Hyperinsulinemia Predicts Fatal Liver Cancer but Is Inversely Associated With Fatal Cancer at Some Other Sites

The Paris Prospective Study

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OBJECTIVE — To investigate whether insulin is a risk factor for death by site-specific cancers.

RESEARCH DESIGN AND METHODS — This was a prospective cohort study of 6,237 nondiabetic French working men between ages 44 and 55 years at baseline from the Paris Prospective Study cohort. Death by site-specific cancers was investigated in relation to baseline insulin concentrations during fasting and 2 h after a 75-g oral glucose tolerance test.

RESULTS — Of the original 6,237 men in the cohort, 1,739 died over the 23.8 years of follow-up, 778 (45%) from cancer. Baseline hyperinsulinemia, both fasting and 2-h, was significantly associated with fatal liver cancer, with age-adjusted standardized hazards ratios of 2.72 (95% CI 1.87–3.94) and 3.41 (2.23–5.21). In contrast, fasting hyperinsulinemia was inversely associated with fatal lip, oral cavity, and pharynx cancer and larynx cancer, with hazards ratios of 0.55 (0.41–0.75) and 0.63 (0.47–0.83), respectively; 2-h insulin concentrations were inversely associated with stomach and larynx cancers (hazards ratios 0.62 [0.43–0.90] and 0.66 [0.50–0.89], respectively). These relationships were stable after adjusting for other risk factors. Insulin concentrations remained negatively associated with deaths from these cancers in analyses restricted to men who smoked and in those who were not chronic alcohol consumers.

CONCLUSIONS — Peripheral hyperinsulinemia, indicative of very high portal insulin concentrations, predicted fatal liver cancer in these nondiabetic men, but was inversely associated with fatal lip, oral cavity, and pharynx cancer; stomach cancer; and larynx cancer.

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A number of studies have examined cancer incidence (or mortality) and hyperglycemia, diabetes, and central obesity, but they have been unable to establish the biological mechanism underlying the epidemiological associations (1–11). All of the site-specific cancers cited in these studies (pancreatic, kidney, colorectal, prostate, liver, biliary tract, stomach, and genital) showed a positive association with diabetes (1,4–10), except for the negative association found for lung cancer in men in one study (5). A coherent argument has been offered for the role of chronic hyperinsulinemia in the initiation and promotion of cancer growth (12); this is supported by recent evidence that incident colorectal cancer was related to hyperinsulinemia (13) and C-peptide concentrations (14). A recent publication from the Helsinki Policeman Study (15) showed an overall positive but nonsignificant relationship between cancer death and the area under the 2-h insulin curve; there were not enough deaths in that study to look at site-specific cancers. In a prospective analysis from the Busselton study (16), hyperinsulinemia was a risk factor for cancer mortality among men aged 60–74 years at baseline, but not among women or younger men.

In French men, cancer death is more common than cardiovascular death (17), a trend also seen in the Paris Prospective Study cohort. In this study, we explored whether peripheral insulin concentrations were a risk factor for death from site-specific cancers over 23.8 years of follow-up in a cohort of middle-aged working men.

RESEARCH DESIGN AND METHODS

Subjects and methods

The 6,237 men studied were ages 44–55 years at baseline and had undergone a 75-g oral glucose tolerance test. They were all followed up for vital status, had no missing data for the baseline variables, and were not diabetic (i.e., were not being treated for diabetes and had fasting glucose <7.0 mmol/l and 2-h glucose <11.1 mmol/l) (18). Blood pressure was measured with the subjects in a seated position, and BMI was determined. The men were questioned about current and previous smoking habits, from which we reported an index of mean tobacco intake over the previous 5 years. The erythrocyte mean corpuscular volume (MCV) was used as a measure of alcohol consumption in this analysis (19), and some men were classified at baseline as chronic alcohol

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Abbreviations: ICD, *International Classification of Diseases*; MCV, mean corpuscular volume.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of 6,237 men ages 44–55 years, listed by cause of death or alive status: the Paris Prospective Study after 23.8 years of follow-up*

