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► To cite this version:

Matthieu Wargny, Beverley Balkau, Céline Lange, Marie-Aline Charles, Philippe Giral, et al.. Association of fasting serum insulin and cancer mortality in a healthy population - 28-year follow-up of the French TELECOM Study. *Diabetes & Metabolism*, 2017, [Epub ahead of print]. 10.1016/j.diabet.2017.03.006 . inserm-01517742

HAL Id: inserm-01517742

<https://inserm.hal.science/inserm-01517742>

Submitted on 3 May 2017

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Title

Association of fasting serum insulin and cancer mortality in a healthy population - 28-year follow-up of the French TELECOM Study

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Content Information

- Number of text pages : 16
- Number of tables: 2
- Number of figures: 2

Funding sources

This work was supported by grants from the National Institute of Health and Medical Research (INSERM), the National Health Insurance for Wage Earners (CNAMTS), and the Institute of Cardiometabolism and Nutrition (ICAN), Paris, France.

Duality of Interest No potential conflicts of interest relevant to this article were reported.

Author Contributions M.W. contributed to the data research and writing of the manuscript. He is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. B.B. contributed to the data analysis and writing of the manuscript. C. L. contributed to the data research and review of the manuscript. M.A.C. contributed to the writing and review of the manuscript. P.G. contributed to the data analysis, the writing and review of the manuscript. D.S. is the principal investigator of the TELECOM Study, and contributed to the data collection, the research for this article, the writing and review of the manuscript.

Abstract (248 words)

Aims—Epidemiologic, pharmacoepidemiologic and pathophysiologic evidence points consistently to an association between type 2 diabetes and cancer. This association could be explained by hyperinsulinemia induced by insulin resistance. We studied the association between fasting serum insulin (FSI) and cancer mortality in a population of non-diabetic individuals.

Methods—We followed 3117 healthy workers (50.2% women), included in the TEL-ECOM cohort study, between 1985 and 1987; their median age was 38 years (Q1-Q3 = 30-50). Baseline FSI was measured by radioimmunoassay, the INSI-PR method. People with diabetes or cancer at baseline were excluded. Vital status and causes of death were available until December 2013. The association between FSI and cancer deaths was analyzed by sex, using a Cox proportional hazards model with age as the time scale, adjusting for body mass index, smoking habits, alcohol consumption, occupational category and ethnic origin.

Results—After 28 years follow-up, 330 (10.6%) deaths were reported, among which, 150 were cancer-related (80 men, 70 women). In men, the association between FSI and death by cancer was J-shaped: compared to the average FSI of 7.1 mU/l, men with 5 mU/l and 12.9 mU/l had respectively adjusted Hazard-Ratios (HR) of 1.88 (95% Confidence Interval, 1.00-3.56) and 2.30 (95% CI, 1.34-3.94). Among women, no significant association was found (adjusted HR, 1.03; 95% CI, 0.96-1.11) for an increase of 1 mU/l in FSI.

Conclusion—These results strengthen the hypothesis of an independent risk of cancer death associated with extreme values of FSI, mainly the highest, among men, but not among women.

Keywords: Cancer mortality, Fasting serum insulin, Diabetes, Cohort study, Epidemiology, Fractional polynomial

Abbreviation

FSI Fasting Serum Insulin

Introduction¹

The link between hyperinsulinemia and death by cancer remains debated [1]. Various studies stress the role of insulin as a growth factor for tumours [2], which is supported by both in vitro and in vivo studies [3-8]. This action of insulin is therefore a possible explanation for the higher cancer mortality associated with obesity [9,10], and with type 2 diabetes [11,12], and for the worse prognosis associated with high C-peptide levels in breast and prostate cancers [13,14].

This is in line with results from pharmaco-epidemiological studies that have found a lower incidence of cancer and cancer mortality in people using drugs increasing insulin sensitivity, such as metformin [15], or the dose-dependent reduction of colorectal cancer incidence with acarbose that indirectly lowers the insulin requirement [16]. In contrast, insulin therapy and insulin-secretagogues such as sulfonylureas are likely to be associated with an increased risk of cancer and death by cancer [17,18].

