Semaglutide and pancreatic cancer: Is the risk real?

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When semaglutide was first approved, regulators required its manufacturer to run a post-authorisation safety study answering a specific question that had been hanging over GLP-1 receptor agonists since early pharmacovigilance reports and rodent studies raised it: does the drug carry a pancreatic cancer risk? New data presented at the EASD Annual Meeting in Milan reports the results of that mandated study.

KEY TAKEAWAYS

- The Pivot: The specific, regulator-mandated question of whether semaglutide raises pancreatic cancer risk now has a large, multi-country registry answer: no.
- The Data: Pooled HR 0.91 (95% CI 0.71-1.16) across 97,464 matched pairs, with no dose-response or duration-response signal.
- The Action: This closes, rather than opens, a safety question, the absence of any cumulative dose or duration effect is the strongest evidence against a causal mechanism.

Researchers led by Professor Anton Pottegård at the University of Southern Denmark used nationwide health registries from Denmark, Sweden and Norway to run an active-comparator, new-user cohort study. New semaglutide users treated for type 2 diabetes were propensity-score matched against new users of non-incretin antidiabetic drugs, sulfonylureas, SGLT-2 inhibitors or insulin, with follow-up starting one year after initiation to allow for a cancer-detection lag period.

No increased risk in any country, or at any dose

The study included 97,464 propensity-score matched pairs, well balanced after matching, with a median age of 59-62 among semaglutide users and 1.40-1.85 years of follow-up after the one-year lag. Pancreatic cancer occurred in 131 semaglutide users and 123 comparator users, across 167,399 and 140,306 person-years of follow-up respectively, incidence rates of roughly 0.6-0.9 per 1,000 person-years in both groups.

Country-specific hazard ratios showed no increased risk anywhere: 1.00 (95% CI 0.66-1.51) in Denmark, 0.82 (95% CI 0.56-1.22) in Sweden, and 0.91 (95% CI 0.55-1.51) in Norway, with no heterogeneity between countries. The pooled hazard ratio was 0.91 (95% CI 0.71-1.16), and the absolute incidence rate difference was essentially zero, 0.10 per 1,000 person-years (95% CI 0.31 to 0.10). Critically, there was no dose-response or duration-response signal either, the pooled HR for high-dose use was 0.74 (95% CI 0.40-1.40) and for long-duration use was 0.79 (95% CI 0.37-1.69), the pattern that would be expected to emerge first if the drug genuinely raised risk.

Why a regulator mandated this study in the first place

The pancreatic cancer hypothesis for GLP-1 receptor agonists did not come from nowhere: early spontaneous adverse event reports and preclinical rodent studies showing pancreatic cellular changes, combined with GLP-1 drugs' known association with acute pancreatitis in some case reports, raised a plausible mechanistic question about chronic pancreatic

inflammation and cancer risk. That is exactly the kind of signal regulators require a dedicated post-authorisation study to either confirm or rule out, rather than leaving it as an open hypothesis.
"These findings also align with current external evidence and thus further strengthen the evidence that semaglutide does not increase the risk of pancreatic cancer," said Professor Pottegård. The study was funded by Novo, semaglutide's manufacturer, as the regulator-mandated sponsor, a funding relationship the authors disclose directly.

The robust methodology employed in this study, particularly the active-comparator design and the one-year lag period, addresses critical limitations often found in observational studies investigating drug safety signals. By comparing semaglutide users to those on other antidiabetic medications, the researchers minimized confounding by indication, a common pitfall when assessing drug effects in a specific patient population. The inclusion of a lag period is crucial for cancer studies, as it accounts for the often-long latency between drug exposure and clinically detectable malignancy, thereby reducing the likelihood of reverse causality where pre-existing, undiagnosed cancer might influence drug selection.

While the study provides strong reassurance regarding semaglutide and pancreatic cancer risk, it is important to acknowledge certain inherent limitations of real-world evidence. Despite propensity-score matching, residual confounding by unmeasured factors, such as lifestyle choices or genetic predispositions, can never be entirely eliminated. Furthermore, the follow-up duration, while adequate for detecting early signals, may not capture extremely rare events or those with very long latency periods that could manifest over decades of use. The median follow-up of 1.40-1.85 years, though substantial for a new drug, is still relatively short in the context of a chronic condition like type 2 diabetes, where patients may be on treatment for many years.

Clinically, these findings should provide significant comfort to healthcare professionals prescribing semaglutide for type 2 diabetes and obesity. The consistent lack of a signal across three Nordic countries, coupled with the absence of a dose-response or duration-response relationship, strongly suggests that the initial concerns regarding pancreatic cancer risk are unfounded. This evidence allows clinicians to focus on the established benefits of semaglutide, including glycemic control, weight loss, and cardiovascular risk reduction, without undue apprehension about this specific oncological risk. When discussing treatment options with patients, clinicians can confidently address any lingering concerns about pancreatic cancer, referencing this large-scale, well-conducted study.

Future research could further strengthen this evidence by extending follow-up durations in similar large cohorts, especially as semaglutide use becomes more widespread and long-term data accrues. Additionally, while the current study focused on pancreatic cancer, ongoing pharmacovigilance for all GLP-1 receptor agonists remains crucial to detect any other potential rare or long-term adverse events. The proactive approach of regulatory bodies in mandating such studies, even in the absence of definitive evidence, underscores the commitment to patient safety and the importance of rigorous post-marketing surveillance for novel therapeutics.

CLINICAL IMPLICATIONS

> For clinicians fielding patient questions about semaglutide and cancer risk, this is about as strong a negative safety signal as pharmacoepidemiology produces: three countries, consistent point estimates, no heterogeneity, and critically, no dose-response or duration-response gradient. If semaglutide genuinely raised pancreatic cancer risk, a dose or duration signal is exactly what would be expected to show up first, and it did not.
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> As with any registry-based safety study, residual confounding from unmeasured factors cannot be entirely excluded, and the roughly 1.4-1.9 years of average follow-up after the lag period, while substantial for a mandated safety study, is still short relative to the natural history of a slow-growing cancer. The authors' own sensitivity and supplementary analyses, described as extensive, consistently found no signal.
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> Given the funding source, this should be read as a rigorous, prespecified, regulator-mandated study rather than an industry-initiated marketing claim, the study design (active comparator, new-user, propensity-matched, pre-specified analysis) is the standard regulators require precisely to guard against sponsor-favourable results.

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REFERENCES

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