Cause of death	ICD-9 code	*n*	Age	Glucose (mmol/l)		Insulin (mU/ml)		BMI (kg/m^2)	Systolic BP (mmHg)
				Fasting	2-h	Fasting	2-h		
Neoplasm-related deaths	140–239	778	47.5	5.60	5.75	11.9	42.4	25.5	147
Lip, oral cavity, pharynx	140–149	40	46.8	5.59	6.07	9.2	32.1	23.8	148
Digestive organs, peritoneum	150–159	204							
Esophagus	150	39	47.3	5.60	6.11	10.0	37.0	23.6	151
Stomach	151	26	47.8	5.70	4.99	11.1	32.7	25.5	147
Colon, rectum, anus	153–154	67	47.4	5.65	5.50	13.3	45.2	27.0	146
Liver	155	25	48.0	5.99	7.06	20.1	112.4	28.1	160
Pancreas	157	35	47.8	5.69	5.81	15.7	38.0	25.9	143
Other		12							
Respiratory, intrathoracic organs	160–165	250							
Larynx	161	44	47.3	5.49	6.04	8.5	30.7	23.8	145
Trachea, bronchus, lung	162	186	47.4	5.58	5.68	12.3	42.1	25.1	146
Other		20							
Bone, connective tissue, skin, breast	170–175	16							
Genitourinary organs	185–189	91							
Prostate	185	47	48.1	5.53	5.41	11.1	39.4	25.5	138
Bladder	188	23	47.2	5.59	5.71	11.0	42.0	25.7	148
Kidney	189	20	47.4	5.80	6.26	14.0	46.8	27.4	151
Other		1							
Other and unspecified sites	190–199	110							
Eye, brain, nervous system	190–192	22	47.6	5.57	5.98	10.6	34.7	26.0	145
Secondary and unspecified sites	196–199	85	47.6	5.60	5.47	10.4	35.0	25.6	148
Other		3							
Lymphatic hematopoietic tissue	200–209	51	47.4	5.45	5.63	11.6	46.1	25.9	148
Benign neoplasms	210–229	3							
Circulatory deaths	390–459, 798	514	47.7	5.61	5.78	12.0	48.7	26.3	151
Other causes of death	—	447	47.6	5.60	5.70	12.5	47.9	25.9	150
Alive	NA	4,498	47.0	5.57	5.48	11.8	42.9	25.8	141

Data are means. Each characteristic differed significantly across these causes of death, excepting age. BP, blood pressure.

users, based on the judgment of the examining physician.

Follow-up methods

Follow-up for vital status and causes of death were complete until the end of 1993, an average follow-up of 23.8 years. Enquiries were made through official sources to ascertain the date of death of deceased subjects; revisions 8 and 9 of the *International Classification of Diseases* (ICD) (20) were used to code the causes of death, which up until the end of 1988 were based on information from the treating physician, hospital records, and the family of the deceased. For those with missing causes of death before this date and for deaths after 1989, the officially certified causes of death were used.

The 6,237 men studied differed significantly from the 1,068 men with missing vital status or values on some variables: mean age, 47.0 vs. 47.2 years ($P < 0.05$); smokers, 58 vs. 61% ($P < 0.01$); chronic alcohol users, 5 vs. 8% ($P < 0.001$).

Statistical analysis

The characteristics of the men according to vital status and causes of death were compared by analysis of variance; the logarithms of the insulin concentrations were used to ensure more symmetric distributions. Standardized hazards ratios from Cox proportional hazards models were used to describe the age-adjusted effect of baseline fasting and 2-h insulin concentrations (one standard deviation change in the logarithm of the insulin concentrations). Men with missing causes of death or causes other than cancer were censored. The log-likelihood ratios were used to test whether a quadratic term in the insulin concentrations was statistically significant and should be included in the Cox model for all site-specific cancer deaths. Further adjustment was made for other possible risk factors: BMI, tobacco smoking (never, ex-smoker, and ≤ and >20 cigarettes per day), erythrocyte MCV and chronic alcohol use, and all factors together (all the aforementioned factors as well as glucose concentrations and systolic blood pressure). For those cancers that were negatively and significantly related with insulin concentrations, the insulin-cancer relationship was studied in the subgroup of smokers and in the men who were not likely to be very heavy alcohol consumers. Analysis of covariance was used to examine the age- and age-and BMI–adjusted mean insulin concentrations, according to smoking habits. In additional analyses, only those men dying of cancer ≥5 years after baseline were analyzed to be more certain of the time se-