However, the link between fasting serum insulin and death by cancer is still subject to discussion in the light of the few prospective epidemiological studies available [19-23]. These studies concluded to either a lack of association, a too small sample size [20-22], or higher cancer mortality for higher insulin values [19,23]. The two articles giving detailed data found that the risk was lowest for average values of fasting serum insulin, suggesting a J- or U-shape relationship between insulin exposition and cancer death [20,21].

Furthermore, most of these studies were in men [20-22], or men and women were combined [23], probably because assuming that the association between fasting serum insulin and death by cancer is the same in men and women, without any sex-specific analyses. One exception is the Busselton study that found, in a limited sam-

¹**Abbreviation.** FSI : Fasting Serum Insulin

ple of 466 elderly people in the 1980s, an increased risk of cancer mortality associated with hyperinsulinemia in men aged 60-74 years, but neither in women nor in young men [19]. If only for the different distribution of frequent sites of cancers by sex, such as breast and prostate, it can be expected that the risk profiles may differ between sexes. So, to our knowledge, other than in the Busselton study, the hypothesis of a difference between men and women has never been assessed in a prospective epidemiological study.

The aim of our study was to assess the relationship between fasting serum insulin and long-term cancer mortality in the French TELECOM study population, emphasizing the differences between men and women, using statistical approaches to provide a dose-response relationship, and taking into account clinical, ethnical and occupational variables as confounding factors.

Methods

Study population The TELECOM study was a monocentric, observational study of people employed by the French telecommunications department, with inclusions in Paris, France, between 1985 and 1987 [24,25]. The original aim of the study was to explore the link between hemoglobin A1c (HbA1c) and the incidence of type 2 diabetes mellitus and its complications, and thus the use of HbA1c as a tool for diabetes diagnosis. The present ancillary study focuses on the association between fasting serum insulin at baseline and death by cancer over 28 years of follow-up.

Participants were TELECOM employees, over 18 years of age, with no known pregnancy or hemoglobinopathy. They were recruited consecutively in a center dedicated to occupational health. In this analysis, people with known diabetes mellitus were excluded.

All participants gave informed consent. The TELECOM study received ethical approval from the French data protection authority (CNIL).

Differences between the studied and excluded populations Overall, 3966 men and women were recruited and included in the original TELECOM study; 32 were excluded because of known diabetes, and then 817 (20.8%) because of incomplete data, mainly for vital status (n = 218) or fasting serum insulin measurement (n = 372), due to a lack of financing at the end of study (Fig. 1). Three individuals were excluded because their death certificates were not available. The populations studied and excluded for missing data were similar for all parameters, excepting that the studied population was slightly younger and had a lower mortality rate (Supplementary table 1). Among those who died, cancer deaths occurred in similar proportions.

Study variables A self-administered questionnaire was completed and checked by a trained nurse at inclusion. The questionnaire recorded medical history, smoking habit (never smoked or quit for at least 6 months vs others), alcohol consumption (units per day, one unit = 10 g of pure alcohol), occupational category in the French public service (A to C, in decreasing order) and ethnic origin. Weight and height were measured to determine body mass index (BMI, in kg/m²).

Blood samples were drawn for biological analyses: fasting serum insulin was assayed by radioimmunoassay with the INSI-PR method (CIS Bio-Industrie, Gif-sur-Yvette, France), with 13.7 and 5.8% intra-assay and 8.0 and 8.6% inter-assay coefficients of variation at insulin levels of 12 and 20 mU/l, respectively. The minimum detectable concentration of the insulin assay varied during the study up to 5.0 mU/l and

was 5.0 mU/l most of the time. Thus, for statistical analyses, we chose to set at 5.0 all the values below 5.0 mU/l (181 values, being 5.8% of the studied sample).

