

SUPPLEMENTARY DATA

Supplementary Table 1: Summary of Principal Findings from Retrospective Cohort Studies Assessing the Association between Insulin Glargine and Cancer, published in *Diabetologia* September 2009

Study	Data Source	Outcomes	N- insulin users	N Using Glargine	Events	Events in Glargine only group	Mean years follow up	Glargine estimate from main model, fully adjusted (95% CI)
Hemkens et al.	Outpatient prescription and inpatient diagnoses from largest German health insurer	Incident cancer any type	127,031	23,855 glargine only	5009*	669 (103 in highest dose group)	1.6	ANY CANCER HR= 1.18 (1.08, 1.28) Overall HR= 1.31 (1.20, 1.42) Highest daily dose only
Calhoun et al.	Scotland diabetes registry and cancer registry	Incident cancer any and site specific	19,899 type 2 diabetics	411 glargine only 1033 glargine + non-glargine combination users	715	22 in glargine only users 29 in glargine + non-glargine combination users	2.5	ANY CANCER HR 1.02 (0.77, 1.36) any glargine HR 1.55 (1.01, 2.37) glaring only HR 0.81 (0.55, 1.18) glargine + non-glargine combination BREAST CANCER HR 3.39 (1.46, 7.85) glargine only HR 1.49 (0.79, 2.83) any glargine
Currie et al.	UK Health Information Network (THIN)-research data extracted from clinical records	Incident cancer any and site specific	7,659 patients in insulin specific models	2,286 glargine-only	373 any solid tumor 48 of breast	Overall count unknown 10 breast	2.4	ANY CANCER Human long-acting insulin vs. glargine only HR 1.24 (0.90,1.70)*** BREAST CANCER Glargine vs. all other insulin regimens HR 0.86 (0.42, 1.75)***
Jonasson et al.	Seven Swedish national diabetes registries	Incident cancer any and site specific	114,841	5,970 glargine only 20,316 glargine + non-glargine	2199 overall 183 breast	149 overall 25 breast	2.0	ANY CANCER IRR** 1.04 (0.88, 1.22) glargine only IRR** 1.00 (0.89, 1.13) glargine + non-glargine BREAST CANCER IRR** 1.97 (1.30, 3.00) glargine only IRR** 1.17 (0.81, 1.68) glargine + non-glargine

For the purpose of summary, principal findings of interest to this review are presented and many sub-analyses excluded.

Reference exposure group was human insulin unless otherwise noted

*number of people with neoplasms rather than count of neoplasms ** incidence rate ratio not relative risk (IRR), HR is hazard ratio, *** note in contrast to other models, for these reference exposure is glargine only. Any glargine use = use of glargine as only insulin or in combination with non-glargine insulins. Glargine only= glargine is the only insulin use recorded in data. ≈ indicate approximate values

SUPPLEMENTARY DATA

Supplementary Table 2: Cancer Identification and Classification Based on Clinical Classification Software

