

## Breast-Cancer Predisposition in Multiple Endocrine Neoplasia Type 1

**TO THE EDITOR:** Multiple endocrine neoplasia type 1 (MEN1) is caused by germline mutations in the *MEN1* tumor-suppressor gene and is typically characterized by parathyroid adenomas, duodenopancreatic neuroendocrine tumors, and pituitary adenomas.<sup>1</sup> Recent studies in animals<sup>2</sup> suggest that *MEN1* is involved in breast-cancer initiation. Through its encoding of menin, a co-regulator of estrogen receptor  $\alpha$ , *MEN1* has been implicated in breast-cancer progression.<sup>3,4</sup>

To clarify the role of *MEN1* in human breast cancer, the International Breast Cancer in MEN1 Study Group assessed the incidence of breast cancer in the Dutch longitudinal MEN1 database, which includes more than 90% of Dutch patients with MEN1.<sup>5</sup> (Study group members are listed in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) In 190 female patients with MEN1, the relative risk of invasive breast cancer was 2.83 ( $P < 0.001$ ), with a standardized incidence ratio of 2.14 (95% confidence interval [CI], 1.18 to 3.86) (Table S1 in the Supplementary Appendix). The mean ( $\pm$ SD) age at diagnosis of mostly luminal-type breast cancer was  $48.0 \pm 8.8$  years, as compared with an age of 60 to 65 years in the general population. Three of the 12 Dutch breast-cancer patients

with MEN1 had a history of hyperprolactinemia. Risk ratios for other major cancers were not elevated (Table S1 in the Supplementary Appendix).

We validated the observations in three independent cohorts from the United States, Tasmania, and France that included a total of 675 female patients with MEN1. In a comparison of breast-cancer prevalence and incidence with corresponding data from the respective national cancer registries, the risk ratios were 2.40 in the United States ( $P = 0.11$ ), 2.31 in Tasmania ( $P = 0.22$ ), and 2.33 in France ( $P = 0.03$ ). (The comparisons were not significant in the United States and Tasmania because of the small numbers of patients in these cohorts.) The standardized incidence ratio in the combined verification cohorts was 1.96 (95% CI, 1.33 to 2.88), and the average age at diagnosis was 51 years.

Nuclear localization of menin was reduced by more than 50% in 8 of 10 breast-cancer samples obtained from Dutch patients with MEN1 on immunohistochemical staining with the use of menin antibody A300-105A (Bethyl Laboratories) (Table 1). Subsequent analysis on DNA sequencing or multiplex ligation-dependent probe amplification revealed loss of heterozygosity at the *MEN1* locus in 3 of 9 tumors. Reduced menin

**Table 1. Characteristics of 10 Patients with Confirmed *MEN1* Germline Mutations and Breast Cancer.\***

Patient No.	Age at Diagnosis yr	Histologic Analysis	Tumor–Node–Metastasis (TNM) Stage	Estrogen Receptor	Progesterone Receptor	HER2	Menin Expression	Loss of Heterozygosity at <i>MEN1</i> Locus
1	55	Ductal	T1N1M0	+	–	–	–	–
2	38	Ductal	T3N1M0	+	+	+	–	–
3	44	Ductal	T1N0M0	–	–	–	+	–
4	61	Ductal	T1N1M0	+	–	–	–	–
5	52	Lobular	T1N0M0	+	+	+	–	–
6	53	Ductal	T1N0M0	+	+	–	–	+
7	45	Micropapillary	T1N1M0	+	–	–	–	+
8	42	Ductal†	T1N0M0	–	+	–	–	+
9	33	Ductal	T1N1M0	+	+	+	+	–
10	46	Ductal	T1N0M0	+	+	–	–	ND

\* A plus sign indicates positivity, and a minus sign negativity. HER2 denotes human epidermal growth factor receptor 2, and ND not determined.

† This patient had a tumor in each breast.

staining was found in only 4 of 88 control breast tumors on a tissue microarray ( $P < 0.001$  by Pearson's chi-square test). All studies were conducted in accordance with regulations of the local institutional review board.

In conclusion, female patients with MEN1 are at increased risk for breast cancer. Loss of menin expression and loss of heterozygosity at the *MEN1* locus in a subgroup of patients suggest a mammary-cell autonomous effect in MEN1-related breast cancer. Our observations indicate that *MEN1* mutations are involved in human breast carcinogenesis. Further research will clarify the relevance of *MEN1* function for patients with nonfamilial breast cancer. Intensified breast-cancer screening at a relatively young age should be considered in female patients with MEN1.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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#### CORRECTIONS

Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection (April 17, 2014;370:1483-93). In the fourth paragraph of the Discussion (page 1491), the first sentence should have ended, “. . . the rates of response were similar in patients with cirrhosis (100% with both regimens) and those without cirrhosis (99% with both regimens),” rather than “. . . patients with cirrhosis (99% with both regimens) and those without cirrhosis (100% with both regimens).” The article is correct at NEJM.org.