Vital status and causes of death For each participant, vital status and date of death were obtained from INSEE (French National Institute of Statistics and Economics Studies) up to 31 December 2013. If a participant was not found in this register, we directly contacted the town hall of their birthplace to determine vital status. If a death was reported, the coding of the causes was obtained in 2015 from the Center for Epidemiology for Causes of Death (CépiDc - INSERM). Causes of death were available until the 31st December 2013. Detailed causes were reported using the International Classification of Diseases (ICD), 9th Revision until 1999, and the 10th revision since 2000. If cancer was coded in any position as a cause of death, it was considered to be a cancer-related death. Cancer sites were recorded if available.

Statistical analyses The populations studied and excluded were compared by t- and chi-squared tests. The characteristics of the participants are described by sex and by sex-specific quintiles of fasting serum insulin, presented as n (%), mean \pm standard deviation or median (interquartile range, **Q1-Q3**) in the case of variables with skewed distributions. They were compared across quintile groups by chi-squared tests for categorical variables, ANOVA between means, while Kruskal-Wallis tests compared ranks for variables with skewed distributions.

The observational period for mortality was from baseline to date of death, loss to follow-up or the 31st December 2013. Annual cancer-related mortality was calculated as the number of deaths by cancer divided by total person-years since baseline.

We used multivariable Cox proportional hazards models, with age as the time scale, to study the association between cancer deaths and fasting serum insulin, controlling for other exposures. We controlled the proportional hazard assumption for each variable of each model. Individuals who died without mention of cancer were right-censored at their date of death, regarding this event as a competing risk. Results are expressed as adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). As we suspected a U- or J-shape for the risks of cancer death with fasting serum insulin and BMI, these two continuous variables were introduced into models using fractional polynomial transformations of degree 2 (FP2) to investigate possible transformations, as proposed by Sauerbrei et al. [26] Although alcohol consumption was a continuous variable, a FP2 transformation had no impact on the association of fasting serum insulin, so we used a linear term. Our secondary analyses present the association of fasting serum insulin categorized by quintiles, to stress a potential influence of model selection and to allow external comparison with previous studies [20,21,23].

All multivariable models were stratified by sex and adjusted for smoking habit, alcohol consumption, BMI, ethnic origin and occupational category. In order to express the risk associated with fasting serum insulin in an easy way for interpretation and for comparison with the quintile approach, we present HR in comparison with a sex-specific reference point. Separately for men and women, we chose the mean of the quintile group of insulin concentration with the minimal hazard as the reference value. In our secondary analyses with a categorical approach, we retained the same quintile group as reference group.

People with incomplete data for any of the parameters of interest stated above were excluded from the analyses. As there were 163 participants with occupational

category as the sole missing data, we omitted this parameter in order to apply the multivariable model to the largest sample and also to assess the stability of our results in a sensitivity analysis. In order to limit reverse-causality bias, we planned to exclude individuals who died in the first two years of follow-up, **but in fact the first cancer death was observed in the fourth year of follow-up.**

P -value < 0.05 was considered statistically significant. Statistical analyses used the R software version 3.0.1 [27], with packages *survival* and *mfp* [28,29]. A two-sided $P < 0.05$ was considered significant.

Results

Characteristics of the studied population The 3117 (78.6%) individuals studied had a maximum follow-up of 28.7 years and 50.2% were women. At baseline, distribution of age was uniform with a median of 35 years **(29-48)** among men and 41 **(31-51)** among women ([Supplementary table 2](#)). BMI was higher among men with a median of 23.9 kg.m⁻² **(22.2-26.0)**, against 22.3 **(20.6-24.7)** for women. Men were more likely to smoke, with 35.2% of current smokers and 22.5% among women. Fasting serum insulin was slightly higher among men, with a median of 7.1 mU/l **(5.6-9.1)** against 6.7 **(5.2-8.7)** among women. The highest occupational category, “A”, was more frequent among men than women (28.7% vs. 7.1%).

