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Richard T. James Jr. M.D.
Editor/Publisher.

The editor thanks
Lois M. James for proof reading
Matthew Ramirez for internet application
8-1 EFFICACY OF HIGH-DOSE VERSUS STANDARD DOSE INFLUENZA VACCINE IN OLDER ADULTS

Between 1990 and 1999, seasonal influenza caused an average of 36,000 deaths and 22,000 hospitalizations per year in the U.S. Adults age 65 and older were particularly vulnerable to complications of flu and accounted for most hospitalizations and deaths.

Although vaccination currently is the most effective intervention against flu and its complications, antibody responses and protection elicited by the vaccine are lower in persons age 65 and older than in younger adults.

Increasing the amount of antigen in the vaccine may improve protection and have a favorable effect on morbidity and mortality.

The high-dose trivalent inactivated influenza vaccine (IIV3-HD) contains 4 times as much hemagglutinin (HA) as the standard dose. On the basis of its safety profile and superior immunogenicity, IIV3-HD was licensed in the U.S. in 2009 with the requirement to show clinical benefit.

The primary objective of this study was to show the effectiveness of high dose vaccine (IIV3-HD) as compared with a standard-dose vaccine (IIV3-SD) for prevention of laboratory confirmed influenza in adults age 65 and older.

STUDY

1. A multicenter, randomized, double-blind trial compared high-dose (IIV3-HD; HD) with a standard-dose vaccine (IIV3-SD; SD) in persons age 65 and older (mean age 73) in 126 centers in the U.S. and Canada September 2011 through May 2013. There were 2 enrollment periods (September 6 through October 9, 2011 and October 9 through October 21, 2012).

2. The study included adults age 65 and older without moderate or severe acute illnesses. Almost half of partisans had chronic cardiovascular or respiratory disorders.

3. Participants were randomly assigned to receive a single dose of IIV3-HD or IIV3-SD. Those who were participants in both years underwent re-randomization in the second year.

4. The standard-dose vaccine (Fluzone) contained 15 ug of HA per strain. The high–dose (Fluzone High-Dose) contained 60 ug per strain. Both were produced on embryonated chicken eggs, and inactivated with formaldehyde. Each vaccine contained 3 strains of influenza virus.

5. Participants were instructed to contact their study site if they developed any respiratory symptoms. In addition, participants were contacted frequently until April 30 each year.

6. Respiratory illness was defined as the occurrence of one or more of: sneezing, nasal congestion,
rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing. This definition has high sensitivity for detection of cases of influenza.

7. A protocol-defined influenza-like illness provides increased specificity and clinical relevance beyond the respiratory illness definition: sore throat, cough, sputum production, wheezing, or difficulty breathing concurrent with one of: temperature above 37.2, chills, tiredness, headache, or myalgia.

8. If a participant met the criteria for any respiratory illness, a nasopharyngeal swab was collected. Laboratory confirmation of influenza virus in the swab was accomplished by a positive result on culture, a polymerase-chain reaction, or both. A hemagglutination (HA)-inhibition assay was performed to determine if the sample strain was antigenically similar to the vaccine strain. Genetic sequencing further evaluated the similarity of the vaccine components.

9. Within 30 days after the start of any respiratory illness, follow-up phone calls were made to collect effectiveness information associated with events occurring within 30 days after the start of any respiratory illness: pneumonia, cardio-respiratory symptoms, health care visits, hospitalizations for any cause, visits to the ER, and non-routine medical visits and medication use.

10. Safety surveillance extended from vaccination to May of the following year.

11. Immunogenicity: Blood samples were collected approximately 30 days after vaccination and were assayed for HA inhibition titers.

12. Measures of efficacy: The primary end point was the occurrence, at least 14 days after vaccination, of laboratory-confirmed influenza caused by any influenza viral types or subtypes, in association with protocol-defined influenza-like illness.

RESULTS

1. A total of 14 500 participants were enrolled in year 1; 17 489 in year 2. (7645 enrolled in year 1 were also enrolled in year 2.)