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease (January 23, 2014;370:311-21). In Results, in the Biologic Markers and Neuroimaging Outcomes subsection, the final sentence of the penultimate paragraph (page 318) should have begun, “Whole-brain volume decreased slightly in the solanezumab group and the placebo group . . .,” rather than “Whole-brain volume increased slightly . . . .” The article is correct at NEJM.org.

Upper-Airway Stimulation for Obstructive Sleep Apnea (January 9, 2014;370:139-49). In the list of authors (page 139), Dr. Vanderveken's first name should have been “Olivier,” rather than “Oliver.” The article is correct at NEJM.org.

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Dreijerink KMA, Goudet P, Burgess JR, Valk GD. Breast-cancer predisposition in multiple endocrine neoplasia type 1. *N Engl J Med* 2014;371:583-4. DOI: 10.1056/NEJMc1406028

Supplemental appendix

Breast cancer predisposition in multiple endocrine neoplasia type 1

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Supplemental Table

Cohort	Female MEN1 patients in cohort	Invasive breast cancer cases	% Invasive breast cancer	Average age at diagnosis breast cancer
1. Netherlands, Dutch MEN1 Study Group (DMSG)	190	12	6.3	48
2. Boston, Research Patient Data Registry (RPDR)	68	4	5.9	56
3. Tasmania, Tasman 1 kindred	71	3	4.2	55
4. France, Groupe des tumeurs endocrines (GTE)	536	26	4.9	50
2,3,4 combined	675	32	4.7	51
1,2,3,4 combined	865	44	5.1	50

Cohort	Relative risk (RR) breast cancer	RR, p value*	Time interval used for RR	Female MEN1 patients within interval	Cases within interval
1. Netherlands, Dutch MEN1 Study Group (DMSG)	2.83	<0.001	1992-2011 (20 year prevalence, >30 years)	148	11
2. Boston, Research Patient Data Registry (RPDR)	2.4	0.11	< 18 years since diagnosis in 2010	68	3
3. Tasmania, Tasman 1 kindred	2.31	0.22	1982-2008 (27 year prevalence)	55	3
4. France, Groupe des tumeurs endocrines (GTE)	2.33	0.03	2003-2007 (5 year prevalence)	322	6

Cohort	Standardized incidence ratio breast cancer (SIR)	SIR, p value#, 95% Confidence interval Wald	Time interval used for SIR	Female MEN1 patients within interval	Cases within interval
1. Netherlands, Dutch MEN1 Study Group (DMSG)	2.14	0.0089, 1.18<2.14<3.86	1992-2011	182	11
2. Boston, Research Patient Data Registry (RPDR)	3.9	0.0032, 1.46<3.89<10.38	1994-2013	68	4
3. Tasmania, Tasman 1 kindred	1.95	0.23, 0.62<1.95<6.05	1982-2009	66	3
4. France, Groupe des tumeurs endocrines (GTE)	1.77	0.01, 1.13<1.77<2.78	1994-2013	475	19
2,3,4 combined	1.96	0.0004, 1.33<1.96<2.88	combined	609	26
1,2,3,4 combined	2.01	<0.0001, 1.45<2.01<2.77	combined	791	37

Other tumor types Netherlands:	RR	RR, p value*	Time interval used for RR	MEN1 patients within interval	Cases within interval
Melanoma	2.2	0.26	1992-2011 (20 year prevalence, >30 years)	240	2
Prostate carcinoma	1.5	0.59	1992-2011 (20 year prevalence, >30 years)	92	2
Lung carcinoma	NA	NA	1992-2011 (20 year prevalence, >30 years)	240	0
Colorectal carcinoma	1.1	0.86	1992-2011 (20 year prevalence, >30 years)	240	2

\*=Pearson's chi-square test, #=chi-square goodness-of-fit test

Cohort	Cancer registry for reference cohort (URL)	Source of demographic data (URL)
1. Netherlands, Dutch MEN1 Study Group (DMSG)	Dutch Cancer Registry ( <a href="http://www.cijfersoverkanker.nl">www.cijfersoverkanker.nl</a> )	Statistics Netherlands ( <a href="http://www.cbs.nl">www.cbs.nl</a> )
2. Boston, Research Patient Data Registry (RPDR)	Surveillance Epidemiology and End Results database ( <a href="http://www.seer.cancer.gov">www.seer.cancer.gov</a> )	U.S. Census Bureau ( <a href="http://www.census.gov">www.census.gov</a> )
3. Tasmania, Tasman 1 kindred	Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality. AIHW, Canberra Cancer Australia ( <a href="http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/">http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/</a> )	Australian cancer registry
4. France, Groupe des tumeurs endocrines (GTE)	Institut National du Cancer ( <a href="http://lesdonnees.e-cancer.fr/">http://lesdonnees.e-cancer.fr/</a> )	National Institute of Economics and Statistics studies ( <a href="http://www.insee.fr">http://www.insee.fr</a> )