Mortality and cancer death The mortality rate during follow-up was higher among men than women (12.5 vs. 8.7%), but among deceased participants, cancer was more frequent in women (51.5 vs. 48.5%). Annual cancer-mortality was 1.96/1000 for men and 1.68/1000 for women.

The most frequent cancer sites for men were digestive (34%), respiratory and intrathoracic organs (23%) and prostate (18%); for women the most frequent were digestive (24%) and genitalia (19%) organs, and breast (20%) ([Supplementary Table 3](#)).

Among men, before any adjustment, age was positively associated with quintile groups of fasting serum insulin ($P < 10^{-4}$) ([Table 1](#)), as were non-smoking status ($P = 10^{-4}$), BMI ($P < 10^{-4}$) and occupational category ($P = 0.008$). Death by cancer was associated with fasting serum insulin ($P = 0.001$), the percentages suggesting a J-shape, with the lowest rates in the second and third quintile groups (respectively 2.6% and 3.8% of cancer deaths), the highest rate in the fifth quintile group (9.9% of cancer deaths) and intermediate rates in the first and fourth quintile groups (4.8% and 5.1% of cancer deaths respectively). Among women, BMI, occupational category and ethnic group were statistically associated with fasting serum insulin ($P < 10^{-4}$, $P = 0.003$ and $P < 10^{-4}$, respectively), but not age ($P = 0.50$) or death by cancer ($P = 0.64$). The rate of cancer deaths was lowest for the first quintile group (3.2%) and quite similar rates were found in the other quintile groups (4.5 to 5.7% of cancer deaths).

Survival analysis In the fully adjusted multivariable Cox model, the fractional polynomial selection procedure proposed a polynomial transformation of insulin for men but not for women. The resulting risks for cancer death associated with insulin, by sex, can be seen in [Figure 2](#), and the HR associated with insulin in comparison with the reference values are presented in [Table 2](#).

For men, the adjusted HR of cancer death followed approximately a J-shape curve and was minimal around 7.1 mU/l, our reference value; the risk was 1.88

greater (95% CI, 1.00-3.56) at 5.0 mU/l and 2.30 (95% CI, 1.34-3.94) greater at 12.9 mU/l; the overall risk associated with insulin was statistically significant ($P = 0.009$). A fully adjusted multivariable Cox model, with fasting serum insulin in quintile groups, showed similar hazards, with an overall trend for the effect of insulin ($P = 0.078$) (Table 2). For women, the increase in cancer death risk was proportional to fasting serum insulin but did not reach statistical significance, with an adjusted HR of 1.03 (95% CI, 0.96-1.11, $P = 0.35$) (Fig. 2, Table 2).

Regarding the confounding factors, BMI with a FP2 transformation was associated with cancer death in men ($P = 0.002$) but not in women ($P = 0.99$, without relevant FP2 transformation) (Supplementary Table 4). For smokers compared to non-smokers, the increased risk was not significant for men (adjusted HR, 1.36; 95% CI, 0.84-2.19) but was significant for women (adjusted HR = 1.85; 95% CI, 1.05-3.26). Occupational category was associated with cancer death among women ($P = 0.018$) but not among men ($P = 0.99$). In both sexes, the adjusted risks associated with alcohol consumption and ethnic origin were not statistically significant.

In the sensitivity analysis, we added the 163 individuals (55 men, 108 women) with occupational category as the only missing data and performed the same multivariable analyses without controlling on this parameter. The FP2 transformations for insulin and BMI were the same as for the main analysis, and the hazard associated with fasting serum insulin remained statistically significant among men ($P = 0.015$), and not among women ($P = 0.26$) (Supplementary Table 4).

Discussion

Our main findings were (i) fasting serum insulin was associated with death by cancer in men, with a J-shaped relationship, controlling for age, BMI, alcohol consumption,

smoking habits, ethnicity and occupational category, and (ii) this association was not found in women.