Clinical Classification Software Cancer Category	Cancer Type	ICD-9 Codes
11	Cancer of head and neck	1401 1403 1404 1408 1409 1410 1411 1412 1413 1414 1415 1416 1418 1419 1420 1421 1422 1428 1429 1430 1431 1438 1439 1440 1441 1448 1449 1450 1451 1452 1453 1454 1455 1456 1458 1459 1460 1461 1462 1463 1464 1465 1466 1467 1468 1469 1470 1471 1472 1473 1478 1479 1480 1481 1482 1483 1488 1489 1490 1491 1498 1499 1600 16011602 1603 1604 1605 1608 1609 1610 1611 1612 1613 1618 1619 1950 2300 2310
12	Cancer of esophagus	1500 1501 1502 1503 1504 1505 1508 1509 2301
13	Cancer of stomach	1510 1511 1512 1513 1514 1515 1516 1518 1519 20923 2302
14	Colon Cancer	1530 1531 1532 1533 1534 1535 1536 1537 1538 1539 1590 20910 20911 20912 20913 20914 20915 20916 2303
15	Cancer of the rectum or anus	1540 1541 1542 1543 1548 20917 2304 2305 2306 79670 79671 79672 79673 79674 79676
16	Cancer of the liver/biliary tract	1550 1551 1552 2308
17	Cancer of the pancreas	1570 1571 1572 1573 1574 1578 1579
18	Cancer of other gastrointestinal tract/peritoneum	1520 1521 1522 1523 1528 1529 1560 1561 1562 1568 1569 1580 1588 1589 1591 1598 1599 20900 20901 20902 20903 2307 2309
19	Cancer of bronchus/lung	1622 1623 1624 1625 1628 1629 20921 2312
20	Cancer; other respiratory and intrathoracic	1620 1630 1631 1638 1639 1650 1658 1659 2311 2318 2319
21	Bone and connective tissue cancer	1700 1701 1702 1703 1704 1705 1706 1707 1708 1709 1710 1712 1713 1714 1715 1716 1717 1718 1719
22	Melanoma of skin	1720 1721 1722 1723 1724 1725 1726 1727 1728 1729
23	Other non-epithelial cancer of skin	1730 1731 1732 1733 1734 1735 1736 1737 1738 1739 20931 20932 20933 20934 20935 20936 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329
24	Breast cancer	1740 1741 1742 1743 1744 1745 1746 1748 1749 1750 1759 2330
25	Cancer of the Uterus	179 1820 1821 1828 2332
26	Cancer of the Cervix	1800 1801 1808 1809 2331 7950 79506
27	Ovarian cancer	1830
28	Other cancer of the female genital tract	181 1832 1833 1834 1835 1838 1839 1840 1841 1842 1843 1844 1848 1849 2333 23330 23331 23332 23339
29	Prostate Cancer	185 2334
30	Testicular cancer	1860 1869
31	Other cancer of the male genital tract	1871 1872 1873 1874 1875 1876 1877 1878 1879 2335 2336
32	Bladder cancer	1880 1881 1882 1883 1884 1885 1886 1887 1888 1889 2337

SUPPLEMENTARY DATA

33	Kidney/renal cancer	1890 1891 20924
34	Other urinary organ cancer	1892 1893 1894 1898 1899 2339
35	Cancer of the brain/nervous system	1910 1911 1912 1913 1914 1915 1916 1917 1918 1919 1920 1921 1922 1923 1928 1929
36	Thyroid cancer	193 25802 25803
37	Hodgkin's Disease	20100 20101 20102 20103 20104 20105 20106 20107 20108 20110 20111 20112 20113 20114 20115 20116 20117 20118 20120 20121 20122 20123 20124 20125 20126 20127 20128 20140 20141 20142 20143 20144 20145 20146 20147 20148 20150 20151 20152 20153 20154 20155 20156 20157 20158 20160 20161 20162 20163 20164 20165 20166 20167 20168 20170 20171 20172 20173 20174 20175 20176 20177 20178 20190 20191 20192 20193 20194 20195 20196 20197 20198
38	Non-Hodgkin's lymphoma	20000 20001 20002 20003 20004 20005 20006 20007 20008 20010 20011 20012 20013 20014 20015 20016 20017 20018 20020 20021 20022 20023 20024 20025 20026 20027 20028 20030 20031 20032 20033 20034 20035 20036 20037 20038 20040 20041 20042 20043 20044 20045 20046 20047 20048 20050 20051 20052 20053 20054 20055 20056 20057 20058 20060 20061 20062 20063 20064 20065 20066 20067 20068 20070 20071 20072 20073 20074 20075 20076 20077 20078 20080 20081 20082 20083 20084 20085 20086 20087 20088 20200 20201 20202 20203 20204 20205 20206 20207 20208 20210 20211 20212 20213 20214 20215 20216 20217 20218 20220 20221 20222 20223 20224 20225 20226 20227 20228 20270 20271 20272 20273 20274 20275 20276 20277 20278 20280 20281 20282 20283 20284 20285 20286 20287 20288 20290 20291 20292 20293 20294 20295 20296 20297 20298
39	Leukemia	20240 20241 20242 20243 20244 20245 20246 20247 20248 2031 20310 20311 20312 2040 20400 20401 20402 2041 20410 20411 20412 2042 20420 20421 20422 2048 20480 20481 20482 2049 20490 20491 20492 2050 20500 20501 20502 2051 20510 20511 20512 2052 20520 20521 20522 2053 20530 20531 20532 2058 20580 20581 20582 2059 20590 20591 20592 2060 20600 20601 20602 2061 20610 20611 20612 2062 20620 20621 20622 2068 20680 20681 20682 2069 20690 20691 20692 2070 20700 20701 20702 2071 20710 20711 20712 2072 20720 20721 20722 2078 20780 20781 20782 2080 20800 20801 20802 2081 20810 20811 20812 2082 20820 20821 20822 2088 20880 20881 20882 2089 20890 20891 20892
40	Multiple Myeloma	2030 20300 20301 20302 2038 20380 20381 20382
41-44	Cancer of uncertain primary:	1640 1641 1642 1643 1648 1649 1760 1761 1762