Table 2—*Smoking habits and markers of alcohol intake in 6,237 men aged 44–55 years at baseline, listed by cause of death or alive status: the Paris Prospective Study after 23.8 years of follow-up*

		Smoking habits					Alcohol intake	
Cause of death	n	Never smoked (%)	Ex-smoker (%)	≤20 cigarettes per day (%)	>20 cigarettes per day (%)	5-Year tobacco intake (g/day)	Chronic alcohol use (%)	Erythrocyte MCV (fl)
Neoplasm-related deaths	778	9	15	61	16	16.7	10	98.5
Lip, oral cavity, pharynx	40	2	15	58	25	20.5	25	100.4
Digestive organs, peritoneum	204							
Esophagus	39	3	10	72	10	14.3	15	100.6
Stomach	26	12	35	38	15	14.4	0	97.2
Colon, rectum, anus	67	19	30	46	4	10.0	0	96.3
Liver	25	4	40	48	8	13.4	12	98.3
Pancreas	35	17	9	66	9	12.6	3	97.9
Other	12							
Respiratory, intrathoracic organs	250							
Larynx	44	2	5	66	27	19.7	23	100.2
Trachea, bronchus, lungs	186	4	9	64	24	21.5	10	99.1
Other	20							
Bone, corrective tissue, skin, breast	16							
Genitourinary organs	91							
Prostate	47	17	17	64	2	10.1	4	96.7
Bladder	23	4	4	78	13	17.1	13	98.9
Kidney	20	10	10	75	5	12.0	10	97.7
Other	1							
Other and unspecified sites	110							
Eye, brain, nervous system	22	23	14	55	9	13.8	9	96.5
Secondary and unspecified sites	85	6	11	67	16	17.8	14	99.1
Other	3							
Lymphatic, hematopoietic tissue	51	12	24	53	12	12.3	8	97.1
Benign neoplasms	3							
Circulatory deaths	514	13	20	56	11	14.1	8	97.9
Other causes of death	447	13	23	52	12	13.4	11	98.2
Alive	4498	21	25	48	6	10.3	3	96.1

Data are means. Each characteristic differed significantly across these causes of death, excepting age.

quence between hyperinsulinemia and cancer. SAS software was used for all analyses.

RESULTS — After 23.8 years of follow-up, 1,739 of the 6,237 men had died; the most common cause of death was neoplasm-related (45%), followed by circulatory causes (30%). The site-specific cancer deaths were grouped according to the major ICD categories (20), and the characteristics of the men studied were grouped according to whether they were still alive or had died from circulatory fatal causes or fatal cancers (Tables 1 and 2). Tobacco and alcohol intake was high in the men with fatal lip, oral cavity, and pharynx cancer; esophagus cancer; and larynx cancer. Tobacco intake alone was high in men with fatal trachea, bronchus, and lung cancer; bladder cancer; kidney cancer; and cancers of secondary and unspecified sites.

After adjusting for age, fasting hyperinsulinemia did not have a significant linear effect on mortality from all neoplasms (Table 3), but there was a significant overall curvilinear relationship ($\chi^2 = 8.4$; df = 2; $P < 0.02$) (Fig. 1*A*). For the 2-h insulin concentration, the relationship was negative, with an age-adjusted standardized hazards ratio of 0.91 (95% CI 0.85–0.98), but there was no statistically significant curvilinearity and no dosage-response relationship (Fig. 1*B*).

Fatal lip, oral cavity, and pharynx cancers were inversely associated with both fasting and 2-h hyperinsulinemia (hazards ratios 0.55 [CI 0.41–0.75]) and 0.75 [0.55–1.02], respectively) (Table 3). There were nonsignificant trends for fasting insulin, with an inverse relationship to esophagus cancer (hazards ratio 0.74 ([0.55–1.01]) and positive relationships for fatal colorectal and pancreatic cancers (hazards ratios 1.22 [0.95–1.56] and 1.18 [0.84–1.66], respectively). The 2-h insulin level was inversely associated with stomach cancer (hazards ratio 0.62 ([0.43–0.90]). There were no significant curvilinear relations with any of these cancers.