Sex and different shape of the association Compared with men at 7.1 mU/l of fasting serum insulin level, risk of cancer death was more than doubled in men with fasting serum insulin values of 12.9 mU/l and nearly doubled in those at 5.0 mU/l, suggesting that both lower and higher values of insulin are detrimental ([Table 2](#)). Strikingly, the minimal hazard for death by cancer was found around the mean insulin value in men. This is in line with the Helsinki Policemen Study [20], where results suggested that men with insulin values in the lowest and highest quintile groups had a higher risk of death by cancer compared to men with insulin values in the three middle quintile groups. The Cardiovascular Heart Study showed a similar shape of the risk for incident colorectal cancer, but with both sexes combined [30]. The other studies providing results for men only did not take into account an eventual U- or J-shape [21,22], even though the Paris Prospective Study presented results with fasting insulin by quintile groups suggesting the hazard was minimal in the third quintile group [21]. These studies concluded to a lack of association between fasting serum insulin and death by cancer. Whether the same conclusion would have been reached with non-linear models to account for U- or J-shaped relationship is not known.

Comparison with the Cremona study is difficult [23], as they combined men and women in the same analysis and compared individuals with the highest levels of fasting serum insulin (above the 4th quintile) to the others, and they found an increased risk. In our population, these results can be reproduced for the men, but not for the women. However, we preferred analyses using insulin as a continuous variable rather than in categories, as discussed by Altman et al. [31] We report striking differences in the shape and magnitude of the associations between men and women,

suggesting that adjustment for sex is not sufficient to take the effect of sex into account. In women, our results suggest that there is no association between insulin and death by cancer, or at least that this association is less strong than in men; the observed shape of an eventual risk is neither a U- nor J-shaped, but rather a linear relation.

Regarding the gender-interaction hypothesis, pharmaco-epidemiological studies are ambivalent. Some studies did not highlight differences between sexes [16,17,32], or found an increased risk of colorectal cancer for men under insulin compared to women [33]. A large population study on incident pancreatic cancer also found a greater protective effect of metformin and a greater risk associated with sulfonylureas for women compared to men [34], inciting future studies to focus on specific drugs and cancer sites.

We have no absolute certainty to explain how both low and high insulin values are associated with higher risks of cancer death in men, and we can only speculate. Concerning high levels, insulin is known to promote cell neoplastic growth [2], and hyperinsulinemia has been suggested to be the cause of the higher cancer prevalence observed in the 10-year period preceding a diabetes diagnosis in a large retrospective, population-based cohort study where, unfortunately, no analysis by sex has been performed [35]. Concerning low levels, if a low fasting insulin level is a reflection of an insulin deficiency, it may be a risk factor for cancer-associated cachexia, and so a poor prognosis factor in case of incident cancer [36]. With this pathophysiological hypothesis, low insulin levels would not increase the cancer risk itself but the risk of death in case of cancer. Anyway, we do not have completely satisfactory hypotheses and, furthermore, they do not explain the difference between sexes.

Our results emphasize the need to study the relationship between fasting serum insulin and death by cancer, separately in men and women. This is clinically relevant, as sex-specific cancers (breast, ovarian, uterus and prostate cancers) are likely to have different insulin-sensitivities.

Confounding factors In order to control for obesity, we chose to use BMI as an adjustment factor and modeled it using a FP2 transformation. This transformation appeared to be stable in the sensitivity model with a slightly larger population ([Supplementary Table 4](#)). It must be stressed that a study looking at the risk of death among men with prostate cancer, as a result of BMI and C-peptide levels measured before diagnosis, found the highest risk in the population with both high C-peptide levels and overweight, in favor of a synergy of these risk factors [14]. Our data did not provide any statistical argument for an interaction effect between BMI and fasting serum insulin (results not shown).

The four other confounders, namely tobacco and alcohol consumption, ethnicity and occupational category, were not statistically associated with the risk of cancer death in men, and did not substantially change the hazard associated with fasting serum insulin. Regarding ethnicity, the lower risk of death by cancer was among the Afro-Caribbean compared to the rest of the population and for both genders, but was not found to be statistically significant (adjusted HR, 0.55; 95% CI, 0.19-1.61 and adjusted HR, 0.52; 95% CI, 0.20-1.36, respectively for men and women). They represented a small part of our population (11%) but this ethnic group needs further investigation, as, to our knowledge, it has not been treated elsewhere.