2. Efficacy: 529 participants met the primary end-point—226 (1.4%) in the high dose vaccine group and 301 (1.9%) in the standard dose group. Efficacy of the high-dose relative to the standard dose for the primary endpoint was 24%. (Ie, the HD vaccine provided 24% more protection against influenza than the SD.) The estimate for relative vaccine efficacy was consistently positive across influenza types, clinical definitions, methods of laboratory confirmation, and study year. Overall, relative efficacy estimates were higher in analyses
restricted to cases caused by vaccine-similar strains (35%)

3. Effectiveness: Most rates for pneumonia, cardio-respiratory conditions, hospitalizations, non-routine medical office visits, and medication use were lower in the high-dose group.

4. Safety: 1323 participants (8.3%) in the high-dose group and 1442 (9.0%) in the standard-dose group had at least one serious adverse event. Relative risk high-dose vs standard dose was 0.92. During the safety surveillance period of 6 to 8 months after vaccination, 0.5% in both groups died. In the high-dose group, 6 died within 30 days after vaccination. All were classified as non-related to the vaccine. Three HD participants had serious events categorized as related to vaccination: cranial nerve palsy starting 1 day after vaccination, hypovolemic shock associated with diarrhea starting 1 day after vaccination, and acute disseminated encephalomyelitis starting 17 days after vaccination. No serious adverse effects were considered to be related to SD vaccine. A total of 99 in the HD group and 103 in the SD group (0.6% in each) discontinued the study due to serious adverse events, none considered to be related to the vaccine. Cardiovascular disorders and infections were the most frequent types of serious events.

5. Immunogenicity: HAI antibody titers and sero-protection rates 28 days after vaccination were significantly higher with HD than with SD for all 3 strains.

DISCUSSION

1. A few randomized controlled trials have shown moderate efficacy of influenza vaccine among older adults. However, given the high burden of influenza in this population, despite increased vaccination rates, improved vaccines are needed.

2. This randomized, double-blind, active controlled efficacy trial showed that HD (IIV3-HD) provided improved protection against laboratory-confirmed influenza among adults age 65 and older. The overall efficacy of 24% against the primary endpoint indicates that one quarter of all breakthrough influenza illness could be prevented if HD were used instead of SD. More than a third of breakthrough influenza illness caused by strains similar to the vaccine could be prevented.

3. This study provides an estimate of the relative efficacy of HD as compared with SD. The absolute efficacy can be inferred only on the basis of estimated absolute efficacy of SD vaccines external to the study. Previous studies have suggested that inactivated vaccines similar to SD provide approximately 50% protection against influenza in older adults. The absolute efficacy of HD could be estimated at 62%, a level of protection similar to that of SD
vaccines in younger adults. An immunogenicity study showed that immune responses induced by HD in adults 65 years of age and older were similar to those observed with SD in younger adults.

4. This study included 2 heterogeneous influenza seasons. The first had low influenza activity and was characterized by moderate-to-good match between the vaccine and circulating strains; the second had high influenza activity and was characterized by mismatch between circulating strains and the vaccine strains. Despite substantial differences between seasons, HD vaccine showed significant efficacy as compared with SD against the primary endpoint in each season, a finding that provides reassurance that the benefit of HD persists despite varying seasonal conditions.

5. The clinical benefit shown in this study translates into public health benefits.

6. The study has limitations: 1) The efficacy estimates were based on a limited number of cases and lacked sufficient precision. 2) Only a minority of flu viruses identified in the study were characterized as similar to the vaccine. Different results might be obtained in years when the relatedness of the vaccine and circulating strains differ materially from that observed in the study. 3) Although the study allowed inclusion of persons with high-risk conditions, participants were excluded if they had moderate or severe acute conditions.

CONCLUSION

The IIV3-HD as compared with the IIV3-SD significantly improved protection against laboratory-confirmed influenza.

IIV3-HD was associated with superior immune responses.


Funded by Sanofi Pasteur

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I enjoyed abstracting this study. It was well planned and executed. The message is very important for primary care and public health. HD vaccine should be used whenever possible.