The strongest relationship seen was with fatal liver cancer, with hazards ratios of 2.72 (CI 1.87–3.94) and 3.41 (2.23–5.21) for fasting and 2-h insulin, respectively. There was a consistent insulin dosage-response relationship, despite the small number of liver cancer deaths (Fig. 2); all but 2 of the 25 cases of fatal liver cancer were classified as primary liver cancers, and the results remained constant after excluding those two men.

For fatal cancers of the larynx, there

Table 3—*Age-adjusted standardized hazards ratios for death by cancer according to fasting and 2-h insulin concentrations, adjusted additionally for BMI, tobacco smoking, erythrocyte MCV and chronic alcohol use, and for all factors (the aforementioned factors plus glucose concentration and systolic blood pressure): the Paris Prospective Study 23.8 years of follow-up*

Cancer type	Age-adjusted ratio	Ratios adjusted for age and			
		BMI	Tobacco smoking	MCV, chronic alcohol use	All factors
Fasting insulin values					
All neoplasms	0.96 (0.89–1.03)	1.00 (0.93–1.08)	0.99 (0.92–1.06)	0.99 (0.92–1.06)	1.02 (0.94–1.10)
Lip, oral cavity, pharynx	0.55 (0.41–0.75)	0.66 (0.48–0.91)	0.57 (0.42–0.77)	0.57 (0.42–0.77)	0.63 (0.44–0.88)
Digestive organs, peritoneuim					
Esophagus	0.74 (0.55–1.01)	0.96 (0.68–1.34)	0.77 (0.57–1.05)	0.72 (0.53–0.99)	0.88 (0.62–1.25)
Stomach	0.91 (0.62–1.32)	0.95 (0.63–1.43)	0.91 (0.62–1.32)	0.93* (0.63–1.37)	0.90* (0.59–1.37)
Colon, rectum, anus	1.22 (0.95–1.56)	1.07 (0.82–1.39)	1.21 (0.95–1.55)	1.22* (0.95–1.58)	1.05* (0.79–1.38)
Liver	2.72 (1.87–3.94)	2.45 (1.63–3.70)	2.71 (1.88–3.92)	2.64 (1.77–3.92)	2.18 (1.38–3.45)
Pancreas	1.18 (0.84–1.66)	1.21 (0.83–1.75)	1.21 (0.86–1.71)	1.24 (0.95–2.33)	1.24 (0.84–1.83)
Respiratory, intrathoracic organs					
Larynx	0.63 (0.47–0.83)	0.77 (0.56–1.04)	0.66 (0.49–0.87)	0.66 (0.50–0.88)	0.81 (0.58–1.12)
Trachea, bronchus, lung	0.99 (0.85–1.14)	1.10 (0.94–1.28)	1.04 (0.89–1.20)	1.05 (0.90–1.21)	1.16 (0.98–1.36)
Bone, connective tissue, skin, breast	0.97 (0.58–1.63)	0.89 (0.51–1.55)	0.99 (0.58–1.67)	1.13 (0.66–1.95)	1.03 (0.56–1.87)
Genitourinary organs					
Prostate	0.93 (0.70–1.23)	0.98 (0.72–1.33)	0.94 (0.71–1.25)	0.92 (0.69–1.24)	0.99 (0.72–1.37)
