

# ADA, ACS Spotlight Diabetes-Cancer Links

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FROM DIABETES CARE

A joint consensus statement from the American Diabetes Association and the American Cancer Society reviews the current state of science regarding the complex relationship between diabetes and cancer.

Epidemiologic evidence suggests that people with diabetes—type 2 in particu-

lar—are at increased risk for cancer. The reasons are poorly understood, but may include risk factors common to both disorders, diabetes medications, and possible direct causal links.

The ADA and the ACS convened a consensus development conference in December to examine these links. The writing group independently developed a statement that solely represents the positions of the nine panel members and

does not reflect official positions of either sponsoring organization (Diabetes Care 2010;33:1674-85).

The panel, chaired by Dr. Edward Giovannucci of Harvard School of Public Health, Boston, recommended that diabetes patients be strongly advised to undergo appropriate cancer screenings.

The statement was organized around answers to four basic questions:

► **Is there a meaningful association be-**

**tween diabetes and cancer incidence or prognosis?** Cancer and diabetes are diagnosed in the same individual more frequently than would be expected by chance, even after adjustment for age. The association appears to be limited to certain types of cancer, while other cancers appear to be less common among people with diabetes. Type 2 diabetes is associated with an increased risk for cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder, but with a reduced risk of prostate cancer. For some other cancer sites there appears to be no association.

► **What factors are common to both disorders?** The association may be due in part to shared risk factors such as aging, obesity, diet, and physical inactivity. Smoking appears to be an independent risk fac-

**Postmarketing Experience**—The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Osteosarcoma:** Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing.
- **Hypercalcemia:** Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following:

- **Allergic Reactions:** Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria;
- **Investigations:** Hyperuricemia;
- **Respiratory System:** Acute dyspnea, chest pain;
- **Musculoskeletal:** Muscle spasms of the leg or back;
- **Other:** Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

**USE IN SPECIFIC POPULATIONS: Pregnancy Category C**—There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses  $\geq$  60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses  $\geq$ 120 times the human dose (based on surface area, mcg/m<sup>2</sup>). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Exposure multiples were normalized based on body surface area (mcg/m<sup>2</sup>). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day).

**Nursing Mothers**—It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**—The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses.

**Geriatric Use**—Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Impairment**—No studies have been performed in patients with hepatic impairment.

**Renal Impairment**—In 5 patients with severe renal impairment (CrCl $<$ 30 mL/min), the AUC and T<sub>1/2</sub> of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

**OVERDOSAGE:** Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

FORTEO® (teriparatide [rDNA origin] injection)

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In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

**Overdose Management**—There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

**DOSAGE FORMS AND STRENGTHS:** Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

**PATIENT COUNSELING INFORMATION:** Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.



**Cancer and diabetes are diagnosed in the same individual more frequently than would be expected.**

DR. GIOVANNUCCI

tor for the development of diabetes and diabetes complications, in addition to cancer. Evidence for the role of alcohol is mixed. Even moderate alcohol consumption increases the risk for certain types of cancer and excess alcohol consumption is also a risk factor for diabetes. But moderate alcohol consumption is linked with a reduced incidence of diabetes.

► **What are the possible biologic links between diabetes and cancer risk?** The document provides detailed summaries of the evidence pertaining to the potential roles of the insulin/insulin-like growth factor receptor axis, hyperglycemia, hyperinsulinemia, and inflammatory cytokines/inflammation.

► **Do diabetes treatments influence cancer risk or cancer prognosis?** The evidence for specific drugs affecting cancer risk is limited, and observed associations may have been confounded by indications for specific drugs, effects on other cancer risk factors, and the complex progressive nature of hyperglycemia and pharmacotherapy in type 2 diabetes. Early evidence suggests that metformin is associated with a lower risk of cancer and that some exogenously administered insulin is associated with an increased cancer risk. Further research is needed to clarify these issues and evaluate if insulin glargine is more strongly associated with cancer risk, compared with other insulins.

The statement also highlights numerous remaining research questions. ■

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