If a patient has had multiple flu shots over the years, would not his immune response grow with the years?

I see no reason why patients under age 65 should not receive HD vaccine.
ASSOCIATIONS BETWEEN ACTIVE COMMUTING, BODY FAT, AND BODY MASS INDEX (BMI): Population-based, cross-sectional study in the UK

Studies have generally suggested that active commuting (walking and cycling) is associated with a lower risk of self-reported overweight.

This study used objectively measured BMI and body fat. It also considered public transport as a potential form of active travel in addition to walking and cycling.

STUDY
1. Cross-sectional study used data from the wave 2 health assessment sample of the UK Household Longitudinal Study.
2. The analysis sample contained 7534 individuals for the BMI analysis and 7424 for the percentage of body fat analysis (measured by electoral impedance).

RESULTS
1. Compared with using private transport, commuting by public or active transport was significantly and independently predictive of lower BMI for both men and women.
2. In the fully adjusted model, commuting by public or active transport was significantly and independently predictive of lower BMI for both men and women. Men who commuted by public or active modes had BMI scores 1.10 points lower and 0.9 points lower respectively than those who used private transport. For women scores were 0.72 and 0.87 points lower.
3. Results for percent body fat were similar.

DISCUSSION
1. Although many factors were adjusted for, residual confounding may still be in operation.
2. Participants were asked only to give their main commuting mode. Mixed model journeys were not considered.
3. The UKHLS is representative of the general population of the UK. These results may not be generalizable to other countries. While the range of demographic, socio-economic, physical activity, diet, and health related covariates were adjusted for, residual confounding may still be in operation.
Association between commuting mode and BMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (Fully adjusted model)</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Private transport</td>
<td>-1.10</td>
<td>-0.72</td>
</tr>
<tr>
<td>Public transport</td>
<td>-0.90</td>
<td>-0.87</td>
</tr>
</tbody>
</table>

The BMJ August 23, 2014;349:10  BMJ 2014;349:g4887
Cross sectional study, first author Ellen Flint, London School of Hygiene and Tropical Medicine.

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*Every little bit helps.*
*Certainly not a new observation, but one that needs emphasis for primary care patients.*

*For patients who drive to work, we might suggest that they park 10 blocks from their office, thus adding 20 blocks of walking a day. Climbing steps at work will also help.*

*Do public modes of transport use more energy than commuting by private automobile? It might entail more walking.*

*This study reminds me of the old observation that London bus conductors, who are active walking up and down the aisle and up and down the steps, are healthier than the bus drivers, who are sedentary at work.*

*I know nothing about measuring body fat by electric impedance.*

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**8-3 FRUIT AND VEGETABLE CONSUMPTION AND MORTALITY FROM ALL CAUSES CARDIOVASCULAR DISEASE, AND CANCER: Systematic Review and Dose-response Meta-analysis of Prospective Cohort Studies**

Fruit and vegetable consumption might be associated with risk of mortality, but the dose-dependency of these associations has not been determined in a meta-analysis.

This meta-analysis of prospective cohort studies shows inverse association between fruit and vegetable consumption and risk of all-cause mortality, with a 5% reduction in risk of all-cause mortality for each additional serving a day of fruit or vegetables (6% for fruit and 5% for vegetables).

**STUDY**
1. Searched the literature up to 2013, without language restrictions. Included prospective cohort studies
that reported risk estimates of mortality from all causes, cardiovascular disease, and cancer by levels of fruit and vegetable consumption.

2. Primary outcome = total and cause-specific mortality.

3. Most included studies adjusted for known risk factors of mortality, including age BMI, physical activity, smoking, and alcohol consumption, but confounding by residual or unmeasured factors could partially explain the findings. In particular, some studies did not adjust for other dietary factors.

RESULTS

1. Sixteen prospective studies were eligible for meta-analysis, including 56,423 deaths (11,512 cardiovascular, and 16,817 from cancer) among 83,323 participants during follow-up periods ranging from 4.6 to 26 years.