Bladder	0.84 (0.56–1.25)	0.83 (0.54–1.28)	0.88 (0.58–1.32)	0.86 (0.57–1.28)	0.83 (0.53–1.30)
Kidney	1.47 (0.94–2.32)	1.26 (0.77–2.06)	1.54 (0.97–2.44)	1.49 (0.95–2.33)	1.21 (0.72–2.03)
Other and unspecified sites					
Eye, brain, nervous system	0.97 (0.64–1.48)	0.95 (0.61–1.50)	0.99 (0.64–1.50)	0.97 (0.64–1.48)	0.95 (0.60–1.50)
Lymphatic, hematopoietic tissues	0.94 (0.72–1.24)	0.93 (0.69–1.25)	0.96 (0.73–1.26)	0.95 (0.72–1.25)	0.96 (0.71–1.30)
2-h insulin values					
All neoplasms	0.91 (0.85–0.98)	0.94 (0.87–1.01)	0.96 (0.89–1.03)	0.93 (0.87–1.00)	0.85 (0.78–0.93)
Lip, oral cavity, pharynx	0.75 (0.55–1.02)	0.88 (0.63–1.23)	0.80 (0.59–1.09)	0.81 (0.60–1.09)	0.75 (0.52–1.08)
Digestive organs, peritoneuim					
Esophagus	0.89 (0.65–1.23)	1.10 (0.78–1.56)	0.95 (0.69–1.31)	0.90 (0.66–1.23)	0.87 (0.60–1.25)
Stomach	0.62 (0.43–0.90)	0.63 (0.43–0.92)	0.63 (0.44–0.91)	0.60* (0.41–0.88)	0.68* (0.42–1.08)
Colon, rectum, anus	1.02 (0.80–1.31)	0.92 (0.72–1.18)	1.02 (0.79–1.30)	1.01* (0.78–1.30)	0.90* (0.66–1.24)
Liver	3.41 (2.23–5.21)	3.05 (1.95–4.77)	3.39 (2.22–5.18)	3.24 (2.07–5.06)	2.18 (1.25–3.79)
Pancreas	0.85 (0.61–1.19)	0.84 (0.60–1.19)	0.89 (0.63–1.24)	0.87 (0.62–1.23)	0.73 (0.48–1.10)
Respiratory, intrathoracic organs					
Larynx	0.66 (0.50–0.89)	0.77 (0.56–1.05)	0.72 (0.54–0.97)	0.71 (0.53–0.93)	0.62 (0.44–0.88)
Trachea, bronchus, lung	0.90 (0.78–1.04)	0.96 (0.82–1.11)	0.97 (0.84–1.11)	0.93 (0.81–1.08)	0.89 (0.74–1.07)
Bone, connective tissue, skin, breast	1.32 (0.77–2.27)	1.27 (0.72–2.24)	1.36 (0.80–2.33)	1.43 (0.81–2.52)	1.33 (0.66–2.69)
Genitourinary organs					
Prostate	0.89 (0.66–1.18)	0.92 (0.68–1.24)	0.90 (0.67–1.21)	0.87 (0.65–1.17)	0.92 (0.63–1.35)
Bladder	0.87 (0.57–1.31)	0.87 (0.57–1.33)	0.93 (0.61–1.40)	0.90 (0.60–1.34)	0.79 (0.48–1.30)
Kidney	1.20 (0.76–1.89)	1.05 (0.66–1.66)	1.25 (0.79–1.97)	1.21 (0.77–1.90)	0.78 (0.45–1.35)
Other and unspecified sites					
Eye, brain, nervous system	0.90 (0.59–1.37)	0.88 (0.57–1.36)	0.91 (0.60–1.39)	0.90 (0.59–1.37)	0.67 (0.40–1.10)
Lymphatic, hematopoietic tissues	0.98 (0.74–1.30)	0.98 (0.73–1.31)	1.00 (0.76–1.33)	0.03 (0.77–1.36)	0.95 (0.67–1.35)