SUPPLEMENTARY DATA

	<p>other and unspecified primary, secondary malignancies, malignant neoplasm without specification of site, Neoplasms of unspecified nature or uncertain behavior</p>	<p>1763 1764 1765 1768 1769 1900 1901 1902 1903 1904 1905 1906 1907 1908 1909 1940 1941 1943 1944 1945 1946 1948 1949 1951 1952 1953 1954 1955 1958 20230 20231 20232 20233 20234 20235 20236 20237 20238 20250 20251 20252 20253 20254 20255 20256 20257 20258 20260 20261 20262 20263 20264 20265 20266 20267 20268 20922 20925 20926 20927 2340 2348 2349 7951 79510 79511 79512 79513 79514 1960 1961 1962 1963 1965 1966 1968 1969 1970 1971 1972 1973 1974 1975 1976 1977 1978 1980 1981 1982 1983 1984 1985 1986 1987 19881 19882 19889 20971 20972 20973 20974 51181 78951 1990 1991 1992 20920 20929 20930 20970 20975 20979 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 23690 23691 23699 2370 2371 2372 2373 237 2375 2376 2377 23770 23771 23772 2379 2380 2381 2382 2383 2384 2385 2386 2387 23871 23872 23873 23874 23875 23876 23877 23879 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 23981 23989 2399</p>
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The date of cancer onset was set to the earliest of: the first inpatient or second outpatient diagnosis. Patients were permitted to contribute only one incident cancer event.

SUPPLEMENTARY DATA

Supplementary Table 3: Diagnoses and ICD-9 Codes used to identify Charlson comorbidities, tobacco-associated disease and diabetes complications

<i>Diagnoses</i>	<i>ICD-9 Codes</i>
Myocardial Infarction	ST-segment elevation MI: ICD-9 Dx codes: 410.0-6, 410.8 5th digit 0 or 1, 410.71, 410.70, 410.90, 410.91 5th digit 0 or 1
Chronic Renal Disease	ICD-9 Dx and V codes: 585-586, V420, V451, V56.x
Congestive Heart Failure	ICD-9 Dx code: 402.01, 402.11, 402.91, 425.0-9, 428.0-428.9, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Pulmonary Disease	Asthmatic Lung Disease: ICD-9 Dx code 493.xx
Dementia	ICD-9 Dx code: 290.xx, 331.0-331.2
Cerebrovascular Disease	ICD-9 Dx code: 362.34, 430-436.9, 437.0, 437.1, 437.9, 781.4, 784.3 997.0
Peptic Ulcer Disease	ICD-9 Dx code: 531- 534
Rheumatologic Disease	ICD-9 Dx Codes: 710.x, 714.x
HIV/AIDS*	HIV: ICD-9 042-044, V08
Hemiplegia/Paraplegia*	ICD-9 Dx Codes: 342.x, 344.x
Mild and Moderate Liver Disease	ICD-9 Dx code: 571.2, 571.5, 571.6, 571.8, 571.9, 572.2-572.4, 456.0x-456.29
Tobacco Exposure Measure (tobacco related disease or diagnosis of tobacco use)	Chronic Non-Asthmatic Lung Disease: ICD-9 Dx code: 415.0, 416.8, 416.9, 491.0, 492.0, 494.0, 496.0 Tobacco use: ICD-9 305.1, V15.82, 989.84 tobacco
Diabetes Complications	250.40,1,2,3 Diabetes with renal manifestations, 250.5(0,1,2,3) Diabetes with ophthalmic manifestations, 250.6(0,1,2,3) Diabetes with neurological manifestations, 250.7(0,1,2,3) Diabetes with peripheral circulatory disorders, 250.9(0,1,2,3) Diabetes with unspecified complication, 357.2 Polyneuropathy in diabetes, 366.41 Diabetic cataract, 362.01 Background diabetic retinopathy, 362.02 Proliferative diabetic retinopathy, 362.0 Diabetic retinopathy unspecified
Peripheral Vascular Disease	ICD-9 Dx code: 440.x, 441.x, 442.x, 443.x, 447.1, 785.4

Charlson et al. 1987 & Romano, et al 1993

Supplementary Figure 1: Study Time Line Diagram