Strengths and weaknesses of the study The strengths of our study include the large population with a long follow-up, the relatively small number of missing data on vital status information (vital status available for 94.5%) and few death certificates not-retrieved at the end of follow-up, from the French Center for Epidemiology for Causes of Death (3 in 330 not retrieved, 1%). Also, the insulin level measured was not the reflection of incident cancer, as no people died of cancer-related deaths in the first 3 years of follow-up (and only 3 in the first five years), so the hypothesis of a reverse causality bias, with cancer incidence explaining high (or, for alcohol-related cancer, low) insulin levels, is unlikely.

Our study presents some limitations. First, while the long follow-up confers a higher statistical power to the study by adding more events, the long period between the determinant, fasting serum insulin, and the alleged consequence, a higher risk of cancer-associated death, requires a careful interpretation of the causal link. Multiple values of fasting serum insulin would have defined the time exposure with better accuracy **and would have given a more accurate assessment of serum insulin than a single measurement, but indeed a fair correlation has been found between fasting serum insulin at baseline and after a 9-year follow-up in the D.E.S.I.R. Study, with $r=0.56$ (3960 individuals with a sex-ratio of 0.97, personal communication)**. Second, assessment of insulin values was limited by the sensitivity threshold of the assay used to measure fasting serum insulin, and almost 20% of the participants had insulin values below the minimal detectable value. Therefore, we lack accuracy in modeling the relationship between low insulin values and the risk of death by cancer. Third, we did not have the medical history and precise circumstances of deaths at our disposal, so we were not able to appreciate accurately if the cancer reported in the death certificate was really the cause of death. Last, cancer inci-

dence was not available in this study. Therefore, we were not able to capture whether insulin increased cancer incidence, worsened cancer prognosis, or led to both.

Conclusion In summary, from the 28-year follow-up of the TELECOM Study, we report that fasting serum insulin was associated with death by cancer, among men but not among women, with a higher hazard at extreme values of fasting serum insulin, mainly in high levels, and this independently of age, smoking status, alcohol consumption, ethnicity and occupational category. Future studies should be conducted in order to confirm and further to explain a sex difference in the relationship between fasting serum insulin and cancer death. Pharmacoepidemiological studies should also systematically consider the possibility of a gender-effect when assessing association between antidiabetic drugs and cancer incidence or mortality.

Acknowledgments The authors thank Dr A. Gallini from the Department of Epidemiology of Toulouse University Hospital for help in the preparation of the manuscript; Mr. G. Coulon and all the staff of the Telecom Center for Preventive Medicine for the quality of data collection; Didier Chevenne for discussion about the serum insulin assay technique.

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Figure captions

Figure 1 - Flow chart after 28 years of follow-up. The French TELECOM Study

Figure 2 – Adjusted Hazard Ratios (HR) of death by cancer according to fasting serum insulin, calculated by comparison to a sex-specific reference point (Ref. point). Multivariable Cox models were adjusted for body mass index, smoking habits, alcohol consumption, ethnic origin and occupational category, with age used as time scale. Black lines: continuous approach with fractional polynomial transformations; dashed lines show the 95% confidence interval. The French TELECOM Study

Horizontal red line: $HR = 1$, corresponding to the hazard at the reference point. Vertical blue bars above: associated histogram for fasting serum insulin, by sex.