Data are ratios (95% CI). *Not adjusted for chronic alcoholism because of low frequency.

were significant negative associations with the fasting and 2-h insulin concentrations, with similar hazards ratios of 0.63 (CI 0.47–0.83) and 0.66 (0.50–0.89). For 2-h insulin, there was a statistically significant curvilinear relationship for cancers of the trachea, bronchus, and lung; however, when the insulin distribution was divided by the quintiles, the hazards ratios for the five groups were 1, 0.57, 0.96, 1.02, and 0.47, respectively, showing no dosage-response relationship; the second and last groups were significantly different from the reference group.

Although kidney cancer was not significantly associated with hyperinsulinemia, fasting insulin carried a high hazards ratio of 1.47 (CI 0.94–2.32), although the ratio for the 2-h insulin was not as strong (1.20 [0.76–1.89]).

For the site-specific cancers, the hazards ratios changed little after adjusting for possible confounding factors (BMI, tobacco smoking, erythrocyte MCV and chronic alcohol use, glucose concentrations, and systolic blood pressure) (Table

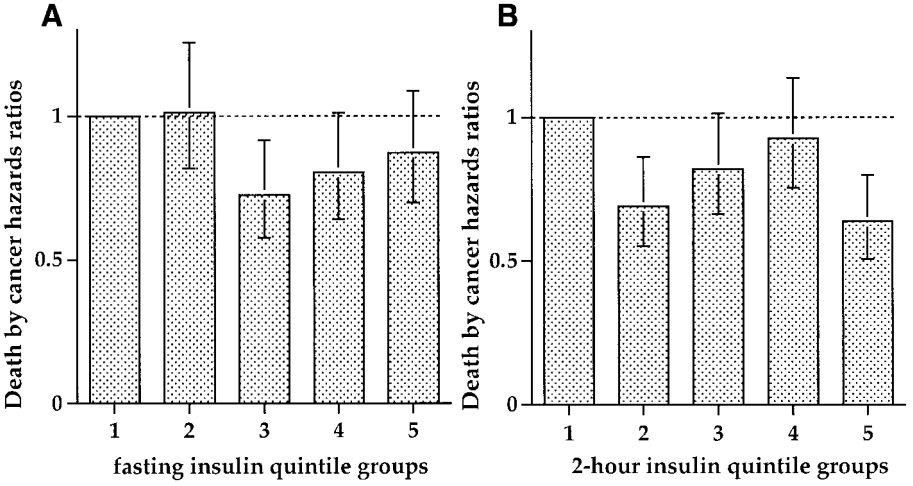

Figure 1—*Standardized hazards ratios (95% CI) for death by cancer (all sites combined) according to quintile groups of the fasting* (A) *and 2-h insulin concentrations* (B). *Data from the Paris Prospective Study after 23.8 years of follow-up.*

3). These results remained stable when the 41 men who died of cancer within the first 5 years of follow-up were deleted.

For men who died of lip, oral cavity, and pharynx cancer and larynx cancer, 83 and 94%, respectively, were smokers. In the Paris Prospective Study, the insulin concentrations were significantly lower in men who smoked than in men who were not current smokers ($P < 0.01$) (21). After adjusting for BMI, the mean insulin concentrations of the smokers and the nonsmokers were closer, but the difference was not explained by the lower BMI of the smokers. To test whether this apparent protective relationship between hyperinsulinemia and these smoking-related cancers was attributable only to the fact that those who smoked had lower insulin concentrations, a further analysis of the 3,630 smokers was performed (there were too few of these fatal cancers in nonsmokers). Although the age-adjusted hazards ratios changed, these cancers remained significantly and negatively associated with the insulin concentrations.

Insulin concentrations have been shown to decrease with alcohol intake (22); of the men who died of lip, oral cavity, and pharynx cancer and larynx cancer, 25 and 23%, respectively, were classified as being chronic alcohol consumers. After deleting the 652 men who were likely to be very heavy alcohol consumers (chronic alcohol users and/or those with erythrocyte MCV ≥103 fl), fasting insulin concentrations were still significantly and negatively associated with lip, oral cavity, and pharynx cancer and larynx cancer, and 2-h insulin levels were significantly and negatively associated with larynx and stomach cancers.

CONCLUSIONS — Although fasting insulin at baseline showed a trend toward a negative association with death from all cancers, in the analysis of the site-specific cancers, insulin showed a heterogeneous risk. Fasting insulin had a positive association with some cancers, such as liver cancer, kidney cancer, pancreas cancer, and colon, rectum, and anus cancer, and a negative association with other cancers, such as lip, oral cavity, and pharynx cancer, esophagus cancer, and larynx cancer, even if the risks for many of these individual cancers did not reach statistical significance. For the 2-h insulin levels, the relationship with all-cancer mortality was negative, with liver cancer being positively and significantly associated with hyperinsulinemia, and stomach and larynx cancers showing a significant negative association. The study of less-frequent site-specific cancers is limited, and we cannot rule out the possibility that other associations exist.

