uterine leiomyoma, Nurses' Health Study II 1991–2001

	Lycopene intake (quintiles)*					
	Q1	Q2	Q3	Q4	Q5	p_{trend}
Baseline						
Person years	137450	140286	138657	137712	138098	
Cases	1276	1215	1277	1307	1227	
Age adjusted HR, 95% CI	1.00	0.92 (0.85, 1.00)	0.96 (0.89, 1.04)	0.99 (0.91, 1.07)	0.92 (0.85, 1.00)	0.19
Multivariate adjusted HR**, 95% CI	1.00	0.95 (0.88, 1.03)	0.98 (0.91, 1.06)	1.00 (0.93, 1.09)	0.93 (0.86, 1.00)	0.18
Cumulative average updated						
Person years	162138	187270	152527	118744	71524	
Cases	1432	1681	1481	1042	666	
Age adjusted HR, 95% CI	1.00	0.99 (0.92, 1.06)	1.04 (0.97, 1.12)	0.94 (0.87, 1.02)	1.00 (0.91, 1.10)	0.61
Multivariate adjusted HR**, 95% CI	1.00	1.00 (0.93, 1.08)	1.05 (0.97, 1.13)	0.95 (0.88, 1.03)	0.99 (0.90, 1.08)	0.43

* The median values of lycopene intake for quintiles 1–5 in 1991 are 3283, 4742, 6064, 8143, and 12511 micrograms/day

** Adjusted for age, age at menarche (<10, 11, 12, 13, 14–15, >16), infertility (yes, no), marital status (ever, never), ancestry (white, black, Asian, Hispanic, other), age at first oral contraceptive use (<13, 13–16,17–20,21–24, ≥25), parity (0, 1, 2, 3, >4), age at first birth (<24, 25–30, >30), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, >16), current BMI (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, >30), diastolic blood pressure (<65, 65–74, 75–84, 85–89, >90), antihypertensive therapy (no, yes), calories (continuous)

Table 3

Association between cumulative average carotenoid intake (quintiles) and risk of diagnosed uterine leiomyoma, Nurses' Health Study 1991 – 2001

	Cases	Age-adjusted HR (95% CI)	Covariate-adjusted HR* HR (95% CI)
Alpha-carotene			
1	1230	1.00	1.00
2	1268	1.00 (0.92, 1.08)	1.04 (0.96, 1.13)
3	1250	0.96 (0.89, 1.04)	1.01 (0.93, 1.09)
4	1318	1.00 (0.92, 1.08)	1.06 (0.98, 1.14)
5	1236	0.93 (0.86, 1.01)	0.99 (0.91, 1.07)
p_{trend}		0.09	0.62
Beta-carotene			
1	1135	1.00	1.00
2	1188	1.00 (0.92, 1.08)	1.02 (0.94, 1.10)
3	1261	1.04 (0.96, 1.12)	1.07 (0.99, 1.16)
4	1375	1.11 (1.02, 1.20)	1.14 (1.06, 1.24)
5	1343	1.06 (0.97, 1.14)	1.07 (0.99, 1.16)
p_{trend}		0.05	0.04
Beta-cryptoxanthin			
1	1214	1.00	1.00
2	1306	1.07 (0.99, 1.15)	1.11 (1.02, 1.20)
3	1275	1.03 (0.96, 1.12)	1.08 (1.00, 1.17)
4	1272	1.02 (0.95, 1.11)	1.09 (1.00, 1.17)
5	1235	0.98 (0.91, 1.06)	1.06 (0.97, 1.14)
p_{trend}		0.22	0.56
Lutein/Zeaxanthin			
1	1132	1.00	1.00
2	1185	1.00 (0.92, 1.09)	1.02 (0.94, 1.11)
3	1278	1.06 (0.98, 1.15)	1.09 (1.01, 1.18)
4	1345	1.09 (1.01, 1.18)	1.12 (1.04, 1.22)
5	1362	1.09 (1.01, 1.18)	1.08 (1.00, 1.17)
p_{trend}		0.008	0.03

*Adjusted for age, age at menarche (<10, 11, 12, 13, 14–15, >16), infertility (yes, no), marital status (ever, never), ancestry (white, black, Asian, Hispanic, other), age at first oral contraceptive use (<13, 13–16,17–20,21–24, ≥25), parity (0, 1, 2, 3, ≥4), age at first birth (<24, 25–30, >30), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, >16), current BMI (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, >30), diastolic blood pressure (<65, 65–74, 75–84, 85–89, >90), antihypertensive therapy (no, yes), calories (continuous)