Sex-specific insulin quintile groups	Fasting Serum Insulin (mU/l)					<i>P</i> ^a
	1	2	3	4	5	
MEN (N = 1553)	N = 315	N = 310	N = 319	N = 316	N = 293	
Insulin range (mU/l)	5.0-5.2	5.3-6.4	6.5-7.8	7.9-9.9	10-33	
Age (years)	33 (28-43)	34 (29-47)	34 (29-47)	36 (30-49)	40 (31-52)	<10⁻⁴
Current smoker ^b	140 (44.4)	117 (37.7)	113 (35.4)	92 (29.1)	84 (26.6)	10⁻⁴
BMI (kg/m ²)	23.0 ± 2.4	23.4 ± 2.5	23.8 ± 2.5	24.5 ± 2.8	26.4 ± 3.1	<10⁻⁴
Alcohol consumption (AU)	1.1 (0-3.2)	1.1 (0-3.2)	0.5 (0-2.5)	1.2 (0-3.2)	1.1 (0-3.6)	0.16
Occupational category						0.008
<i>category A</i>	92 (29.2)	100 (32.3)	98 (30.7)	67 (21.2)	88 (30.0)	
<i>category B</i>	124 (39.4)	113 (36.5)	125 (39.2)	151 (47.8)	96 (32.8)	
<i>category C</i>	99 (31.4)	97 (31.3)	96 (30.1)	98 (31.0)	109 (37.2)	
Afro-Caribbean	30 (9.5)	27 (8.7)	30 (9.4)	40 (12.7)	37 (12.6)	0.32
Death by cancer	15 (4.8)	8 (2.6)	12 (3.8)	16 (5.1)	29 (9.9)	0.001
WOMEN (N = 1564)	N = 345	N = 290	N = 325	N = 297	N = 307	
Insulin range (mU/l)	5.0	5.1-6.1	6.2-7.4	7.5-9.3	9.4-54	
Age (years)	40 (32-49)	42 (32-52)	41 (32-52)	40 (29-51)	40 (30-51)	0.50
Current smoker ^b	89 (25.8)	76 (26.2)	71 (21.8)	55 (18.5)	61 (19.9)	0.08
BMI (kg/m ²)	21.5 ± 2.6	22.2 ± 2.7	22.9 ± 3.0	23.3 ± 3.1	25.4 ± 4.6	<10⁻⁴
Alcohol consumption (AU)	0 (0-1.08)	0 (0-1.08)	0 (0-1.08)	0 (0-0)	0 (0-0.54)	0.053
Occupational category						0.003
<i>category A</i>	21 (6.1)	27 (9.3)	21 (6.5)	25 (8.4)	17 (5.5)	
<i>category B</i>	165 (47.8)	129 (44.6)	137 (42.2)	124 (41.8)	101 (32.9)	
<i>category C</i>	159 (46.1)	134 (46.3)	167 (51.4)	148 (49.8)	189 (61.6)	

Afro-Caribbean	19 (5.5)	23 (7.9)	35 (10.8)	42 (14.1)	67 (21.8)	<10⁻⁴
Death by cancer	11 (3.2)	13 (4.5)	15 (4.6)	17 (5.7)	14 (4.6)	0.64

Data are n (%), mean \pm SD or median (Q1-Q3).

AU = alcohol unit, 10 g of pure alcohol/day.

^a *P* values from χ^2 , ANOVA or Kruskal-Wallis tests

^b current smokers: declared having smoked in the last 6 months

Table 1 - Main characteristics of the population presented by sex and sex-specific quintiles of fasting serum insulin. The French TELECOM Study, N = 3117