2. Higher consumption of fruit and vegetables was significantly associated with a lower risk of all-cause mortality. Pooled hazard ratio of all-cause mortality was 0.95 for an increment of one serving a day of fruits and vegetables (0.94 for fruit and 0.95 for vegetables. There was a threshold of 5 servings of fruits and vegetables a day, after which the risk of all-cause mortality was no longer reduced.

3. There was a significant inverse association for cardiovascular mortality (hazard ratio for each serving a day of fruits and vegetables 0.96). Higher consumption of fruits and vegetables was not appreciably associated with risk of cancer mortality.

CONCLUSION

Evidence from prospective cohort studies show that high consumption of fruit and vegetables is associated with a reduced risk of mortality from all causes, particularly cardiovascular disease, but not appreciably with cancer mortality.

The BMJ August 12, 2014; 349:g4490 doi 10.1136/bmj.g4490 First author Xia Wang, Shandong University, Jinan, China

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This and the preceding article emphasize important aspects of a healthy lifestyle (physical activity and diet). Primary care clinicians should constantly advise healthy lifestyles to all patients and be themselves exemplars of a healthy lifestyle.
SHOULD U.S. WOMEN BE SCREENED FOR CERVICAL CANCER WITH PAP TESTS, HPV TESTS, OR BOTH?: Ideas and Opinions

The Papanicolaou (Pap) test, introduced by Dr. George Papanicolaou in 1940s, is considered one of the greatest achievements in women’s health. It reduced cervical cancer deaths by 80%. However, it has relatively low sensitivity, and results are often poorly reproducible. Women must be tested frequently to reduce cancer risk.

In the 1990s, it was recognized that the human papilloma virus (HPV) causes nearly all cervical cancers. HPV testing was introduced into routine practice in 2003 as a method of triaging women with minimally abnormal Pap tests (atypical squamous cells of undetermined significance [ASCUS]).

In 2012, cervical cancer screening guidelines recommended co-testing with HPV and Pap every 5 years, or Pap alone, every 3 years for women age 30-65.

In 2014, the FDA approved the HPV test for primary screening for cervical cancer for women age 25 and older. However, professional societies have not yet produced guidelines for adopting primary HPV testing in clinical practice.

Cervical cancer screening tests aim to detect cervical pre-cancer (moderate to severe cervical dysplasia) to allow timely treatment. When choosing a screening test, one looks for high sensitivity (to detect most disease) with acceptable specificity (low rate of false positive tests).

Data on more than 120,000 women in 4 countries confirm that a single HPV test is superior to a single Pap test for the determination of cervical pre-cancers and cancer, having both higher sensitivity and specificity. A single screening with HPV testing detects 95% of pre-cancerous lesions, compared with 40% to 70% for Pap testing alone.

A trial which compared HPV with Pap in a population of previously screened women found that the risks for severe cervical dysplasia or cancer within 3 years of a negative test result were 0.78% for Pap alone and 0.34% for HPV alone and 0.30% for co-testing with both. Each test misses some abnormalities.

Which is the best testing method for screening—Pap alone, HPV alone, or co-testing?

Pap and HPV tests require speculum examinations and use special collection techniques identical to Pap alone, so the patient experience is identical. Current data indicate that HPV alone is at least equal to Pap testing alone at 3-year intervals in women age 30 and older. Primary HPV testing in women age 25-29 would have higher false positive rates because many young women have transient HPV infections that do not cause cervical dysplasia. Screening intervals will affect both benefits and costs of all tests. At present, Pap and HPV co-testing is recommended at 5-year intervals. Pap testing alone is recommended at 3-year intervals. No interval has yet been recommended for primary HPV testing.
Although the relative merits of screening tests and screening intervals warrant additional discussion, we cannot lose sight of the fact that most cervical cancers occur in women who have not had any recent screening.

To decrease the rates of invasive cervical cancer, increasing population screening coverage with any test, and ensuring that women are not lost to follow-up are more important than the choice of test.

Human papilloma virus vaccination also reduces the risk for pre-cancer by 75% among young women vaccinated before age 14. Improving vaccination rates will be crucial in preventing further disease.