Two of the three sites showing a negative association with hyperinsulinemia (lip, oral cavity, and pharynx cancer and larynx cancer, but not stomach cancer) were associated with the joint habit of tobacco smoking and high alcohol intake. Smoking was negatively related to insulin levels (21), even though the number of cigarettes smoked per day had no significant effect on insulin concentrations; however, the inverse association of these cancers with insulin persisted when the analysis was restricted to the smokers. Men who died from other smoking-related fatal cancers, such as trachea, bronchus, and lung cancer, had average insulin levels, and the risks were not related with insulin. Alcohol consumption tends to lower insulin levels (22). There were no questions asked about alcohol consumption in this study, and the measures of excessive alcohol consumption available were the erythrocyte MCV and the examining physician's appreciation of whether the subject was a chronic alcohol consumer; the mean values of these mea-

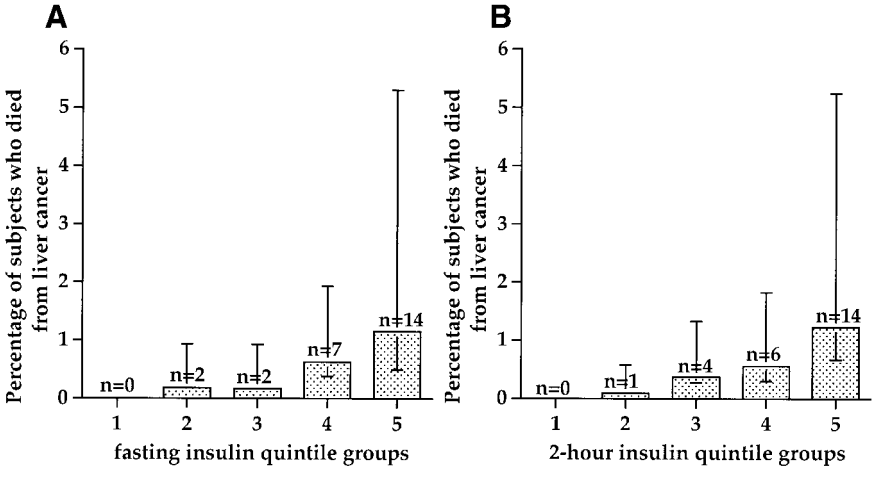

Figure 2—*Percentage of subjects and number of deaths from liver cancer (95% CI) according to quintile groups of the fasting* (A) *and 2-h insulin concentrations* (B). *Data from the Paris Prospective Study after 23.8 years of follow-up.*

sures were higher in those who had lip, oral cavity, and pharynx cancer and larynx cancer. These negative relationships persisted in men who were not very heavy alcohol consumers. We have no explanation as to why insulin should appear to be protective for these cancers, and we have not been able to find other published reports on these negative associations.

Liver cancer was the only cancer for which hyperinsulinemia was a significant and consistent risk factor, with a convincing dosage-response curve. Recent molecular biological studies have shown that hepatocellular carcinoma cells have an increased expression of insulin receptor substrate-1, which is related to the size of the tumor (23). This observation suggests a mechanism to explain enhanced hepatic tumor growth in the presence of high insulin concentrations. An alternative and additional reason may be that hyperinsulinemic obese individuals are more vulnerable to hepatic carcinogens because they have an impaired adenosine triphosphatase homeostasis in the liver (24).

Hepatocellular cancer has increased (both in incidence and prevalence) in the U.S. (25) in parallel with the increase in obesity (26). Assuming that obesity is accompanied by chronic hyperinsulinemia, this increase in liver cancer might be partly a consequence of increasing obesity. The insulin concentration in the portal vein is approximately twice that in the peripheral veins; thus the liver, in comparison to other organs, is exposed to high insulin concentrations (27). Furthermore, the increase in chronic infections, such as hepatitis C, might contribute to both prolonged insulin resistance (and hence to diabetes) and liver cancer. Diabetic patients have been observed to have an increased frequency of hepatitis C in comparison with the general population (28).

In summary, after 23.8 years of follow-up, death by liver cancer was shown to be positively related with both fasting and 2-h insulin concentrations. Lip, oral cavity, and pharynx cancer and larynx cancer were negatively related with fasting insulin concentrations, and stomach and larynx cancers were negatively related with the 2-h insulin concentrations, relationships that persisted even when analyses were restricted to smokers and to those men who were not heavy alcohol drinkers.

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