MEN (<i>n</i> = 1553)						
Sex-specific insulin quintile groups	1	2	3	4	5	<i>P</i>
	N = 315	N = 310	N = 319	N = 316	N = 293	
Insulin (mU/l): mean (range)	5.0 (5.0-5.2)	5.9 (5.3-6.4)	7.1 (6.5-7.8)	8.8 (7.9-9.9)	12.9 (10.0-33.0)	
HR (95% CI) associated with fasting serum insulin^a						
<i>Unadjusted</i>						
as a continuous variable	1.54 (0.83-2.83)	1.03 (0.84-1.24)	1 (ref.)	1.27 (1.10-1.47)	2.34 (1.48-3.69)	0.003
<i>Adjusted</i>						
as a continuous variable ^b	1.88 (1.00-3.56)	1.10 (0.90-1.35)	1 (ref.)	1.24 (1.04-1.46)	2.30 (1.34-3.94)	0.009
as a categorical variable	1.70 (0.79-3.69)	0.73 (0.29-1.78)	1 (ref.)	1.11 (0.52-2.35)	1.84 (0.91-3.69)	0.078
WOMEN (<i>n</i> = 1564)						
Sex-specific insulin quintile groups	1	2	3	4	5	<i>P</i>
	N = 345	N = 290	N = 325	N = 297	N = 307	
Insulin (mU/l): mean (range)	5.0 (5.0-5.0)	5.6 (5.1-6.1)	6.8 (6.2-7.4)	8.3 (7.5-9.3)	12.7 (9.4-54.0)	
HR (95% CI) associated with fasting serum insulin^a						
<i>Unadjusted</i>						
as a continuous variable	1 (ref.)	1.02 (0.99-1.06)	1.07 (0.96-1.20)	1.14 (0.93-1.39)	1.36 (0.85-2.15)	0.20
<i>Adjusted</i>						
as a continuous variable ^c	1 (ref.)	1.02 (0.98-1.06)	1.06 (0.94-1.21)	1.12 (0.89-1.41)	1.30 (0.76-2.23)	0.35
as a categorical variable	1 (ref.)	1.30 (0.58-2.92)	1.22 (0.56-2.69)	1.63 (0.73-3.55)	1.27 (0.55-2.97)	0.83

HR: Hazards ratio. 95% CI: 95% confidence interval. Ref. : Reference value

^a HR from multivariable Cox models first unadjusted and then adjusted on smoking habits, alcohol consumption, body mass index (continuous variable), ethnic group and professional category, with age used as time scale.

- For fasting serum insulin as a continuous variable, the reference value was chosen as the mean of the quintile group with the lowest hazard (3rd quintile group for men, 7.1 mU/l, 1st for women, 5.0 mU/l), and the HR was calculated between the mean of each of the quintile groups and the reference value.

- For fasting serum insulin in quintile groups, the reference group was chosen as the one including the former defined reference value

^b For men, fractional polynomial transformation for fasting serum insulin:

$$f_1(x) = (x/10)^{-2} \text{ and } f_2(x) = (x/10)^{-2} * \log(x/10)$$

and fractional polynomial transformation for body mass index:

$$g_1(x) = (x/10)^3 \text{ and } g_2(x) = (x/10)^3 * \log(x/10)$$

^c For women, no fractional polynomial transformation was proposed for fasting serum insulin or BMI:

$$f_1(x) = f_2(x) = x$$

For both sexes, *P*-values associated with the different representations of insulin were obtained with likelihood ratio tests, by comparison to models without insulin

Table 2 – Hazards Ratios (HR) and 95% confidence intervals of death by cancer according to sex-specific quintile groups of fasting serum insulin; HR from multivariable adjusted Cox models with categorical and continuous approaches. The French TELECOM Study, N = 3117

TELECOM study population at baseline, N = 3934 individuals,
after the exclusion of 32 individuals because of known diabetes mellitus

- 162 (4.1%) : birthplace not known
- 56 (1.4%) : not found in vital status request *and*
not identified at birthplace town hall records
or not born on French territory

Vital status obtained at least once between baseline and 31/12/2013:
3716 individuals (94.5%), including

- 413 (11.1%) deceased
- 3303 (88.9%) not deceased, including
 - 11 alive in 01/01/2008, no news available since
 - 3292 confirmed alive on 31/12/2013, in vital status records or town hall

- BMI (1),
- smoking habits (14),
- alcohol consumption (4),
- fasting serum insulin (372),
- ethnic origin (48),
- professional category (190),
- death certificate not retrieved (3)

3117 (1553 men, 1564 women) remaining individuals with full data,
among whom 330 deaths before 31 December 2013 (10.6%),
including 150 (80 men, 70 women) cancer-related deaths (45.5%)