Comparison of screening algorithms:

A. Pap only
   1) Negative—routine screening at 3-year intervals age 21-65
   2) ASCUS—HPV testing—colposcopy if HPV +
   3) High grade abnormality—colposcopy, no HPV testing

B. Primary HPV
   1) HPV negative—routine screening age 25 and older. Interval and upper age limit not determined.
   2) HPV+ (not types 16-18) a. PAP test—negative Pap and HIV co-testing at 12 months
      b. Pap—ASCUS+—colposcopy
   3) HPV 16 and18 +—colposcopy

C. Pap + HIV
   1) Pap and HPV negative—routine screening at 5-year intervals age 30-65
   2) Pap ASCUS; HPV negative—repeat co-testing at short intervals
      Pap negative; HPV +—repeat co-testing at short intervals
   3) HPV + or any high grade Pap lesion regardless of HPV result—colposcopy

Opinions will change over time. For primary care practice, HPV alone has advantages.
I do not know the costs of Pap and HPV, but I do not believe that adding Pap to HPV will be cost effective.

The major intervention is to ensure that tests are repeated at set intervals, and that patients are followed regularly.
8-5 BODY-MASS INDEX AND RISK OF 22 SPECIFIC CANCERS: Population-based cohort study of 5.24 million UK adults

Prior research has suggested that body-mass index (BMI; kg per height in meters squared) is a predictor of cancer risk. A Norwegian cohort study, the US Million Women Study and meta-analyses reported associations with several cancers.

However, there are important limitations to these studies including insufficient power, and potential confounders.

This study investigated the linkage between BMI and the most common site-specific cancers using BMI and outcome data collected from UK primary care. It estimated the BMI associations with a wide range of cancers with higher precision than had previously been possible.

METHODS

A cohort study (1982-2012) used previously collected computerized primary care data that covered about 9% of the UK population.

Excluded all subjects with any recorded cancer before study entry.

Outcomes: the 22 most common cancers in the UK: female breast, prostate, colon, rectum, lung, malignant melanoma, bladder, stomach, esophagus, non-Hodgkin lymphoma, leukemia, ovary, pancreas, multiple myeloma, uterus body, brain and central nervous system, liver, kidney, cervix, oral cavity, thyroid, and gall bladder.

Related BMI to risk of each cancer.

Considered covariates: Age, smoking, alcohol use, diabetes, index of deprivation, and sex.

RESULTS

1. Included 5.2 million individuals; 166,955 developed cancers of interest.
2. BMI was associated with 17 of 22 cancers, but the effects varied substantially by site.
3. Each 5 kg/m squared was roughly linearly associated with cancer of:

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus</td>
<td>1.62</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>1.31</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.25</td>
</tr>
<tr>
<td>Cervix</td>
<td>1.10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.09</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.09</td>
</tr>
</tbody>
</table>
4. BMI was positively (non-linearly) associated with cancer of:
   - Liver 1.19
   - Colon 1.10
   - Ovary 1.09
   - Breast (post-menopausal) 1.05
   (These 10 cancers were overall positively associated with BMI)

5. Estimated inverse effects on cancer of:
   - Prostate 0.98
   - Breast (pre-menopausal) 0.89

6. No association (not significant):
   - Lung 0.99 (non-smokers)
   - Oral cavity 1.07 (non-smokers)

7. Assuming causality, 41% of uterine and 10% of gallbladder, kidney, liver, and colon cancers could be considered attributable to excess weight. An estimated 1 kg/m squared population-wide increase in BMI would result in 3790 additional annual UK patients developing one of the cancers positively associated with BMI.

DISCUSSION

1. This large data-set recorded associations between BMI and 17 of 22 cancers studied. But the effects varied substantially by cancer type.
2. Higher BMI was roughly linearly related with increased risk of cancers of the uterus, gallbladder, kidney, cervix, thyroid, and leukemia.
3. Associations were non-linear (effect of BMI varying across the BMI range) for cancer of the liver, colon, ovary and post-menopausal breast. BMI had net inverse association with risk of pre-menopausal breast and prostate cancers. For lung and oral cavity cancers, an overall association seemed to be driven by smoking and was not observed in non-smokers.
4. There was no strong evidence of associations between BMI and cancers of the rectum, brain, central nervous system, non-Hodgkins lymphoma, or multiple myeloma, and only weak evidence for cancer of the prostate.
5. Heterogeneity in the effects of BMI suggests that there are different mechanisms associated with different sites, and in different patient groups. Several pathways have been proposed for the association between BMI and cancers: changes in hormone metabolism (particularly with regard to insulin, insulin-like growth factor, and sex hormones), and adipokines (singling proteins secreted by
fat tissue). Their precise role is incompletely understood.

6. Limitations: Individuals without BMI determinations were not included; the decision to measure BMI in primary care might be related to the patient’s apparent weight or their health status indicating selection bias.

7. Assuming these relationships to be causal, many cancers are attributable to overweight and obesity.

8. Over the past 12 years, mean BMI in England has been increasing at a rate equivalent to a 1 kg/m squared.

CONCLUSION

BMI is associated with cancer risk, with substantial population-level effects. The heterogeneity in the effect suggests that different mechanisms are associated with different cancer sites and different patient groups.

Lancet August 30, 2014;384:755-65 Cohort study, first author Krishnan Bhaskaron, London School of Hygiene and Tropical Medicine

Funded by National Institute for Heath Research, Wellcome Trust, and Medical Research Council, UK

The strength of this study was the very large cohort on which it was based, and concurrence with past observational studies.

However, I will not be convinced until definite causal mechanisms are established.

Should primary care clinicians discuss this possible risk with obese patients? I would not, unless the patient raises the subject.

8-6 FISH OIL SUPPLEMENTS

Long-chain omega-3 polyunsaturated fatty acids (PUFA) are present in cold water fish (eg, salmon and herring). They are commercially available over the counter and by prescription. They can decrease fasting triglyceride (TG) production and increase triglyceride clearance. With long-term intake, they may increase HDL-cholesterol.

The results of recent studies do not offer any convincing evidence that fish oil supplements either prevent cardiovascular disease or improve outcomes in patients who already have CVD.
Lovaza (formerly Omacor), a combination of eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA) was the first PUSA product to be approved by the FDA for treatment of severe hypertriglyceridemia. Daily doses of 3-12 grams can lower triglycerides by 20-50%, but they have not been shown to prevent pancreatitis (a major concern in patients with very high TGs).

Adverse effects: PUFA are usually well tolerated. DHA can increase LDL-cholesterol levels. Apparently EPA does not. Adverse effects include eructation, dyspepsia, and unpleasant aftertaste. Worsened glycemic control has been reported in diabetics taking large doses. In large doses they can inhibit platelet aggregation and increase bleeding times.

Conclusion: PUFA have not been shown to decrease risk of pancreatitis. The results of recent studies do not offer any convincing evidence that they prevent cardiovascular disease.

Some fish oil products:

<table>
<thead>
<tr>
<th>Fish oil capsules</th>
<th>Formulations</th>
<th>Usual dose</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascepa (Anarin)</td>
<td>1000 mg caps</td>
<td>2 caps bid</td>
<td>$184</td>
</tr>
<tr>
<td>Lovazza (GSK)</td>
<td>1000 mg caps</td>
<td>2 caps bid</td>
<td>210</td>
</tr>
<tr>
<td>USP-verified</td>
<td>1120 mg caps</td>
<td>4 caps daily</td>
<td>18</td>
</tr>
</tbody>
</table>

*Approximate wholesale cost per 30-day treatment
Available without a prescription.

The US Pharmacopeia has verified that certain fish oil products contain their labeled content, and contain no heavy metals or contaminants.

JAMA August 27, 2014; 312:839 From the Medical Letter on Drugs and Therapeutics

JAMA has paired with the Medical Letter to reproduce selected articles
Omega-3 PUFAs are still being advertised to the general public. Two large ads appeared in the Charlotte NC “Observer” recently.